Clinical Oncology: Case Reports

Review Article

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Phytotherapy of Prostate Cancer: How far are we?

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Abstract

Prostate cancer (PCa) is the second most diagnosed cancer in men, principally affecting men over 50 years old, and is the fifth leading cause of cancer-related deaths in men worldwide. In recent years, the use of complementary and alternative medicine (CAM) has increased, especially among oncology patients. Treatment options are limited in androgen-independent prostate cancer. To reduce this tremendous health burden, new approaches have been directed toward extremes of the disease spectrum centering on strategies for prostate cancer prevention and for treating advanced androgen-independent cancers. Medicinal herbs and their derivative phytocompounds are being increasingly recognized as useful complementary treatments for cancer. Great number of clinical studies have reported the beneficial effects of herbal medicines on the survival, immune modulation, and quality of life (QOL) of cancer patients, when these herbal medicines are used in combination with conventional therapeutics. Although, tremendous efforts have been done in phytomedicine and phytotherapy, we still have a long way to go.

Keywords

Clinical trial; Herbal medicine; Prostate cancer; Phyototherapy

Introduction

Cancer, a cohort of diseases in which abnormal cells divide without control and are able to invade other tissues (through the blood and lymph systems), brings devastating consequences for the patients' life and indeed is a leading cause of death worldwide [1]. Being a multifaceted issue; it is a therapeutically challenging disease and rapidly emerging pre-clinical and clinical studies have started to shed light on the molecular mechanisms, which underlie cancer development and progression [2]. Prostate cancer (PCa) is the second most diagnosed cancer in men, principally affecting men over 50 years old [3]. It is the fifth leading cause of cancer-related deaths in men worldwide [4]. Current screening techniques are based on the measurement of serum prostate specific antigen (PSA) levels and digital rectal examination.

The incidence of prostate cancer is high. Autopsy studies have demonstrated that 60-70% of older men have some area showing cancer within the prostate [5,6]. It is estimated that a 50-year-old man has a lifetime risk of 42% of developing prostate cancer, but only a 9.5% risk of developing the disease clinically and being diagnosed and a 2.9% risk of dying from prostate cancer [7]. The clinical behavior can vastly differ in different men with prostate cancer of similar staging, PSA levels, and histological appearance. The existing clinical biomarkers for prostate cancer (PCa) are not ideal, since they cannot specifically differentiate between those patients who should be treated immediately and those who should avoid overtreatment [8].

Prostate Cancer Diagnostic and Treatment

Over the past several decades, tremendous efforts have been made to screen and characterize useful cancer biomarkers for the use in clinical practice. According to the biomarkers statistics database from the Division of Cancer Prevention of the American National Cancer Institute, prostate cancer biomarkers represent the leading large group of investigated biomarkers by scientists, then followed by ovary, breast and lung cancers, respectively (Figure 1). This shows that among the various neoplasms that suffer men, prostate cancer remains the critical health issue. Several sources for the study of these potential novel biomarkers for PCa are being analyzed, each one with its advantages and disadvantages [9]. According to their clinical use, they currently fall into three major categories: (1) prognostic, (2) predictive, and (3) pharmacodynamics markers [10].

Conventional prostate cancer treatments include prostatectomy, radiotherapy, hormonotherapy, chemotherapy, and biological therapy. Side effects such as sexual function disorder, impotence, diabetes, and cardiovascular disease have been observed [11]. Currently used diagnostic standards consist of determination of prostate specific antigen (PSA), clinical stage, and total Gleason grade. Unfortunately, they do not give sufficient justification for choosing the optimal therapy for a particular patient [12]. Hence, it is necessary to search for new biomarkers to allow for the prediction of disease dynamics and personalization of therapy [13].

Prostate Cancer Phytotherapy

Statistically, in 25% of men worldwide with PCa that develop metastatic disease, the bones are the principal targets of PCa metastasis [14]. Given the fact that PCa is characterized by a long latency period, a strong dietary influence, and limited treatment strategies for the advanced disease; therefore, many patients turn to complementary and alternative medicine (CAM) with the belief that these medicines represent a viable therapeutic option that may be free of adverse side effects [15]. This folkloric belief is strongly upheld in many Asian cultures. Herbal remedies have been used for thousands of years with very minimal side effects and clearly merit extended research for their ability to selectively kill prostate cancer cells. Several herbal products have recently been incorporated into cancer research [16,17], among them is Nigella sativa whose seeds have been used medicinally for centuries in a variety of diseases [18].

There has long been a keen interest in herbal or alternative therapies for prostate cancer, particularly those that may not have the same side effects as androgen deprivation therapy. Numerous pharmacologic interventions have been developed in attempts to retard prostate tumor growth after the emergence of androgen-independent disease [19]. Several cytotoxic chemotherapeutics have shown substantial palliative benefits but little improvement delaying disease progression or mortality [20]. The inability of conventional approaches to

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reverse the progression of advanced disease coupled with a desire for therapies with fewer perceived toxicities has prompted patients and clinicians to consider unconventional or complementary alternatives [19]. Although there are often multiple cell-based and even animal models demonstrating efficacy of the CAM, the problematic remains the paucity of clinical trial data. The reliable source of the CAM, lot-to-lot variability, lack of reliable biomarkers, and a paucity of pharmacokinetics data to base decision regarding schedule or dose, are the various issues that make clinical trials more difficult to run until the end [21]. Complementary medicine has suffered for many years from lack of solid evidence in order to justify its use in clinical medicine. It appears that we have reached the phase that this claim is less and less valid, as more evidence-based products are allowed to be commercialized and used under the supervision of an authoritative professional (oncologist, palliative care specialist, pain specialist, and others) [1].

PC-SPES (FDA non-approved combination of eight different herbs), was commercially available in China since 1996. The complementary therapy garnered significant interest due to clinical studies reporting measurable responses in advanced prostate cancer [19]. A series of clinical studies were conducted to assess the effect and mechanism of PS-SPES activity [22,23]. Although the therapeutic application of PC-SPES seemed to be promising, unfortunately, PC-SPES was recalled and withdrawn from the market because certain batches of testing PC-SPES samples were found to be contaminated with US Food and Drug Administration-(FDA) controlled prescription drugs [24].

The widespread use and possible success of PC-SPES led to a search for other "natural" or "herbal" remedies after it became unavailable [25]. Today, as many as one-third of prostate cancer patients use alternative medications [26]. In most cases, these therapies are not endorsed and often not even monitored by physicians, making it hard to discern their value. Therefore, it has been an urgent matter and a great interest to carry out clinical studies on phytotherapy of Prostate Cancer. Several clinical studies are currently in process and are shown in (Tables 1a-1c). While some of them have been completed, few have been withdrew or terminated due to various reasons. However, future more studies are in need to find the "Golden Phytotherapic Drug" for patient with prostate cancer.

Conclusion

For centuries if not millennia, various plants have been used as medicines and disease therapeutics in most human cultures. Recently, scientists have showed great interest in herbal medicines as anti-tumor

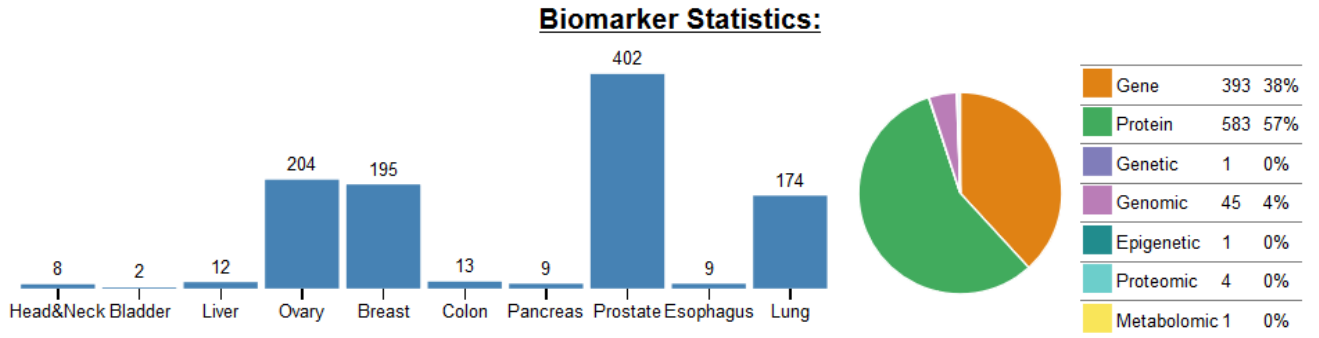

Figure 1: All Cancers Biomarkers Statistics.

Table 1a: Clinical trials on Prostate Cancer Phytotherapy.

No	ClinicalTrials.gov Identifier	Phase	Patients	Allocation (Masking)	Intervention/Treatment	Primary Purpose	Status	Country
1	NCT01682941	II	40	Randomized/Double	Soy Bread Soy-Almond Bread	Treatment	C	USA
2	NCT03211104	N/A	107	Randomized/Double	Curcumin Placebo	Treatment	C	N/A
3	NCT00005828	II	54	Single group/Open label	Green tea extract	Treatment	C	USA
4	NCT00731848	II	30	Single group/Open label	Pomegranate liquid extract	Treatment	U	USA
5	NCT00719030	N/A	25	Randomized/Open Label	Pomegranate pill Pomegranate pill placebo	Prevention	C	USA
6	NCT00060086	NA	40	Single group/Open label	Pomegranate juice	Treatment	AnR	USA
7	NCT00732043	II	200	Randomized/Quadruple	Pomegranate extract Pomegranate juice Placebo	Prevention	U	USA
8	NCT00685516	NA	113	Randomized/Open Label	Green Tea Placebo Decaffeinated Black Tea	Treatment	AnR	USA
9	NCT00765479	III	284	Randomized (Open Label)	Soy protein isolate Placebo	Treatment	C	USA
10	NCT00058266	II	36	Randomized (Open Label)	Genistein Conventional Surgery	Treatment	T	USA
11	AnR : Active, non-recruiting; C: Completed; R: Recruiting; NA: Non-available; N/A: Non applicable (It is used to describe trials without FDA-defined phases, including trials of devices or behavioral interventions.); PCa: Prostate Cancer; T: Terminated; U: Unknown							

Table 1b: Clinical trials on Prostate Cancer Phytotherapy.

No	ClinicalTrials.gov Identifier	Phase	Patients	Allocation (Masking)	Intervention/Treatment	Primary Purpose	Status	Country
1	NCT01912820	I	31	Randomized/Double	Green tea extract Quercetin Conventional Surgery	Prevention	AnR	USA
2	NCT00607932	N/A	66	Randomized/Double	Brassica vegetable Indole-3-carbinol Questionnaire administration Adjuvant therapy	Treatment	C	USA
3	NCT01340599	II	5	Randomized/Double	Defined green tea catechin extract. Placebo. Questionnaire administration Conventional surgery.	Treatment	T	USA
4	NCT00535977	N/A	22	Non-randomized Open Label	Broccoli Peas	Basic Science	C	UK
5	NCT01917890	N/A	40	Randomized/Double	Curcumin Placebo	Supportive Care	C	IRAN
6	NCT00617617	II	52	Randomized/Triple	Prevastein HC® Placebo	Prevention	C	USA
7	NCT02759380	N/A	240	Randomized/Single group	Phytoestrogen-rich foods	Prevention	R	Sweden
8	NCT03087903	N/A	41	Single group/Open label	Grape Seed Extract	Treatment	R	USA
9	NCT00200824	II	NA	Randomized/Double	Soy Isoflavone Nutritional Supplements	Prevention	C	USA
10	NCT01083771	N/A	21	Single group/Open label	Olive Oil	Prevention	C	USA
11	NCT03084913	N/A	30	Randomized/Open Label	Plant- based, olive oil diet PCa Foundation diet	Treatment	C	USA
12	NCT00669656	II	43	Single group (Open label)	Prostate Health Cocktail	Treatment	C	USA
13	NCT02766478	II	24	Randomized/Double	Genistein/Placebo	Prevention	R	USA
14	NCT01521949	II	21	Single group (Open label)	Acai Juice Product	Treatment	C	USA
15	NCT01950143	N/A	78	Randomized/Double	Standard broccoli soup Beneforte broccoli soup Beneforte extra broccoli soup	Prevention	AnR	UK
16	AnR : Active, non-recruiting; C: Completed; R: Recruiting; NA: Non-available; N/A: Non applicable (It is used to describe trials without FDA-defined phases, including trials of devices or behavioral interventions.); PCa: Prostate Cancer; T: Terminated; U: Unknown							

Table 1c: Clinical trials on Prostate Cancer Phytotherapy.

No	ClinicalTrials.gov Identifier	Phase	Patients	Allocation/Masking	Intervention/Treatment	Primary Purpose	Status	Country
1	NCT01912820	I	31	Randomized/Double	Green tea extract Quecertin Placebo	Prevention	AnR	USA
2	NCT01126879	II	36	Randomized/Double	Genistein/Placebo	Treatment	AnR	USA
3	NCT01681823	II	60	Single group/Open label	PectaSol-C Modified Citrus Pectin (MCP)	Treatment	R	ISRAEL
4	NCT00336934	N/A	183	Randomized/Quadruple	Pomegranate juice Placebo	Treatment	C	USA
5	NCT00651417	II	101	Randomized/Quadruple	Organic Germanium Placebo	Prevention	U	USA
6	NCT02144649	N/A	45	Randomized (Open Label)	Tangerine tomato juice Red tomato juice Questionnaire administration	Treatment	C	USA
7	NCT01126879	II	36	Randomized/Double	Genistein Placebo Conventional Surgery	Treatment	AnR	USA
8	NCT01009736	II	60	Single group/Open label	Tomato-soy juice Conventional Surgery	Treatment	C	USA
9	NCT01823549	N/A	120	Cohort	Question administration	NA	AnR	USA
10	NCT01100866	N/A	1	Randomized/Quadruple	POMELLA™ (pomegranate extract) Placebo	Treatment	T	CANADA
11	AnR : Active, non-recruiting; C: Completed; R: Recruiting; NA: Non-available; N/A: Non applicable (It is used to describe trials without FDA-defined phases, including trials of devices or behavioral interventions.), PCa: Prostate Cancer; T: Terminated; U: Unknown							

and chemoprevention agents. While continuous and systematic effort is needed, a number of notable "breakthroughs" have occurred in the field of medicinal plant research and botanical drugs in the last few years. In April 2008, a partially purified fraction of the water extract of green tea leaves from Camellia sinensis, named "Veregen", was the very first FDA approved botanical drug, for topical treatment of external genital and perianal warts [27]. In January 2013, the FDA approved, for the first time, an oral botanical drug, "Crofelemer", for treatment of diarrhea in HIV/AIDS patients [24]. Although these two pioneer FDA-approved botanical drugs are not therapies for cancer, they certainly pave way for such future developments [24]. "PHY906" (also known as KD018) is a four herbal-plant-composed TCM formulation, which has been conferred with good chemotherapy evidence [28]. Its ongoing FDA phase III clinical trial lead the way and will bring hope in the development of CAM for cancer patients. With the various other new clinical trials ongoing, CAM may start playing critical roles in future health care of aging populations [24].

Although considerable effort has been made in phytotherapy, there is a lot still to be done and we hope that several traditional remedies or multiple herb formulations will receive FDA approval as phytomedicines and botanical drugs for chemotherapy/chemoprevention.

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