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Prostate Cancer Chemoprevention: A Current Review

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Abstract

Purpose: To provide an updated review on prostate cancer chemoprevention agents, including 5-ARI's and pomegranate, which will help guide the ensuing direction of the management of prostate cancer.

Materials and methods: We searched MEDLINE using search criteria 'prostate cancer, chemoprevention' and reviewed all ideal trials and scholarly articles in the past 10 years.

Results: Many studies were considered, but PCPT and the REDUCE trial were the only studies that tested 5-ARI's on the period prevalence of prostate cancer. Additionally, follow-up studies of 5-ARI trials and studies on the use of pomegranate that met ideal design criteria were utilized for review.

Conclusions: PCPT and REDUCE trials reveal that 5-ARI's have the ability to reduce low grade prostate cancer, but also show a slight increase high grade prostate cancer diagnosis. Follow-up studies suggest that these findings may be due to detection bias, but official guidelines recommend against 5-ARI use due to the potential risk. As an alternative to 5-ARI's, studies on pomegranate have shown promise but more studies and phase III clinical trial results are needed for future direction of pomegranate use. Potential of chemoprevention agents is based on exploration of approaches, agents, and validity of design. Efficacy of chemoprevention agents enables: prevention of over-diagnosis, decreased use of overly aggressive treatment, and enhanced quality of life by reducing suffering, mortality, and economic burdens.

Introduction

Prevalence and importance of prostate cancer

The Center for Disease Control (CDC) ranks cancer as the second highest cause of death in the U.S., attributing 23.2% of all deaths. Many forms of cancer comprise this unfortunate statistic, prostate cancer being a top contributor [1]. According to the most recent estimate from the American Cancer Society released in 2010, approximately 217,730 new cases of prostate cancer will be diagnosed and 32,050 men will die of prostate cancer in the next year [1]. Concerning men in the United States, approximately 1 out of every 6 will be diagnosed with prostate cancer, and 1 in 36 will die of prostate cancer [1]. The prevalence of prostate cancer has shed light on the importance of all aspects of the disease. This insight has led to increased awareness, research, and efforts to be directed towards the management of cancer, particularly through the use of chemoprevention methods.

Rationale for prostate cancer chemoprevention

Chemoprevention is an intervention that uses a chemical or some other agent to prevent, curtail, or reverse the carcinogenesis process. It is important to note that the phenotype or physical manifestation of cancer is influenced by both genotype and environmental factors including diet, exercise, smoking, etc. There are three methodological categories for chemoprevention approaches, which include: primary, secondary and tertiary chemoprevention. Primary chemoprevention attempts to diminish the presence of cancer, while secondary chemoprevention aims to reduce the risk of progression of cancer that has already developed [1]. Tertiary chemoprevention methods aim to prevent the development of new cancer when a previous instance of cancer has already been diagnosed and cured [2]. Given that prostate cancer is characterized by a slow progression period and is exceptionally prevalent, chemoprevention is an ideal strategy for the management of prostate cancer. Furthermore, chemoprevention provides an alternative to the aggressive forms of treatment that are frequently implemented rendering the diagnosis of prostate cancer. Often times, diagnosed prostate cancer may present little to no danger to the patients' health. In this way, chemoprevention enables a decrease in the over diagnosis and over treatment of prostate cancers [2]. Thus, chemoprevention makes possible the reduction of prostate cancer through the use of safer, more effective, and less intense forms of intervention. Furthermore, the prevention of prostate cancer has the potential to alleviate suffering and mortality, and to benefit the public on physical, emotional, social, and economic levels.

Contents of subsequent review

Throughout this review, chemoprevention approaches and their corresponding current clinical trial results will be considered. Various studies on chemoprevention agents are currently underway or have been completed. Currently, the only studies that have yielded a significant reduction in prostate cancer are the studies on 5 alpha-reductase inhibitors (5-ARI's). The two most significant studies on 5-ARI's include: the Prostate Cancer Prevention Trial [PCPT] and Reduction by Dutasteride of Prostate Cancer Events [REDUCE] trial. Other dietary studies, such as pomegranate supplementation, have been undertaken and may provide further insight to the prevention

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of prostate cancer. The current status of chemoprevention agents will be presented through the discussion of the most recent clinical data, including both advantages and disadvantages of their use. This information should be used to guide in the future direction and with decisions regarding the use of certain prostate cancer chemoprevention agents.

Materials and Methods

Search methods and materials

We reviewed both existing and completed chemoprevention trials that met ideal design criteria. We searched MEDLINE to identify large-scale randomized trials from June 2001-June 2011 using the keywords 'chemoprevention, prostate cancer.' This search yielded >300 search results for evaluation. We focused on primarily 5-ARI trials, and considered other dietary/antioxidant approaches, particularly the pomegranate studies. Data for continuing studies was accessed through protocols and author access to *Clinical Work Station*. Additionally, a thorough evaluation of updated, relevant medical journal literature on prostate cancer was reviewed.

Types of studies reviewed: It is important to note the types of studies that were considered for this review. First, a prospective study 'looks forwards.' A prospective study identifies a cohort of subjects and observes them going forward in time. Second, a retrospective study 'looks backwards.' A retrospective study aims to identify a relationship between a certain condition and its correlating risk factors or exposures [3]. For our purposes, the studies reviewed were prospective in nature. Although prospective studies are generally more costly than retrospective studies, they facilitate the assessment of the relative risk or occurrence of an outcome based upon a particular exposure [3]. Furthermore, prospective studies allow one to account for and reduce possible confounding factors and biases. In addition to being prospective in nature, the studies considered for this review were well designed, large-scale, randomized, and blinded [3].

Results

Basis for 5-ARI trials

The role of the 5 alpha-reductase enzymes in the prostate is to convert testosterone to androgen dihydrotestosterone (DHT). DHT aids in the development and function of normal, hyperplastic, and malignant prostate tissue. Thus, the inhibition of 5 alpha-reductase enzymes decreases the amount of DHT, and may then reduce the risk for prostate cancer [4]. In the PCPT, the drug finasteride inhibits solely type II 5 alpha-reductase enzymes. In the REDUCE trial, the drug dutasteride inhibits both type I and type II alpha-reductase enzymes [5].

The Prostate Cancer Prevention Trial (PCPT)

Design: The PCPT study was initiated in 1993 under the coordination of the Southwest Oncology Group and funding of the U.S. National Cancer Institute. PCPT was the first large-scale, randomized, placebo-controlled, double-blinded, and population-based trial to test a chemopreventative agent on the development of prostate cancer. PCPT was implemented at more than 200 clinical sites throughout the United States from 1993 until 2003. PCPT tested the hypothesis that finasteride lowers DHT levels by inhibiting type II 5-alpha inhibitor, and thus prevents prostate cancer [6]. The study began with the enrollment of 18,882 men who met certain criteria. Specific criteria for trial included: men ≥ 55 yeas of age, no suspicion of prostate cancer, serum prostate-specific antigen (PSA) level < 3.0 ng/ml, and a normal digital rectal examination (DRE). The pool of 18,882 men was randomized to receive either 5 mg finasteride/day (9,459 men) or placebo (9,423 men) for a period of seven years. PSA measurements and DRE's were recorded annually, and a prostate biopsy was encouraged if an irregular PSA (>4.0 ng/ml) or non-normal DRE was detected [6]. However, given that finasteride lowers PSA levels, the finasteride groups' PSA measurements needed to be adjusted in order to equilibrate with the placebo groups' PSA measurements. In years 1-3 the PSA's of the finasteride group were doubled, and then were multiplied by 2.3 from year 3-7 [2]. All men were encouraged to have a prostate biopsy at year 7, which was the end of the trial period. The trial was ended 15 months early because it had achieved its primary objective which was to show that finasteride reduced the risk of prostate cancer [6].

Initial results

The final analysis data consisted of men who had a prostate cancer biopsy throughout the study or at the end of the study. 9,060 of the 18,882 were included in the final analysis data, 4,368 from the finasteride arm and 4,692 from the placebo arm. Of the 3,573 for-cause biopsies (PSA >4.0 ng/ml or irregular DRE), 1,639 were from the finasteride arm (38%) and 1,934 were from the placebo arm (41%). Thus, the finasteride group had 15% less for-cause biopsies than the placebo group. Out of the total cancers diagnosed for-cause (1,006), 435 were from finasteride group (54%) and 571 were from placebo group (50%). Therefore, the finasteride group had 10% fewer cancers when accounting only for-cause biopsies. In the total 1,950 instances of cancer, 803 were in the finasteride arm and 1,147 in the placebo arm [5]. Overall, finasteride demonstrated a 24.8% risk reduction of low-grade prostate cancer (Gleason score≤6). Unfortunately, the finasteride group showed a slight increase in mid to high-grade cancer (Gleason score 7-10). Specifically, there were 280 cases (6.4%) in the finasteride arm and 237 cases (5.1%) in the placebo arm. End of study biopsies yielded a more promising 92 cases in finasteride arm and 89 cases in placebo arm [5].

Reduction by Dutasteride of Prostate Cancer Events (REDUCE)

Design

The REDUCE study was initiated in 2003 and sponsored by GlaxoSmithKline. The REDUCE trial was the second large-scale, randomized, placebo-controlled study on the effects of 5-ARI's on prostate cancer prevention [6]. The REDUCE trial was implemented at international clinical sites and ran from 2004-2009. The REDUCE trial was designed to study the ability of dutasteride to decrease the risk of prostate cancer that is detectable with biopsy amongst high-risk men [2]. REDUCE tested the hypothesis that dutasteride lowers DHT levels by inhibiting both type I and type II 5-alpha inhibitors, therefore preventing prostate cancer. The study began with the enrollment of 8,122 men who met certain criteria. Study criteria included: men age 50-75 years, entry serum PSA levels 2.5-10.0 ng/ml, prostate volume <80 ml, and a negative prostate biopsy of 6-12 cores that had been independently taken within 6 months of enrollment to the study [4]. The pool of 8,122 men was randomized to receive either 0.5 mg of dutasteride daily (4,049 men) or placebo (4,073 men) over a period of four years [5]. For-cause biopsies were administered throughout the study if PSA >4.0 ng/ml or irregular DRE was detected. All men in the study had prostate biopsies at year 2 and 4, unless they already had a for-cause biopsy that year [7].

Initial results

The final analysis data consisted of all 8,122 men that were enrolled in the trial [5]. A total of 6,729 men who were biopsied, 3,305 (82%) were from the dutasteride arm while 3,424 (84%) were from the placebo arm. Of the total number of 12,024 biopsies, 5,956 were from the dutasteride arm and 6,068 were from the placebo arm [6]. There were 810 protocol-independent biopsies (PSA >4.0 ng/ml or irregular DRE other than at year 2 or 4), 344 (5.8%) were from the dutasteride arm and 466 (7.7%) were from the placebo arm. In the total 98 cancers diagnosed on protocol-independent biopsies, 41 (6.2%) were from the dutasteride arm and 57 (6.6%) were from the placebo arm [4]. Of the total 1,517 cancers, 659 (19.9%) were from the dutasteride arm and 858 (25.1%) from the placebo arm [7]. Overall, there was a 23% decrease in risk of prostate cancer for dutasteride group. Unfortunately, dutasteride group showed a slight increase in mid to high-grade cancer (Gleason score 7-10) [2].

Follow-up results on 5-ARI's

Although a slight increase in the diagnosis of high-grade prostate cancer emerged in both the REDUCE and PCPT trial, it is important to note that potential explanations to this finding have been issued. Publishing from *Clinical Cancer Research* and other medical researchers attribute the increase in high-grade prostate cancer diagnosis to detection bias. Specifically, these sources suggest that 5-ARI's enhanced PSA utility and made the high-grade prostate cancer easier to detect but did not increase the occurrences of high-grade prostate cancer [7].

Discussion of 5-ARI's

Benefits of 5-ARI's:

-Decrease in the diagnosis of low-grade prostate cancer.

-Improved diagnosis of high-grade prostate cancer due to drug effects on PSA utility and prostate volume.

-Decreased urinary retention, urinary tract infections, and other urinary side effects.

-Possible decrease in over treatment and over diagnosis of low-grade prostate cancer [2,5].

Harms of 5-ARI's:

-Increase in adverse sexual functions including: impotence, decreased libido, and erectile dysfunction.

-Slight increase in diagnosis of high-grade prostate cancer.

-Possibility of over-detection and over-diagnosis of prostate cancer due to effects on PSA levels and prostate volume [2,5].

Weighing benefits vs. harms: Most recent guidelines on 5-ARI use

The latest update on the use of 5-ARI's for the prevention of prostate cancer was issued on June 9, 2011. In these guidelines, the US Food and Drug Administration (FDA) informed the healthcare community about changes in labeling for 5-ARI's, including finasteride and dutasteride. The FDA reviewed the results of the finasteride trial (PCPT) and the dutasteride trial (REDUCE) which revealed both a hopeful decrease in low-grade prostate cancer, and a distressing increase in high-grade diagnosis of prostate cancer. Specifically, the FDA called for labeling the drugs with the warning that "there is an increased risk of being diagnosed with high-grade prostate cancer when taking these drugs." Prior to the most recent guideline release, the FDA's Oncologic Drugs Advisory Committee (ODAC) voted and convened with an overwhelming majority in opposition to the recommendation of 5-ARI use for prostate cancer prevention [8]. Although the increase in high-grade prostate cancer is small and may be due to detection bias, the FDA wants healthcare representatives to be fully informed and to take the possible danger seriously in order to most appropriately weigh the benefits and harms of the use of 5-ARI's with their patients. Overall, the FDA holds that according to the current clinical trial outcome status, the possible risk of a slight increase in the diagnosis of high-grade prostate cancer far outweighs the decrease in low-grade prostate cancers. Reconvening and reconsideration of these guidelines will be made in the near future with the aid of additional data and clinical trial results on 5-ARI use [8].

In addition to the FDA, the American Society of Clinical Oncology/ American Urological Association issued guidelines in April 2009 on the use of 5-ARI's for prostate cancer chemoprevention. The main points of the physician guidelines include [9]:

1."Inform the man who is considering a 5-ARI that these agents reduce the incidence of prostate cancer, and be sure to be clear that these agents do not reduce the risk of prostate cancer to zero;

2.discuss the elevated rate of high-grade cancer observed in the PCPT and inform men of the potential explanations;

3.make it known to men that no information on the long-term effects of 5-ARI's on prostate cancer incidence exists beyond approximately 7 years, and whether or not a 5-ARI reduces prostate cancer mortality or increases life expectancy remains unknown;

4.inform men of possible but reversible sexual adverse effects; and

5.inform men of likely improvement in lower urinary tract symptoms [9]."

Nutraceuticals/dietary agents/antioxidants: particularly pomegranate

Introduction and current status: Nutraceuticals are alternative dietary and holistic substances that are used for the treatment or prevention of multiple forms of cancer [10]. Many dietary agents and antioxidants that have been extracted from plants and other organic materials have been proposed as plausible chemopreventative agents. Some examples of nutraceuticals include selenium, vitamin E, vitamin C and soy. Unfortunately, no phase III trials on these agents have yielded consistent and significant results thus far. However, the antioxidant content of the nutraceutical pomegranate has yielded optimistic results in phase II trials by slowing the prostate cancer progression period. The pomegranate fruit is found on the Mediterranean tree called *punica granatum*. Pomegranate is rich in antioxidants including flavonoids and tannins [11]. Currently, multiple in vitro, in vivo, and phase II clinical trials on animals and humans have suggested that pomegranate extract affects the cell cycle and induces apoptosis. Trial results suggest that these processes drive the anti-proliferation and inhibition of cancer cell and tumor growth [12].

Discussion of pomegranate: Collectively, results suggest that pomegranate extract may have the ability to prevent the progression of prostate cancer. Continuing studies need to be done to test and support these initial results. Since there is currently no universal and satisfying chemoprevention agent the studies on pomegranate and other nutraceutals should be pursued thoroughly and without further delay,

given that their use may provide a practical cancer prevention option that comes without harmful side effects. Efficacy in pursuit of these nutraceuticals have the ability to enhance quality of life for patients, prevent progression of prostate cancer, and provide a less-invasive option for the management of prostate cancer. The completion and review of current studies on pomegranate and other nutraceuticals will guide the future of the use of these agents for the prevention of prostate cancer.

Conclusion

Status of chemoprevention today and in the future

Currently, only the studies on 5 alpha-reductase inhibitors (REDUCE and PCPT) have revealed a considerable reduction in the occurrence of prostate cancer. However, as previously discussed the decrease in low grade prostate cancer parallels an increase in high grade prostate cancer. After weighing the advantages with disadvantages of 5-ARI's, the official guidelines recommend against the use of 5-ARI's as chemopreventative agents. Nevertheless, there still remains the possibility that the status of 5-ARI's could change, given additional clinical trial results on 5-ARI's that yields promising results void of an increase in diagnosis of high-grade prostate cancer. Aside from 5-ARI use, studies on supplementation of pomegranate have shown promise in the prevention of prostate cancer. However, continuing phase III and large-scale randomized trials are necessary for the validity and progression of the use of pomegranate as a chemopreventative agent [13].

The future direction and efficacy of the prevention of prostate cancer is impingent upon new agents, strategies, and most importantly ideal design and validation of trials. Regarding all chemoprevention agents, especially 5-ARI's and POM, ideally designed, large-scaled, and randomized trials are a necessary precursor for the direction, development, and progression of the management of prostate cancer. As of now, men who are at high-risk for prostate cancer should be informed and educated about all chemoprevention options, and weigh the advantages versus the disadvantages on an individual basis with the consultation of their physician [7].

Overall, this review is intended to provide an accessible, up-to-date, and concise source concerning the status of chemoprevention agents. This review aims to provide a more thorough understanding of prostate cancer chemoprevention agents for both the healthcare community and its patients. Hopefully, such knowledge will help reduce over diagnosis and over treatment of low grade prostate cancer. Success in these areas will help reduce death, suffering, and unnecessary aggressive treatment in the management of prostate cancer. Ultimately, the efficacy in pursuit of chemoprevention agents for prostate cancer has the potential to alleviate suffering and mortality, and to benefit the public on physical, emotional, social, and economic levels.

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