

Survey of ADT-induced estrogen deficiency related side effects in a contemporary cohort of men with advanced prostate cancer

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Background

Androgen Deprivation Therapy (ADT) is a mainstay in the treatment of advanced prostate cancer. ADT-induced estrogen deficiency related side effects may cause men to delay, pause, or discontinue ADT, increases morbidity and mortality, and can significantly impact quality of life. ADT-induced effects include hot flashes, bone loss and fractures, fatigue, decreased libido, and metabolic and lipid changes. Currently there are no FDA approved treatments for ADT-induced hot flashes in men with advanced prostate cancer. In this study, a survey was conducted on the impact of hot flashes, one of the hallmark ADT-induced estrogen deficiency effects, in a contemporary cohort.

Methods

During the period of August/September 2019, 212 men with advanced prostate cancer on ADT participated in a digital survey conducted by the Prostate Cancer Research Institute (PCRI) focused on the frequency, severity and impact of their hot flashes. The men were at least 50 years of age with 61% being 70 or older. ADT types included LUPRON® (64%), ELIGARD® (12%), ZOLADEX® (7%) and other forms of hormonal therapy (17%).

Results

Of the 212 men surveyed, 99% reported hot flashes with 80% indicating that they experience clinically significant, moderate to severe hot flashes. 77% of men reported that the number of hot flashes stayed the same or increased during their hormonal therapy. 37% of the men experienced more than 5 hot flashes per day and 23% indicated that they felt embarrassed about their hot flashes. Only 51% of the men surveyed had either researched how to address their hot flashes or discussed them with their physician. Importantly, 16% considered halting ADT as a result of their hot flashes.

Conclusions

This contemporary survey underscores the significant unmet medical need to treat moderate to severe hot flashes which occurred in 80% of the men studied. As about half of the men have not discussed their symptoms with a physician either because of embarrassment or lack of treatment options, the number of men with moderate to severe hot flashes appears to be greatly underreported. As men on ADT are living longer with prostate cancer, finding an effective and safe treatment for debilitating hot flashes must be a priority. Zuclophene citrate is a non-steroidal weak estrogen that is now being evaluated in a Phase 2 placebo-controlled randomized study in men with advanced prostate cancer on ADT that have moderate to severe hot flashes. This Phase 2 will be completed by the end of January 2020 and will be followed in 2020 by two Phase 3 studies of similar design.

Funding Source

A research grant from Veru Inc

BACKGROUND

Androgen deprivation therapy for advanced prostate cancer Side effects

- Androgen deprivation therapy reduces testosterone and estrogen to castrate levels

Low estrogen side effects

- Hot flashes
- Bone loss and fractures
- Loss of libido
- Memory loss/cognitive changes
- Metabolic syndrome
- Unfavorable lipid changes

Low testosterone side effects

- Muscle loss
- Frailty
- Muscle weakness
- Increase fat body composition

Adapted from: Freedland S et al. Prostate Cancer and Prostatic Diseases 12:333-338 2009

Hot flashes accompany a cluster of symptoms

- Although hot flashes are a common and impactful side effect of ADT-induced estrogen deficiency, they do not occur in a vacuum
- Other associated issues are
 - Sleep
 - Health related quality of life
 - Cognitive impairment
 - Sexuality
 - Fatigue

Engstrom CA. Am J Men's Health 2008; 2(2):122-132

MATERIALS AND METHODS

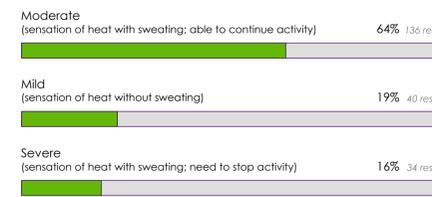
During the period of August/September 2019, 212 men with advanced prostate cancer on ADT participated in a digital survey conducted by the Prostate Cancer Research Institute (PCRI) focused on the frequency, severity and impact of their hot flashes. The men were at least 50 years of age with 61% being 70 or older. ADT types included LUPRON® (64%), ELIGARD® (12%), ZOLADEX® (7%) and other forms of hormonal therapy (17%).

RESULTS

Moderate and severe hot flashes remain through the course of ADT

80% of Survey Responders Suffer Moderate/Severe Hot Flashes

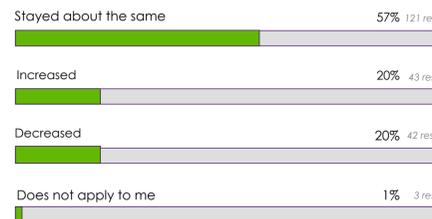
What type of hot flashes do you suffer from?



210 out of 212 answered

77% of Patients on ADT Have Consistent or Worsened Levels of Hot Flashes

Have the number of hot flashes increased or decreased over the course of your hormonal treatment?



209 out of 212 answered

RESULTS

Hot flashes are under-reported and significantly impact men on ADT and are a major reason behind their dissatisfaction

16% of Men on ADT Therapy Have Considered Stopping Treatment Due to Hot Flashes

Have you ever considered halting ADT treatment because of the hot flashes you have experienced?



209 out of 212 answered

16% of ADT Patients Have Had to Change Their Lifestyles Due to Hot Flashes

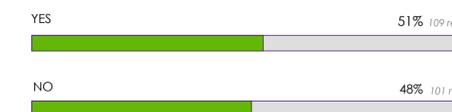
Have you had to change your lifestyle at all because of your hot flashes?



210 out of 212 answered

48% of Men on ADT Who Suffer From Hot Flashes Have Not Discussed it with Their Doctor

Have you ever researched how to treat your hot flashes or discussed this issue with your doctor?



210 out of 212 answered

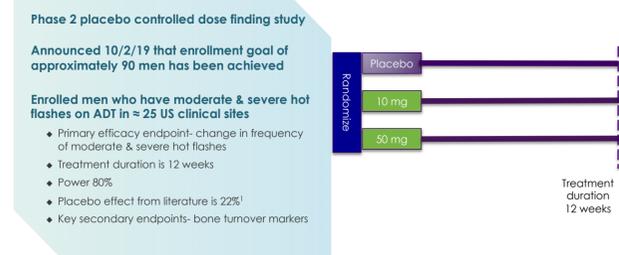
CONCLUSIONS

- 80% of men on ADT have clinically significant, moderate to severe hot flashes
- 16% said they had to change their lifestyle because of hot flashes
- Hot flashes are under-reported
 - 23% felt embarrassed because they were having hot flashes
 - Nearly 50% have not discussed issue with their physician
- 16% of patients surveyed would consider halting their prostate cancer treatment because of hot flashes
- Novel therapeutic approaches are necessary in order to address this problem

CURRENT/FUTURE CLINICAL TRIALS

- Zuclophene is a weak oral non-steroidal estrogen receptor agonist
- New chemical entity (NCE) with proprietary formulation
- Oral once per day dosing
- Weak estrogenic activity provides for a potentially greater therapeutic index

Zuclophene clinical development plan: Phase 2 trial design



Phase 3 trials – pathway forward

- Two Phase 3 trials are being planned
 - Randomized, double-blind placebo-controlled
- Subjects
 - Advanced prostate cancer on ADT who have experienced moderate to severe hot flashes for at least one month prior to study entry
- Primary endpoints are the change in the frequency and severity of moderate to severe hot flashes at weeks 6 and 12
- Secondary endpoints include
 - Bone mineral density
 - Libido
 - Fatigue
- Approximately 200 subjects per Phase 3 trials (randomized 1:1)