Misleading Advertising Claims by Proton Beam Therapy Centers

Proton beam therapy (PBT) is increasingly being used for a variety of cancers, but it remains controversial because of the huge cost of establishing and maintaining treatment facilities and the still-unanswered question of how it compares to conventional radiotherapy for many types of cancers. Nevertheless, the number of centers offering PBT is increasing exponentially, and consensus guidelines now support PBT use in a limited number of disease sites or in clinical trials. However, direct-to-consumer advertising (DTCA) from PBT centers is telling a different story. The information content and claims made by these centers are often inconsistent with international consensus guidelines, according to a new study.

“Patients who are interested in PBT will often go to the website of a hospital or cancer center in order to obtain information about the procedure. Therefore, it can be problematic if the advertising is not accurate,” say the researchers. The results were presented at the 2019 American Society of Clinical Oncology (ASCO) Annual Meeting. DTCA has received the most attention for pharmaceuticals and has stirred up quite a bit of controversy. In 2015, the American Medical Association’s (AMA) House of Delegates and the American Medical Association’s (AMA) Council on Ethical and Judicial Affairs recommended that the AMA’s Declaration of Helsinki should apply to DTCA from PBT centers.

The results were presented at the 2019 American Society of Clinical Oncology (ASCO) Annual Meeting. DTCA has received the most attention for pharmaceuticals and has stirred up quite a bit of controversy. In 2015, the American Medical Association’s (AMA) House of Delegates and the American Medical Association’s (AMA) Council on Ethical and Judicial Affairs recommended that the AMA’s Declaration of Helsinki should apply to DTCA from PBT centers.

(Continued on page 4)

Apalutamide for Metastatic Castration-Sensitive Prostate Cancer

N Engl J Med 31 May 2019; Epub ahead of print

Apalutamide is an inhibitor of the ligand-binding domain of the androgen receptor. Whether the addition of apalutamide to androgen-deprivation therapy (ADT) would prolong radiographic progression-free survival (rPFS) and overall survival (OS) as compared with placebo plus ADT among men with metastatic, castration-sensitive prostate cancer (mCSPC) has not been determined.

In this double-blind, phase 3 trial, we randomly assigned men with mCSPC to receive apalutamide (240 mg per day) or placebo, added to ADT. Previous treatment for localized disease and previous docetaxel therapy were allowed. The primary end points were rPFS and OS.

A total of 525 patients were assigned to receive apalutamide plus ADT and 527 to receive placebo plus ADT. The median age was 68 years. A total of 16.4% of the men had undergone prostatectomy or received radiotherapy for localized disease, and 10.7% had received previous docetaxel therapy; 62.7% had high-volume disease, and 37.3% had low-volume disease. At the first interim analysis, with a median of 22.7 months of follow-up, the percentage of men with rPFS at 24 months was 68.2% in the apalutamide group and 47.5% in the placebo group (hazard ratio [HR] for radiographic progression or death, 0.48; 95% confidence interval [CI], 0.39 to 0.60; P<0.001, a statistically significant finding). The antitumor effects of the regimen were consistent with international consensus guidelines, according to a new study.

“We hypothesized that dual inhibition of the androgen receptor signaling [pathway] by different mechanisms of action would improve the antitumor effects of the regimen,” said study author Michael Morris, MD, Memorial Sloan-Kettering Cancer Center, New York City.

“But we conclude that adding abiraterone to enzalutamide does not improve overall survival [OS] relative to enzalutamide alone, and the current standard of care should not be changed by this study,” he emphasized. The study was presented at the American Society of Clinical Oncology (ASCO) 2019 Annual Meeting.

The study was conducted in men with progressive mCRPC; 657 men were randomly assigned to receive enzalutamide, and 654 were allocated to receive enzalutamide plus abiraterone. Enzalutamide was given at a dosage of 160 mg/day. The men in the combination arm received abiraterone 1,000 mg once a day plus prednisone 5 mg twice a day.

(Continued on page 8)
Time to Biochemical Relapse After Radical Prostatectomy and Efficacy of Salvage Radiotherapy in Patients with Prostate Cancer

Pak S, You D, Jeong IG, et al.

Int J Clin Oncol 13 May 2019; Epub ahead of print

This study investigated the prognostic and therapeutic implications of time to biochemical relapse (BCR) in patients with prostate cancer after radical prostatectomy. The records of 3,210 consecutive men with prostate cancer who underwent radical prostatectomy between January 1998 and June 2013 were retrospectively reviewed. Patients with BCR were divided into three groups based on quartiles of time to BCR, namely an early group (first quartile), an intermediate group (second and third quartiles) and late group (fourth quartile). 817 (25.5%) patients experienced BCR at a median of 24.9 months after surgery. The 8-year rate of distant metastasis-free survival (64.3% vs. 41.3%, p = 0.002) and cancer-specific survival (86.6% vs. 63.4%, p < 0.001) was higher in the salvage radiotherapy (SRT) group than the androgen deprivation therapy (ADT) group in patients with early BCR, whereas those rates (91.3% vs. 87.9%, p = 0.607 and 100.0% vs. 93.1%, p = 0.144, respectively) were similar in patients with late BCR. In the intermediate BCR group, the impact of SRT over ADT on 8-year cancer-specific survival was modest (91.9% vs. 82.3%, p = 0.057) and was limited to patients with pT2 or pT3a disease. SRT may decrease the risk of distant metastasis and cancer-specific mortality in patients with early BCR. However, a survival benefit for those with late BCR was not apparent. For patients with intermediate BCR, SRT was associated with a cancer-specific survival benefit in patients with pT2 or pT3a disease. Novel genomic tests and imaging modalities may support clinical decision-making in these patients.

Evaluating the Safety of Active Surveillance: Outcomes of Deferred Radical Prostatectomy After an Initial Period of Surveillance

Balakrishnan AS, Cowan JE, Cooperberg WR, et al.

J Urol 8 April 2019; Epub ahead of print

As enrollment in active surveillance (AS) expands, it is increasingly important to assess potential risks of deferred treatment. We evaluated the risk of prostate specific antigen (PSA) recurrence in a large cohort of men undergoing radical prostatectomy (RP) after initial AS. The study included men undergoing RP after a period of AS with Gleason grade group (GG) 1 or 2 at diagnosis, clinical [stage] ≤T2, and a low- or intermediate-risk disease at diagnosis. Men were stratified by a composite variable of GG and volume of high-grade cores at diagnosis. Pathological characteristics and recurrence after RP were evaluated. Of 1,916 men enrolled in AS between 1994 and 2017, 448 (23.4%) underwent deferred RP. Median time to RP was 27 months (IQR 15.5-46.5). At diagnosis, 388 men (86.6%) had GG1 disease, 31 men (6.9%) had GG2 disease with one high-grade core, and 29 men (6.5%) had GG2 with ≥2 high-grade cores. GG2 with ≥2 high-grade cores at diagnosis was associated with an increased risk of recurrence when compared to GG1 disease (Hazard Ratio 3.29, 95% Confidence Interval 1.49 to 7.26, p<0.01, a statistically significant difference), while GG2 with one high-grade core did not significantly differ from GG1. Our results support the careful use of AS in men with GG2 and one high-grade core at diagnosis. Men with ≥2 high-grade (GG≥2) cores at diagnosis may benefit from immediate treatment.

NEW! A Prostate Cancer Forum for Gay Men and Their Partners Us TOO Call-In Support Group

A Prostate Cancer Forum for Gay Men and Their Partners is an ongoing conference call series which provides gay men and their partners with important peer-to-peer support. Usually, both the man living with prostate cancer and his husband or partner are deeply impacted, and each is subject to his own physical and emotional concerns. It can be helpful to address these concerns by speaking with others in a similar situation.

Contact Terri Likowski at terril@ustoo.org or 336-842-3578 to reserve your spot and to get the call-in information! Space is limited.
Doc Moyad’s What Works & What is Worthless Column – Also Known as “No Bogus Science” Column

“Fruit Juice = Sugary Soda = Freaking Out?!”

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

Editor’s Note: Us TOO invites certain physicians and others to provide information and commentary for the Hot SHEET 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.

Cola is a healthy beverage today. What? Did Moyad just say “cola with sugar is healthy?” What’s the matter with Moyad? Has he lost it? First of all, I have never had “it” but, in reality, when you look at many cola or soda drinks with sugar, they are being blamed for almost everything unhealthy. The obesity epidemic? Perhaps. The reduction in life expectancy? Perhaps. The increase in type 2 diabetes? Perhaps. The reason our dog ran away from home? Sure!

My point is that there has been a relentless assault on sugary soda beverages and now many (not just some) parts of the country are considering adding a large tax to these nefarious sugary products. However, what has always intrigued me over 30 years is that I never understood the difference between sugar-filled soda and fruit juice. Can someone explain this to me? Because when I look at the label on many fruit juices, they have more sugar and calories than most cola drinks, or at least similar amounts. Yeah, but fruit juice is loaded with nutrients, right Moyad?

Who cares?! You can load up cola with nutrients and it does not make the product healthy because the overall product and sugar and concentrated caloric content appears unhealthy to me. Take a look at some fruit juices in terms of sugar and calories and, even in a few cases, it would arguably be healthier for you to drink a cola! Therefore, it should not be surprising that a preliminary large U.S. study recently found that the greater consumption of sugary beverages, including fruit juices, was associated with “increased all-cause mortality among older U.S. adults.”

YIKES! Just like the sugary soda/cola beverage category, the harm appears to exceed the benefit! Critics will argue that this is just one large observational U.S. study, but I would argue that more studies are not really needed to essentially think about common sense for a moment. It’s always better to eat the whole fruit with the fiber, which has the ability to make you feel full compared to the sugary concentrated caloric version of the fruit (aka “fruit juice san fiber”). All of this is a big deal because, as we all get bigger in America, research continues to find that weight gain or obesity makes the prostate bigger and also increases the risk of aggressive prostate cancer. Pass me the whole apple or orange and leave the juice alone to sit at the grocery store right next to its other family members which, in my mind, includes cola beverages or other sugary soda!

And, the next time I see another kid at the airport sucking down some type of juice in a box/carton with the parent(s) simultaneously smiling and fully encouraging this habit I am going to freak out! This means I am going to freak out in the next few days! Aaargh!!!!

#dontletmoyadfreakout
#dontletmoyadfreakout

References:

Magnetic Resonance Imaging-Targeted Biopsy vs. Systematic Biopsy in the Detection of Prostate Cancer: A Systematic Review and Meta-Analysis


Eur Urol 23 May 2019; Epub ahead of print

Magnetic resonance imaging (MRI)-targeted prostate biopsy (MRI-TB) may be an alternative to systematic biopsy for diagnosing prostate cancer.

The primary aims of this systematic review and meta-analysis were to compare the detection rates of clinically significant and clinically insignificant cancer by MRI-TB with those by systematic biopsy in men undergoing prostate biopsy to identify prostate cancer.

A literature search was conducted using the PubMed, Embase, Web of Science, Cochrane library, and Clinicaltrials.gov databases. We included prospective and retrospective paired studies where the index test was MRI-TB and the comparator test was systematic biopsy. We also included randomised controlled trials (RCTs) if one arm included MRI-TB and another arm included systematic biopsy. The risk of bias was assessed using a modified Quality Assessment of Diagnostic Accuracy Studies-2 checklist. In addition, the Cochrane risk of bias 2.0 tool was used for RCTs. We included 68 studies with a paired design and eight RCTs, comprising a total of 14,709 men who either received both MRI-TB and systematic biopsy, or were randomised to receive one of the tests. MRI-TB detected more men with clinically significant cancer than systematic biopsy (detection ratio [DR] 1.16 [95% confidence interval (CI) 1.09-1.24], p<0.0001) and fewer men with clinically insignificant cancer than systematic biopsy (DR 0.66 [95% CI 0.57-0.76], p<0.0001). The proportion of cores positive for cancer was greater for MRI-TB than for systematic biopsy (relative risk 3.17 [95% CI 2.82-3.56], p<0.0001).

MRI-TB is an attractive alternative diagnostic strategy to systematic biopsy.

We evaluated the published literature, comparing two methods of diagnosing prostate cancer. We found that biopsies targeted to suspicious areas on magnetic resonance imaging were better at detecting prostate cancer that needs to be treated and avoiding the diagnosis of disease that does not need treatment than the traditional systematic biopsy.

PROSTATE CANCER HELPLINE: 1-800-808-7866 WWW.USTOO.ORG
Delegates called for a ban on DTCA of prescription drugs and medical devices, although others have supported such advertising and feel that it can educate patients and spread valuable information about the particular product.

“DTCA is often controversial, but this is not just limited to drug advertising,” said lead author Mark T. Corkum, MD, of the University of Western Ontario, London, Canada.

“In comparison to many previous studies, our study of DTCA in PBT focused on online advertising content and claims by hospital/cancer center websites, vs. more typical print/media advertising which must conform to nationally-regulated standards,” he explained.

In contrast to traditional media, online DTCA has no such oversight, and online DTCA has already been shown to be controversial in other technology-driven advancements, such as stereotactic body radiotherapy and robotic prostatectomy.

“Provisos that acknowledge treatments need to be individualized — ‘ask your doctor if drug X is right for you’ — are a mainstay of other forms of DTCA, but they were not a prominent feature of the websites we examined,” he told Medscape Medical News. “Whether proton beam therapy can offer clinically meaningful differences to quality or quantity of life is not always clearly defined, and can be subject to interpretation.”

Misleading Information
The goal of the study was to evaluate DTCA content and claims made by PBT center websites. Corkum and his colleagues identified English language websites worldwide using the Particle Therapy Co-Operative Group website and used eight international guidelines to determine the appropriate indications for PBT.

They looked at a total of 48 proton therapy centers with 46 English websites. More than half (58%) did not provide any references for the claims that they made regarding the use of PBT. These claims included improved disease control or cure (61%), fewer side effects (85%), or that PBT was the standard of care (13%).

The most frequently cited cancer sites indicated for PBT were prostate (87%), head and neck (87%), and pediatric (83%) cancers, and these were consistent with international guidelines.

However, pancreatobiliary (52%), breast (50%), and esophageal (44%) cancers were frequently advertised even though treatment with PBT has not been endorsed for these cancer types in any consensus guidelines.

“Randomized trials in proton radiation are lacking and have proven to be difficult to accrue to,” said Corkum. “When one considers the significant additional costs of proton radiation, we believe there should be compelling data to support its use.”

He pointed out that there are many examples in oncology where advances on paper or in single-arm studies, such as the dosimetric benefit in proton therapy, “may not pan out to be true benefits to patients.”

Corkum commented that the first step is to acknowledge that a problem exists and for healthcare providers to be aware of what information is available to patients.

“Many patients with cancer will turn to the internet for information — however, it is worrisome that these patients may be finding information on hospital/cancer center websites not in keeping with clinical guidelines, particularly when these websites would be seen as more trustworthy than other internet sources,” he said.

“At the same time,” Corkum added, “it is important to keep in mind that DTCA by an institution does not necessarily reflect the level of discussion that occurs at the provider/patient level. But it could potentially be a driver for increasing referral/treatment volumes to a particular center,” he said.

“Moving forward, we believe more can be done to standardize the messages patients are receiving.”

Presented at the 2019 ASCO Annual meeting, Abstract 6599. Medscape Medical News 3 June 2019

Enzalutamide Joins Initial Treatment List for Metastatic Prostate Cancer

The oral androgen receptor inhibitor enzalutamide is an effective first-line treatment option for men with metastatic prostate cancer (PCa), conclude researchers reporting the phase 3 ENZAMET trial.

“Enzalutamide significantly improved overall survival (OS) in comparison with a conventional nonsteroidal antiandrogen (NSA; bicalutamide, nilutamide, or flutamide) when both were added to standard of care (SOC) in this setting,” reported lead author Christopher Swee...
Men in the two treatment arms were well balanced in terms of age, performance status, race, and risk group,” Morris pointed out. Disease characteristics were also well matched between the two treatment arms; 56.8% of enzalutamide recipients and 54% of those treated with abiraterone had disease of Gleason grade 8, 9, or 10.

“At a median follow-up of 34.2 months in the enzalutamide-plus-abiraterone arm and 32.5 months in the enzalutamide-alone arm, there was no difference in OS between the two arms,” Morris reported. Rates of decline in PSA levels were also similar between the two arms.

“Radiographic progression-free survival (rpFSS) rates were modestly in favor of the doublet arm, at 33%, compared with 42% for the single-agent arm. The median on-treatment rpFSS rate was 25.2 months for the doublet arm and 20.7 months for the single-agent arm. There was thus a modest (but statistically significant) improvement with the addition of abiraterone (P = 0.02),” Morris noted.

Similarly, there was a modest improvement in the median on-treatment and off-treatment rpFSS rate of 25.2 months for enzalutamide plus abiraterone, vs. 22.4 months for enzalutamide alone, but again, these differences were “nothing to write home about and were barely statistically significant (P = 0.05),” he commented.

“The number one reason men came off treatment was radiographic progression,” Morris noted. “On the other hand, slightly fewer than 20% of patients in each arm experienced clinical progression before there was evidence of radiographic progression; these men came off treatment because of clinical progression,” he added.

“Among the patients who received the combination therapy, the withdrawal rate from treatment because of AEs was more than double that of the men who received enzalutamide alone,” Morris continued.

For example, the rate of grade 3 or 4 fatigue was 11.4% in the combination arm, vs. 6.2% in the enzalutamide arm. The rate of grade 3 or 4 hypertension was also higher, at 30.1%, for patients who received enzalutamide plus abiraterone, compared with 22.6% for the single-agent arm.

The atrial fibrillation rate, although low in both arms, was higher, at 1.1%, for the doublet arm, vs. 0.5% for single-agent enzalutamide. Increases in levels of liver enzymes also occurred in more of the patients given the combination, at 8.6 vs. 2.2% for those treated with enzalutamide alone.

In total, 68.5% of patients in the enzalutamide-plus-abiraterone arm experienced a grade 3 or 4 nonhematologic AE, compared to 56.6% for those who received enzalutamide alone. Despite the greater risk for AEs in the combination arm, “the median difference in treatment duration between the two arms was 51 days, so not that big of a difference between the two arms, those receiving enzalutamide having a longer duration of treatment,” Morris said.

“And the likely reason why this trial ended up being a negative study was simply that there was not much more anticancer activity in one arm vs. the other,” he concluded.

Commenting on the findings, discussant Michael Carducci, MD, AEGON professor in prostate cancer research, Hopkins Kimmel Cancer Center, Baltimore, Maryland, felt that Alliance was an important study in which “timely” and “significant” questions for clinical practice were addressed.

“We know that there are patients who have fast-paced disease, so we do need to develop new drugs based on targets and their molecular features, but we also have to be mindful that if we overtreat patients and give them more therapy, we can make the time they have left actually fairly miserable,” he said.

“So while both drugs are capable of extending survival, they can take a toll on quality of life as well as cost, so we have to make sure that we put it all together for our patients,” he added.

Also commenting on the findings, Celestia Higano, MD, professor of medicine and urology, University of Washington, noted that enzalutamide and abiraterone have different mechanisms of action and different resistance mechanisms, “so it certainly made sense to study this combination.”

However, because the addition of abiraterone to enzalutamide did not improve OS, “we should not do that” in clinical practice, Higano emphasized.

“And while this was a negative trial, I think it’s an example of how a negative trial can be very useful for us clinically,” she said.

Presented at the ASCO 2019 Annual meeting, Abstract 5008.

Medscape Medical News 5 June 2019

Satisfaction with Care Among Men with Localised Prostate Cancer: A Nationwide Population-Based Study

Bergengren O, Garmo H, Bratt O, et al.

Eur Urol Oncol 15 May 2019; Epub ahead of print

Information about how men with prostate cancer (PCa) experience their medical care and factors associated with their overall satisfaction with care (OSC) is limited.

To investigate OSC and factors associated with OSC in men with low-risk PCa, Men registered in the National Prostate Cancer Registry of Sweden as diagnosed in 2008 with low-risk PCa at the age of ≤70 years who had undergone radical prostatectomy (RP), radiotherapy (RT), or started on active surveillance (AS) were invited in 2015 to participate in this nationwide population-based survey (n=1,720).

OSC data were analyzed using ordinal logistic regression.

(Continued on page 8)
metastatic PCa, commencing testosterone suppression."

**Complex Study Design**

The results are big news, but Sweeney acknowledged that interpreting these early three-year results is complex. "The complexity stems, in part, from the findings on prespecified subgroups of men who did and those who did not also receive DOC as part of SOC in the study. ENZAMET is the first metastatic hormone-sensitive PCa trial to report OS data of an androgen receptor inhibitor (enzalutamide) and outcomes among a set of patients who also concurrently received DOC," explained Sweeney.

For the men whose SOC treatment included DOC (N = 503), there was no significant difference in OS between the enzalutamide arm and the NSAA arm at three years (HR, 0.90). "We do not see a significant treatment effect [of enzalutamide] in this early analysis," said Sweeney. "That's the first information that we, as investigators, will have to think through — what to give our patients if they've had DOC," he added.

"In other words, if there is no survival benefit with enzalutamide for men who also receive DOC, then perhaps enzalutamide, being a more expensive therapy, can be withheld at this early point, because DOC can do the job instead, especially in select patients," he suggested.

"Enzalutamide is priced in the neighborhood of $10,000 per month," said Sweeney, "whereas chemotherapy is much less costly."

However, this clinical scenario needs an asterisk. Most of the men in the DOC subgroup (71%) had high-volume, poor-prognosis metastatic disease (four or more visceral metastases).

On the other hand, for the men whose SOC treatment did not include DOC (N = 622), there was indeed a notable difference in OS between the enzalutamide arm and the NSAA arm at three years (HR, 0.53). Only about a third (37%) of these men had high-volume disease. In other words, enzalutamide was effective in improving survival, when not competing with DOC, and in men with mostly low-volume disease.

Serious adverse events (AEs) within 30 days of the study occurred among 42% of men in the enzalutamide arm and 34% in the NSAA arm, which was "commensurate with the different durations of study treatment," the study authors report in their meeting abstract.

However, in terms of AEs, Sweeney pointed out that, in comparison to the NSAA arm, the enzalutamide arm had higher rates of grade 2 and 3 hypertension, fatigue, falls, and syncope, as well as seizures (any grade). "We as physicians have to ask, 'Are the patients fit enough, even for the hormone enzalutamide?'" said Sweeney, adding that clinicians need to counsel patients about risk.

He also highlighted the fact that the rate of treatment discontinuations due to drug-related adverse events was 16% in the enzalutamide arm vs. 4% in the NSAA arm. Also, seven men (1%) in the enzalutamide group experienced seizures, vs. no patients in the NSAA group.

Currently, in the United States, enzalutamide is indicated for the treatment of patients with metastatic castration-resistant PCa who have previously received DOC. It is also indicated for the treatment of men with earlier, nonmetastatic, castration-resistant PCa.

"Enzalutamide will now also be used in this new setting of metastatic hormone-sensitive PCa," predicted Charles Drake, MD, PhD, director of genitourinary oncology, New York-Presbyterian/ Columbia University Medical Center, and associate director for clinical research, Herbert Irving Comprehensive Cancer Center, New York City, who was not involved in the new study. "I think this will be a regimen that people use in the first line," he said.

"There are currently two established treatment options in the first line," he noted. "Men with metastatic hormone-sensitive PCa experience a survival benefit with the addition of either DOC chemotherapy or abiraterone acetate to androgen deprivation therapy; both approaches are current standards of care and are supported by evidence from the major clinical trials," said Drake, who was asked for comment.

"Men with metastatic hormone-sensitive PCa and their clinicians in this first-line setting now have more choice," he said. "But the current trial is only a partial help."

In hypothetical head-to-head trials, Drake suspects that the current choices would be very similar in efficacy: "I doubt that abiraterone would beat chemo, or chemo would beat abiraterone. I doubt that enzalutamide would beat chemo or abiraterone."

"Enzalutamide has the advantage of not requiring steroids (like abiraterone) but has the disadvantage of causing fatigue, among other adverse events," he added. "DOC is associated with peripheral neuropathy and other side effects. Abiraterone use is not advisable for men who are at risk for diabetes and cardiovascular disease," he said.

**Major Collaboration**

The new study was a collaboration between the University of Sydney; the Australian and New Zealand Urogenital and Prostate Cancer Trials Group; the National Health and Medical Research Council, Australia; Cancer Trials Ireland; and the NCIC Clinical Trials Group.

Sweeney explained that ENZAMET randomization was stratified by a number of variables, including the aforementioned early DOC vs. no DOC. Another variable was volume of disease: high volume (four or more visceral metastases) vs. low volume. The authors performed related subgroup analyses to assess possible modulation of the treatment effect.

Presented at the ASCO 2019 Annual meeting, Abstract LBA2

*Medscape Medical News* 3 June 2019
Doctor Chodak’s Bottom Line


Editor’s Note: Us TOO has invited certain physicians and others to provide information and commentary for the Hot SHEET 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.

P1, “More is Not Better…”
Major improvement in outcomes has occurred from the use of both enzalutamide and abiraterone in men with advanced disease. Since their mechanisms of actions differ, combining the two was an important study to undertake. Moore and co-workers reported on a randomized study comparing enzalutamide to enzalutamide plus abiraterone in men with metastatic castrate resistant disease. Sadly, the combination did not result in better overall survival, but did result in a higher incidence of side effects. Going forward, there is no reason to use the two together. Now it remains to determine if there is an advantage to choosing either of the drugs first before switching to the second and, if so, whether any factors can identify which drug will benefit which patient.

The Bottom Line: Patients with advanced disease do not benefit from using enzalutamide and abiraterone together.

P1, “Misleading…”
A personal pet peeve for quite some time has been the lack of oversight in the way medical advertising promotes different treatments, in this case Proton beam radiotherapy (PBT). Now an online analysis of websites by Corkum, et al. has also assessed potential bias. They looked at 48 websites promoting PBT and found many made claims about improved efficacy or reduced side effects with few providing any support. As the authors state, first the problem needs to be acknowledged and then a decision can be made about what to do.

At the least, men should be discouraged from relying on websites promoting various treatments, as there is a great potential for bias. One suggestion might be to have the specialty boards create review groups that evaluate a medical website for content, accuracy, balance and bias and provide a stamp of approval if found to meet the necessary requirements. Men could then look for that stamp when deciding if the material is worth reading.

The Bottom Line: Websites promoting PBT often provide misleading or unsupported claims to the public and men should be aware of this bias.

P1, “Apalutamide for…”
Men with castrate sensitive metastatic prostate cancer now have another option for treatment – apalutamide. A randomized study by Chi, et al. was recently published showing that the combination of apalutamide with conventional androgen deprivation therapy (ADT) resulted in a better radiographic progression-free survival and overall survival compared to the ADT alone. This occurred without a significant increase in grade 3 or 4 side effects. The drug has already been approved for men with non-metastatic disease and this study is likely to result in an additional approval. When that occurs, the next question will be, which drug is better for the combination with ADT, apalutamide, enzalutamide or abiraterone?

The Bottom Line: Apalutamide combined with ADT results in better overall survival than ADT alone.

P2, “Time to Biochemical…”
Each patient faced with a rising PSA after radical prostatectomy (RP) has several choices: continue observation, salvage radiation therapy (RT) or early ADT. Pak, et al. conducted a retrospective analysis to assess the benefit of RT vs. ADT according to the timing of biochemical relapse, which was divided into four equal periods.

They found that men in the earliest time period of PSA recurrence had a lower metastatic rate and lower prostate cancer mortality after RT compared to ADT. A similar benefit was not seen in the latest PSA recurrence group. Although these data suggest that RT is better than ADT for the early recurrences, there are problems with the design that could bias the results.

First, it is retrospective, so the decision to select RT or ADT was not uniform. Second, it is unclear why quartile time periods were used. Had the men been divided into three or five time periods, the results might be different. Only a randomized study can confirm if RT offers a real benefit.

The Bottom Line: It remains unclear if salvage RT is significantly better than ADT for PSA recurrence after RP.

P2, “Evaluating the Safety…”
A critical component of active surveillance (AS) is the long-term risk if deferred treatment is needed. Balakrishnan and co-workers conducted an analysis of over 1,900 men on AS diagnosed between 1994 and 2017, of which about 25% underwent delayed RP. They found the characteristic associated with risk of recurrence was the presence of two or more cores of higher-grade disease. This suggests that having a Gleason 3+4 cancer does not mean AS should be avoided but it may need to be limited to those men with only one core showing the higher Gleason score. However, since only 29 men were in this higher-risk group, more data are needed to substantiate these findings.

The Bottom Line: AS may need to be re-evaluated carefully in men with two or more areas of Gleason grade 4 cancer, but more data are still needed to substantiate this finding.

P3, “Magnetic Resonance…”
Which is better? MRI-targeted biopsies (MRI-TB) or systematic biopsies? More data is appearing on this topic, but the answer is still not clear. A meta-analysis conducted by Kasivisvanathan, et al. provides an assessment of the studies that have been published. Based on 68 reports, plus eight randomized trials, the authors found that MRI-TB was significantly better at finding tumors needing treatment while finding fewer men with tumors not needing treatment. Whether this is enough to support abandoning systematic biopsies in favor of MRI-TB remains unclear.

The Bottom Line: Increasingly, it appears that MRI-TB has advantages over systematic biopsy and may soon become the standard of care.
Apalutamide
(Continued from page 1)
tistically significant difference). OS at 24 months was also greater with apalutamide than with placebo (82.4% in the apalutamide group vs. 73.5% in the placebo group; HR for death, 0.67; 95% CI, 0.51 to 0.89; P = 0.005, a statistically significant difference). The frequency of grade 3 or 4 adverse events was 42.2% in the apalutamide group and 40.8% in the placebo group; rash was more common in the apalutamide group.

In this trial involving men with mCSPC, OS and rPFS were significantly longer with the addition of apalutamide than with placebo and were less likely to believe they would die from PCa (3.8 vs. 3.9 vs. 8.0%). Limitations include the nonrandomized retrospective design and potential recall bias.

Information and participation in decision-making, as well as access to a nurse navigator, are key factors for OSC, regardless of treatment. Men on AS need more information about their treatment need more participation in decision-making. OSC was as high among men who had nurse-led follow-up as among men who had doctor-led follow-up. Information about how men with low-risk prostate cancer experience their medical care is limited. In this nationwide population-based study we found that information and participation in decision-making as well as access to a nurse navigator are key factors for satisfaction, regardless of treatment.

Men who are being closely watched for prostate cancer without immediate curative treatment need more information than they now receive and need to participate more in decision-making than they currently do.

Satisfaction with Care Among Men with Localized PCa (Continued from page 5)

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QUESTION FROM PROSTATE CANCER SURVIVOR:
I had radiation along with hormone therapy two years ago and, since then, I have not had any erections. I expected this and this is bad enough but my penis has almost disappeared. I can hardly find it when I need to urinate and it has made things really awkward at the golf course or any public restroom. Why has this happened and what can I do about it?

RESPONSE FROM DR. ANNE KATZ:
Genital shrinkage is very common after radiation therapy and especially after hormone therapy (or androgen deprivation therapy as it is correctly termed). This shrinkage is a complex process resulting, in part, from lack of testosterone (the purpose of androgen therapy) and lack of erections that limits blood flow to the penis. As a result, penile tissue is starved of oxygen and other nutrients and penile tissue becomes like scar tissue (not flexible etc.). The androgen deprivation also results in shrinkage of the testicles. All of this may impact negatively on a man’s body image. It also has some practical problems as you describe; men tell me that they do not have the penile length to urinate into a urinal and they may drip urine on their clothing and/or shoes. And they are embarrassed to urinate in a public restroom where other men may see that they have a ‘problem’ with a short/small penis.

There are two things that might help. The first is to do daily gentle penile massage to encourage blood flow to the tissues. The intent is not necessarily to try and have an erection but merely to get oxygen into the tissues. There is some evidence that using a penile pump is helpful for this too. Success may depend on how long it has been since treatment and the onset of the shrinkage. The other potential is for the man to lose weight if he is overweight. The fat pad over the pubic bone will shrink with weight loss and give the penis some extra length outside the body (estimated to be about half an inch with each 15 lbs of weight lost!). Surgery may be suggested, however, there is not a lot of evidence supporting this and many men are not interested in this after everything else they have been through with treatment.

Watch Dr. Katz’ presentation on sexual health and intimacy from the Prostate Cancer Pathways for Patients and Caregivers event recorded at Englewood Health in Englewood, NJ on September 29, 2018. https://www.youtube.com/watch?v=A2ZdDHw2WGY&t=8542s.

Read previous issues of Between the Sheets at www.ustoo.org/BTS.

Do you have a question about sexual health or intimacy? If so, we invite you to send it to Us TOO. We’ll select questions to feature in future Between the Sheets columns.

Please email your question to: uestooBTS@ustoo.org

Or mail your letter to:
Us TOO International
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Advancements in prostate cancer research provide hope for finding a cure and lead to the discovery of new treatments to minimize the impact of a man’s prostate cancer and maximize his quality of life. This regular Hot SHEET supplement includes some of the latest research from the Prostate Cancer Foundation (www.pcf.org).

The PCF is the world’s leading philanthropic organization funding and accelerating prostate cancer research. Founded in 1993, the PCF has raised more than $745 million and provided funding to more than 2,000 research programs at nearly 200 cancer centers and universities.

No Clinical Benefit with Metformin Added to Docetaxel in mCRPC
At the 2019 ASCO Annual Meeting in early June, Dr. Marc Pujalte Martin presented results of TAXOMET, the first randomized-controlled trial of metformin’s impact when given in combination with docetaxel treatment (a form of chemotherapy) for metastatic castration-resistant prostate cancer (mCRPC). The results showed that metformin does not have a benefit in non-diabetic patients with mCRPC receiving docetaxel.

Interest in Metformin
Preclinical data (studies in a lab) and some retrospective studies (looking back at data from patients’ medical records) suggest that metformin, a drug typically used to treat Type 2 diabetes, may have preventive and therapeutic effects in cancer. Researchers have observed that patients with Type 2 diabetes who are treated with metformin have a lower risk of cancer incidence and mortality. Other studies point to metformin’s antitumor activity—namely, a link between the drug and the prevention of tumorigenesis, or the development of cancer. This has led scientists to further explore the relationship between metformin and prostate cancer. A randomized-controlled trial is the “gold standard” study that allows scientists to measure the effect of a particular treatment in a certain type of patient.

The TAXOMET Trial
The study was designed to observe the difference between prostate cancer patients who received metformin with their chemotherapy treatment and those who did not. Participants were non-diabetic and had mCRPC (metastatic prostate cancer that had become resistant to hormone therapy). Patients were randomly assigned to two groups in which they either: (A) received docetaxel treatment with metformin or (B) received docetaxel with a placebo. Researchers tracked 99 patients over nearly 3 years, recording information such as their PSA levels, progression-free and overall survival rates, toxicity, and quality of life. (PSA response rate was defined as 50% [or greater] decrease from baseline PSA level. Progression-free survival is time to disease progression or death from any cause. Overall survival is time to death from any cause).

The results showed that the addition of metformin to docetaxel did not improve PSA response rate (72% in both arms) or median progression-free survival (7.3 months in arm A vs. 5.8 months in arm B) or overall survival (24.2 months vs. 19.7 months) compared with docetaxel alone in patients with mCRPC. (While the duration of survival is longer numerically in Arm A, statistical analysis indicates that those differences could be due to chance alone). More patients who took metformin had diarrhea vs. patients who did not (70% vs. 50%). This study indicates that metformin was not effective in combination with docetaxel treatment in mCRPC patients.

What Does This Mean for Metformin in the Treatment of Prostate Cancer?
It is possible that metformin is simply not effective in men with mCRPC, or that the combination with docetaxel is not efficacious. At ASCO, the results of a small, early phase trial suggested that metformin in combination with enzalutamide was found to be clinically active in men with CRPC. However, based on the results of TAXOMET, given the lack of clinical benefit, and increased gastrointestinal toxicity, non-diabetic patients with mCRPC should not take metformin in combination with docetaxel for an “anti-cancer” effect.

1. Pujalte Martin M, Borchiellini D, Viotti J, et al. TAXOMET: A French prospective multicenter randomized controlled phase II study comparing docetaxel plus metformin versus docetaxel plus placebo in mCRPC. J Clin Oncol 37, 2019 (suppl; abstr 5004)
2. Parikh M, Robles D, Pan C-X, et al. Results from a phase Ib/II study of enzalutamide and metformin in men with castration resistant prostate cancer (CRPC). J Clin Oncol 37, 2019 (suppl; abstr 5054)

For more information visit www.pcf.org, email info@pcf.org, or call 1-800-757-2873.