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Review Article

Gossypol: An Effective Anti Cancer Drug Against Molecular Target of Bcl-2 Protein Family in Human Prostate Cancer

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Abstract

Prostate cancer is a malignant tumor of prostate gland in males - remaining subclinical for many years, but later, can metastasize and spread to surrounding tissues and other crucial body parts. Elevated levels of blood prostate specific antigen (PSA) and routine digital rectal examination (DRE) may lead to early diagnosis of prostate cancer. Organ confined and locally advanced prostate cancer can be treated with surgical removal, cryotherapy, brachytherapy, radiotherapy and hormonal therapy, but with advanced metastatic prostate cancer, only chemotherapy and/with hormonal therapy has been effective. Gossypol, an FDA approved drug is reported as an effective chemotherapeutic agent not only effective against prostate cancer, but also against urinary bladder cancer. It acts as a natural Bcl-2 homology domain 3 (BH3) mimetic agent and down-regulates anti-apoptotic genes expression (Bcl-2/Mcl-1/Bcl-xL). Clinical trials against the efficacy of gossypol as an adjuvant therapy are already under investigation for human hormone-refractory prostate cancer with Bcl-2/Mcl-1/Bcl-xL over expression.

Keywords: (-)-Gossypol; metastasis; prostate cancer; Bcl-2; Bcl-xL; apoptosis; chemotherapy.

Introduction

Cancer is caused by uncontrolled division of abnormal cells that may invade surrounding or other tissues via blood and lymphatic systems. Metastatic cancer development starts from persistent damage to genetic material of normal cell, resulting into somatic mutations. Later, these mutations cause tumor formation. Vascularization and invasive properties of these tumor cells provide them the flexibility to metastasize in other body areas. Hence, a benign tumor is non-cancerous and static while a malignant tumor is cancerous and metastatic.

Prostate gland produces and stores a constituent of semen in male reproductive system. Its malignancy may lead to the development of prostate carcinoma. Tobias and Hochhauser [1] reported prostate carcinoma to be usually asymptomatic and initially diagnosed as an enlarged and hardened gland. There are chances that it may extend towards the lateral pelvic walls that may cause pain in the bones of pelvic region.

Cancer is a major health problem in the United States and developed countries. At present, one out of every four deaths is owed to cancer. As reported previously, in the United States the second largest cause of death in males after skin cancer results from prostate cancer while in UK, it ranks third [2]. Further studies have shown that the ratio of incidence and mortality are significantly higher in black than white men [3]. In spite of the high occurrence, the clinical course is mostly unpredictable.

Etiology and Risk Factors

It has been reported that the change of diet especially animal fat and red meat are primarily associated with the increasing incidence of prostate carcinoma [4]. Obesity is suggested to be a more potential cause than specific food components. A study among different ethnic groups in United States and Canada revealed significant statistical association between prostate cancer risk and total fat (saturated fat) intake in blacks, whites and Asian-Americans. Saturated fat intake was reported to be associated with higher risks in Asian-Americans than blacks and whites, and suggested a causal role of saturated fat intake in prostate cancer [5].

Prostate cancer does not occur in impotent men while androgens stimulate its growth. A recent report has revealed the possible protective action of non-steroidal anti-inflammatory drugs such as aspirin against prostate carcinoma (6).

Screening Methods

Tobias and Hochhauser [1] reported two frequently used methods

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for the diagnosis of prostate cancer, digital rectal prostatic palpation (histological examination of trans-rectal biopsy) and blood prostate specific antigen (PSA) level [1,7,8]. These diagnostic methods are essential to determine the stage of disease, and likewise, to determine the distant metastases for proper treatment suggestions. PSA is an efficient tumor marker for the assessment of extent of the disease. Low PSA level suggests normal condition of prostate gland while elevated level indicate benign or cancer condition, but this criteria is not sufficient. It has been reported that prostate cancer diagnosed in 15.2% of men showed blood PSA level at or below 4.0 ng/mL whereas < 4.0 ng/mL was previously reported as normal level [9].

Insulin like growth factor-1 is also reported as a potential new marker, a hormone involved in stimulation of cell growth [10] and inhibition of apoptosis. Elevated concentration of IGF-1 increases the risk of malignant transformation in prostate epithelial cells.

Genes involved in Prostate Carcinoma

Several types of mutations are involved in the development of prostate carcinoma including deletion, alteration, amplification, chromosomal aberration, etc. These mutations accumulate after some period of time and later, show their drastic effects. Previously reported [4] prostate cancer susceptibility genes include RNASEL, ELAC2, MSR1, AR, CYP17 and SRD5A2 whereas GSTP1, NKX3.1, PTEN, CDKN1B and AR are involved in somatic gene alterations.

Treatment of Prostate Cancer

According to the physicians, prostate cancer patients are characterized on the basis of cancerous cell`s position. It can be organ-confined in the initial stages, then advances locally and finally metastases. Depending upon mass, fierceness, and extent of the tumor, its treatment options are recommended. Previous findings indicated that prostate cancer was mostly dependent on hormonal induction [11]. Androgenic hormones directly stimulate both normal and cancerous cells in term of their growth and development. Therefore, use of hormonal manipulation agents like goserelin (gonadotrophin-releasing hormone analogue) and flutamide (antiandrogen) that interferes with testosterone binding to the androgen receptor are well known for hormonal therapy [12]. (Figure 1).

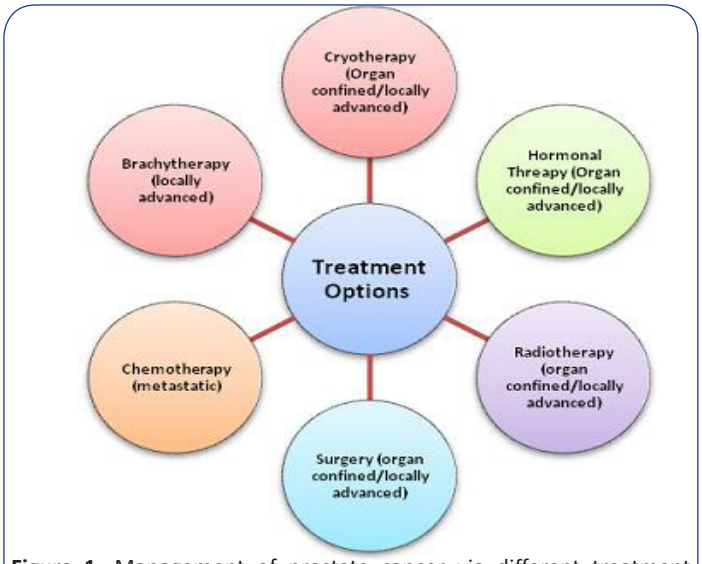

Figure 1. Management of prostate cancer via different treatment procedures. (a) Cryotherapy, using low temperature in order to destroy cells by crystallizing the cytosol. (b) Hormonal therapy, administration of hormonal antagonists which block or inhibit hormonal activity or production of cancer cells. (c) Radiotherapy, application of radiation against cancer cells for treatment. (d) Surgery, physically removing cancerous tissue/mass. (e) Chemotherapy, using chemical drugs against cancer cells for treatment. (f) Brachytherapy, a type of radiotherapy in which a radioactive material is placed in vicinity of treatment area.

Chemotherapy for Advanced Prostate Cancer

Chemotherapeutic agents are effective against advanced metastatic prostate cancer condition. These include methotrexate, 5-fluorouracil,mitoxantrone, the taxanes, docetaxel and cisplatin [1]. It has been reported that docetaxel, the first cytotoxic drug in addition with prednisolone with mitoxantrone, have shown marked additional 12 months of life in 1 of 10 patients [13]. Some of the common chemotheraputic drugs given against metastatic prostate cancer are listed below (Table 1).

Gossypol, a promising chemotherapeutic agent

Gossypol, a naturally occurring small molecule of polyphenolic nature is extracted from cotton plants, that was not considered to be a valuable natural product with useful biological activities until its anticancer and male infertility activities were discovered [14,15]. Randel and colleagues reported thatin males, the effect of gossypol are dose- and time-dependent, while at effective doses, it

Table 1. Chemotheraputic drugs commonly used against metastatic prostate cancer

Estrogens, Hormone Replacement Therapy	Gonadotropin Releasing Hormones, Hormones/Anti-neoplastics	Mitotic Inhibitors, Antimetabolites, Alkylating Agent	Anti-androgens, Hormones/ Anti-neoplastics
Conjugated estrogens	Goserelin	Docetaxel	Micalutamide
Esterified estrogens	Leuprolide	Capecitabine	Flutamide
Estradiol		Cyclophosphamide	Nilutamide
			Mitoxantrone

causes immobility of sperm and reduced sperm counts [16].On the other hand, Amiao and Adekumoconcluded that although rabbit bucks fed with gossypol-containing diet had deleterious effects over testicular histological and spermatogenesis, however,vitamin E supplementation with the same diet ameliorated the adverse effects [17]. Several studies have reported that gossypol possesses anti-neoplastic and pro-apoptotic activities in a wide variety of malignancies including head and neck, prostate, and colon cancers - both in vitro and in vivo [18–21]. Results have shown that (–)-gossypol is a more potent inhibitor than (+)-gossypol and (±)-racemic gossypol [22,23]. Meanwhile, gossypol and its analogs are studied extensively due to broad-spectrum biological activities such as anti-parasitic [24,25], anti-malarial [26–28], anti-HIV [29,30] and anticancer [31–33].

Huang et al. [34] showed that rat prostate tumor (MAT-LyLu) and malignant hematopoietic (MLL)cell lines presented a similar result in reaction to (–)-gossypol treatment. (–)-Gossypol plays an active role in metastasis repression and its mechanism of action in these cell line models may engage down-regulation of Bcl-2 and Bcl-xL protein while up-regulation of nm23-H1 protein. These studies highlight the anti-metastatic ability of (–)-gossypol by equally decreasing the invasion of the parental MAT-LyLu cells in vitro and the isolated MLL cells, respectively. These findings suggest a chemotherapeutic activity of (–)-gossypol and most likely, a potential candidate for further assessments and clinical trials. Huang et al. data reported that MLL cells were more aggressive than MAT-LyLu cells when grown over Matrigel, but (–)-gossypol turned out as a strong metastatic inhibitor in prostate cancer cells. In addition, (–)-gossypol repressed MAT-LyLu and MLL cells migration and movement. The underlying mechanism behind anti-metastatic activity of (–)-gossypol in MAT-LyLu and MLL cells were attributed to down-regulation of Bcl-2 and Bcl-xL genes but unfettered nm23-H1 protein expression.

Molecular Targeting of Advanced Prostate Cancer

Tumor cells have the ability to bypass the apoptosis (programmed cell death) after drug affected damage when chemotherapeutic drugs cannot kill these cells. Apoptosis regulates the homeostasis of affected tissues by eliminating the damaged and dysfunctional cells within the human body and acts as a barrier for cancer, but at the same time, it acts as a rate limiting step towards the efficacy of cancer therapy.

A new method is targeting the pathway of programmed cell death especially the Bcl-2 family of proteins for cancer therapy [35]. The apoptotic and anti-apoptotic property of a cell is governed by the Bcl-2 protein family members, and the pro-survival Bcl-2 subfamily, which protects cells from exposure to certain cytotoxic conditions (Table 2).

The Bax-like pro-apoptotic family and the Bcl-2 homology domain 3 (BH3) only subfamily, which initiate cells to pass through death by disrupting the dimerization of pro-survival proteins with Bax-like pro-apoptotic proteins. There is a balance and competitive dimerization between anti-apoptotic (Bcl-2, Bcl-XL, Bcl-W, Mcl-1, A1) and pro-apoptotic (Bax, Bak, Bad, Bid) Bcl-2 family members that decides cell fate and controls the response to apoptotic signals. Some tumors escape apoptosis and get a survival advantage through abnormal Bcl-2 expression and the oncogenic potential of Bcl-2 (Figure 2). The subsequent release of these pro-apoptotic proteins is related, directly or indirectly, with the activation of caspases and the initiation of apoptosis [35,36].

Gossypol has been identified to regulate Bcl2 family protein activities, and to specifically promote pro-apoptotic activities in cancer cells due to its small molecule inhibitors nature that target these proteins. Gossypol acts as a BH3 mimetic and interacts with the BH3-binding pockets of the pro-survival Bcl2 proteins, thereby, inhibits their anti-apoptotic function as demonstrated by various studies through molecular modeling, NMR methods, and fluorescence-polarization assays [37,38].

Previous findings have shown that (–)-gossypol increased apoptosis, down-regulated Bcl-2 and Bcl-xL, and activated caspase activity (Figure 3) in cancer cells [39,40]. The racemic mixture of gossypol is the only accessible oral Bcl2 subfamily small molecule inhibitor to be analyzed and tested for clinical trials to treat metastatic adrenal

Table 2. Apoptotic and anti-apoptotic protein family members

Pro-survival Bcl2 Subfamily Proteins (Anti-apoptotic)	Bax like Pro-apoptotic Family (Apoptotic) Proteins	BH3-only Subfamily (Apoptotic) Proteins
Bcl-2	Bax	Bik
Bcl-xL	Bak	Bad
Bcl-w	Bok	Bid
Mcl-1		Bim
A1		Bmf
Bcl-B		Hrk
		Noxa
		Puma

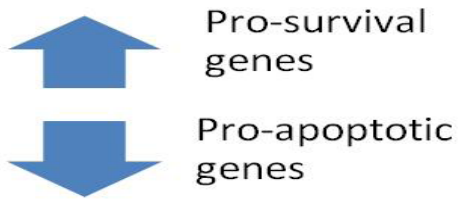

Figure 2. Relationship of pro-apoptotic and pro-survival genes during cancer. Schematic representation of increased expression levels of Bcl-2 and Bcl-xL while decreased expression levels of Bax and Bad in cancer cells.

and breast cancers, and seems to be tolerated with little toxicities in patients [41-43]. (-)-Gossypol is reported to considerably increase the antitumor activity against human hormone-refractory prostate cancer, both in vitro and in vivo, through chemotherapeutic treatment involving Bcl-2/Bcl-xL/Mcl-1 over expression [44].

Studies from phase II clinical trials explored the combination of racemic(-)-gossypol together with androgen ablation therapy as an effective treatment against prostate cancer. Luteinizing hormone-releasing hormone agonists (bicalutamide) and agents, together with R-(-)-gossypol acetic acid as AT-101 drug were given to patients with newly diagnosed metastatic prostate cancer. A total of 55 participantswere recruited with elevated Prostate-specific antigen(PSA) levels (≥ 5ng/ml) prior to registration. Patients received hormone therapy with LHRH agent (leuprolide acetate and/or goserelin) and bicalutamide (50 mg/day po) for 6 weeks, and later, AT-101 in combination with LHRH agonist were administrated at 6 weeks (20 mg/day po) for 3 weeks of every 4 weeks that lasted for 8 cycles.After 8 cycles, patients continued hormonal

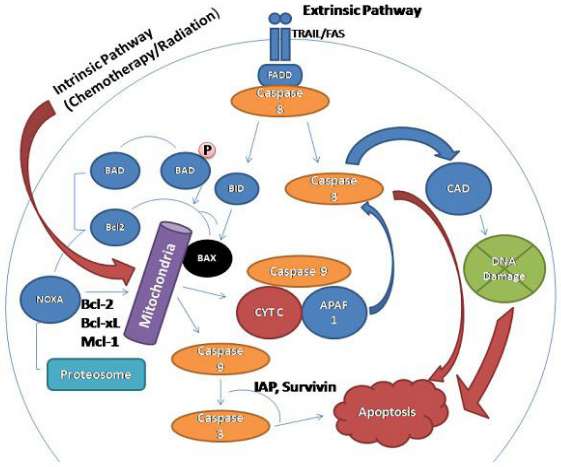

Figure 3. Intrinsic and Extrinsic Pathways of Apoptosis. The Extrinsic Pathway: ligands binding to FAS/TRAIL receptors, induces apoptosis through signal cascade activation resulting from caspase 8 to caspase 3. The Intrinsic Pathway: radiation/chemical drugs causes mitochondrial stress through DNA damage and heat shock leading to binding of BAX to mitochondrial outer membrane that eventually signals the release of cytochrome c.

therapy. Results from phase II clinical trials outcomesreported 60% of patients with overall PSA < 0.4 ng/ml, that suggests a promising role of gossypol as an effective chemotherapeutic drug,although no further statistical analysis were provided with the efficacy study [45].

Conclusion

Gossypol, an FDA approved drug is a very promising therapeutic agent against metastatic prostate carcinoma. Administration of chemotherapeutic drugs against metastatic prostate carcinoma is a well-established and effective therapy than hormonal therapies. Molecular biologists, oncologists, urologists and pharmacologists must now work and co-operate in a synergistic way to develop new techniques and approaches to overcome obstacles in prostate cancer treatment. Clinical trials are already under progress using gossypol as an effective chemotherapeutic drug against human prostate carcinoma and urinary bladder carcinoma. It is believed that gossypol in combination with other chemotherapeutic drug(s) can mediate effective inhibition of cancer cell growth by apoptotic pathway. This molecular targeting approach against cancer cells is anticipated to be very effective and successful in future for the cure of cancer. It is also empirical to design efficient go/no-go decisions to advance promising chemotherapeutic drugs into phase III clinical trials.

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