AN ELECTIVE SPECIALIST (GANODERIC ACID) FOR THE THERAPY OF ADVANCED PROSTATE CANCER

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ABSTRACT

In the Western world, prostate cancer is the most frequently diagnosed cancer in men and is responsible for significant morbidity and mortality. While conventional treatments are effective in eradicating cancer in its early stages, they frequently fail to treat metastatic disease in its later stages. As a result, alleviating the disease and enhancing patient outcomes necessitate the development of an efficient treatment that targets metastasis and growth of prostate tumors.Recent research has focused on natural extracts, particularly those with lower cellular toxicity to healthy tissue.Gano- deric acid, an extract from the Ganoderma lucidum mushroom that has been tested in multiple cancer models, is the subject of our discussion in this review as one potential candidate. Intriguingly, in late-stage metastatic disease, ganoderic acid DM (GA-DM) has been shown to be toxic to both androgen-dependent and independent prostate cancer cells with reduced osteoclastogenesis. The current understanding of this GA-DM extract and its potential use in the treatment of advanced prostate cancer will be discussed in this review.In addition, we will discuss the nanoparticle-based targeted delivery of GA-DM, which has the potential to reduce the toxicity of bystanders and increase the drug's efficacy. Natural chemotherapeutics, particularly those used to treat advanced prostate cancer, will advance as a result of a better understanding of this drug and its applications.

Keyword : - *Androgen, 5-a-reductase, dihydrotestosterone, prostate cancer, osteoclastogenesis, ganoderic acids, and chemotherapy etc….*

1. INTRODUCTION

In the Western world, prostate cancer is the most frequently diagnosed cancer in men and the second most common cause of cancer-related death [1-3].Age, race, and geographical location all have an impact on a person's risk of developing prostate cancer [4].Additionally, certain genetic factors increase a person's risk of developing prostate cancer. Prostate cancer may be caused by mutations in the BRCA-2 gene, which belongs to the family of genes that suppress tumors [5].Additionally, dietary habits may influence the development of prostate cancer.Red meat and calcium-rich diets are thought to increase the risk of prostate cancer, whereas diets that include vitamins E and K may lower that risk [6-8].Additionally, a study [9] indicates that older men who exercise frequently have a significantly lower risk of dying from prostate cancer

A growing interest in finding more effective prostate cancer treatment options has resulted from the disease's prevalence and mortality. Prostatectomy, radiation, and chemotherapy are currently the most common treatment options for prostate cancer patients [10].While these treatments are effective for the majority of localized forms of prostate cancer, many cases progress to castrate-resistant disease, necessitating the use of alternative treatments. The propensity of prostate cancer to spread, particularly to bone, is one of the most significant issues [11].Osteoclastogenesis, a normal cellular process that results in the formation of large, multinucleated cells that resorb bone, is exploited by some forms of prostate cancer [12].This mineralized bone is invaded and colonized by metastatic prostate cancer. Recent research and development have focused on immune therapies like vaccines and dendritic cell therapies to combat these problems [13–16].

The search for an effective long-term treatment for later-stage prostate cancer continues, particularly one with the ability to induce apoptosis in cancer cells, despite the fact that some immunotherapeutics have shown promise in clinical trials.Gano- deric acid, a triterpene extract from the Ganoderma lucidum mushroom, is one potential candidate with such therapeutic properties [17].Although the mushroom itself has long been used in Eastern herbal medicine to increase vitality and life expectancy, recent research [17] has demonstrated that it has anti-metastatic and anti-tumor properties in a variety of cancer cell types.Similarly, ganoderic acid DM (GA-DM), a purified extract of the G. lucidum mushroom, has been shown to be a potential candidate for reducing prostate cancer metastasis [12].The anti-tumor and anti-metastatic properties of various ganoderic acids, with a particular emphasis on the current knowledge of GA-DM in treating metastatic prostate cancer, will be summarized, as will the factors that influence the progression of prostate cancer to its metastatic form.

2. CANCER OF THE PROSTATE AND OSTEO-CLASTOGENESIS

A small percentage of men who develop metastatic disease progress to castrate-resistant prostate cancer (CRPC), despite the fact that the majority of prostate cancer cases can be treated conventionally [18].The majority of deaths related to prostate cancer are attributed to this form, which, as the name suggests, is resistant to both chemical and physical castration treatments [18].Metastasis to bone is another aspect of prostate cancer that accounts for a significant portion of prostate cancer-related mortality [19].There are a number of factors that must happen in order for tumor cells to metastasize. The ability of the tumor cells to adhere to one another and their cell-matrix adhesion characteristics must first be eliminated [20].As motility develops, this process occurs simultaneously with the breakdown of the cadherin-catenin complex's integrity.

A significant proportion of advanced, metastatic prostate cancer cases have abnormally low levels of transmembrane proteins known as cadherins and downregulation of catenins [20].E-cadherin is the most important of these, and its absence facilitates bone metastasis and cell detachment [20].Other cadherins, such as N-cadherin and cadherin-11, have also been found in prostate cancer cells (such as PC-3) and are involved in the growth and spread of cancer cells [21, 22].Cadherin-11 knockdown also significantly reduced prostate tumor growth and bone metastasis, according to a study [21].Because they are able to degrade the extracellular matrix, which makes it possible for cancer cells to invade, matrix metalloproteinases (MMPs) are also important in the development of metastatic prostate cancer [20].MMP-2 and MMP-9 play a significant role; These have been mentioned as important prostate cancer biomarkers [23].MMPs have been found to be more abundant in the sera of cancer patients than in those with benign prostatic hyperplasia (BPH), a benign condition [23].Upregulation of Ras and Rho synthesis also affects cancer cell motility [20].Rho is Ras-dependent and a crucial promoter of cell motility, while Ras is a crucial component in the regulation of cellular proliferation and invasion [20].The immune system frequently clears the cells once they become motile. However, this migratory process enables some cells to attach to distant locations like bone. Although the majority of prostate cancer metastases are located in bone, their activities vary greatly.

Recent research [24, 25] has focused on the factors that contribute to the divergent activity of prostate cancer metastases in bone. The tumor microenvironment is thought to play a significant role in determining whether osteoblastic or osteoclastic activity occurs [24, 25].Prostate tumors that induce osteoblasts cause excessive bone formation in a unique, woven pattern as a result of the disorderly arrangement of bone layering; This procedure frequently raises the likelihood of bone fractures [24].Type I collagen is produced as a result of osteoblastic responses [24].The overexpression of procollagen (I) carboxyterminal peptide, or PICP, is one indicator of osteoblastic activity [24].Endothelin-1, fibroblast-growth factor 8, bone morphogenic proteins, and VEGF are some of the other growth factors that have been linked to the development of osteoblastic responses to prostate cancer metastasis [24].An osteoblastic response has also been demonstrated to be stimulated by prostate-specific antigen (PSA), which is a significant marker in a large proportion of prostate cancers and the basis for one of the more prevalent methods of screening for prostate cancer [24].Osteolytic prostate cancer cells use the natural process of bone resorption to invade mineralized bone and proliferate and expand within bone tissue [12], whereas osteoblastic prostate cancer cells are induced by many forms of the disease.

3. ANDROGENS AND PROSTATE CANCER

Androgens work through the androgen receptor (AR) to maintain normal prostate development and function [28].The development of androgen resistance, which typically takes place between fourteen and thirty months following the initial treatment with androgen ablation [29], is perhaps the most important indicator of the

progression of prostate cancer.Because it converts testosterone into its active form, dihydrotestosterone (DHT), 5-a-reductase plays a significant role in androgen development in prostate cancer cells [30].Five-a-reductase exists in two forms, each of which is regulated by a distinct gene [31].5-a-reductase 1 is found in the skin, liver, and prostatic epithelium, whereas 5-a-reductase 2 is linked to prostate cancer and BPH [31].Prostate cancer cells may become more resistant to apoptosis when DHT binds to the AR and moves into the nucleus [12].The impact of AR activity on PSA expression is an intriguing aspect [2].One of the most common methods of early prostate cancer detection is a PSA screening test, which is an important marker for prostate cancer.AR activity is thought to influence PSA expression [2].Androgen ablation has consistently been a treatment option because androgens play a significant role in the development of prostate cancer.

However, these treatments are ineffective because many forms of prostate cancer progress to an androgen-independent form [32].Cadherin-11 expression is upregulated during androgen ablation therapy, which suggests that androgen deprivation therapy promotes a switch to androgen independence [33].Another interesting finding from the same study was that when AR was re-expressed, downregulation of cadherin-11 expression occurred in PC-3 cells, which naturally do not express AR [33].Finasteride, a potent steroidal inhibitor, has been used to block 5-a-reductase activity [12, 30]. However, finasteride has been linked to side effects like gynecomastia and myopathy as well as sexual side effects [12, 30].Finasteride's significance and frequency of side effects have been questioned in more recent research [30, 34]. As a result, therapeutics that target 5-a-reductase activity while being minimally toxic to normal cells are currently in development.In the absence of DHT, metastatic prostate cancer upregulates testosterone expression to mirror the effects of DHT on the AR, which is another issue associated with the use of 5-a-reductase inhibitors [35].

Prostate cancer cells upregulate AR expression as well as the expression of enzymes involved in the conversion of androgen precursors into testosterone in an anorchid environment [35].As DHT levels decrease, testosterone concentrations in metastatic prostate cancer are noticeably higher than in early stage prostate cancer [35].Additionally, even when isolated from the same patient, different types of prostate cancer cells can respond differently to an orchid environment, indicating the need for alternatives to androgen deprivation therapy [36].As a result, novel chemotherapy, immunotherapy, or a combination of chemotherapy and immunotherapy have gained popularity as research topics.

4. THERAPEUTICS FOR PROSTATE CANCER

Patients with prostate cancer have a variety of treatment options, but a study recommends four types of initial treatments:a) Patient vigilance, b) Surgery, c) Radiation therapy, and d) Hormone therapy [37]Chemotherapy and palliative care are the most common treatments for prostate cancer as it progresses [38].If newer options become available, patients can also participate in a clinical trial. Patients with prostate cancer may also enroll in clinical trials prior to, during, or after beginning treatment. However, follow-up tests and improved collaboration with trial investigators are required in clinical trials.

Active surveillance is frequently used with prostate cancer patients [10, 39] due to the often indolent nature of the disease and the fact that certain types of prostate cancer may be exacerbated by overtreatment. The absence of serious side effects associated with treatments like chemotherapy, radiation, or prostatectomy is the one obvious advantage of active surveillance over more aggressive treatment options [10, 37].However, increased psychological distress has been observed in patients under active surveillance [10].Although radical prostatectomy is successful in many cases of prostate cancer, the significant side effects on sexual and urinary function have a negative impact on these patients' quality of life [10, 40].The two most common treatments for prostate cancer, radiotherapy and brachytherapy, both have serious side effects like irritative voiding and incontinence that can last for years [10, 41].Alternative treatments like chemotherapy, immunotherapy, and a combination of chemo-immunotherapy have been looked at because of the problems with traditional treatments.

Docetaxel has emerged as the primary chemotherapeutic agent for CRPC treatment in recent years [38].Docetaxel was approved by the FDA as a first-line therapy along with prednisone after clinical trials showed a slight increase in survival benefit over existing chemotherapeutics [38].Docetaxel, on the other hand, remains the only widely used chemotherapeutic for metastatic prostate cancer, and the failure of docetaxel treatment in patients with late-stage disease leaves few other viable treatment options [15].As a result, a recent study has looked at combined docetaxel and other treatments [15].PROVENGE® (sipuleucel-T) is one of the most notable treatments to

win clinical trials.PA2024, a fusion protein of GM-CSF and prostatic acid phosphatase (PAP), is co-cultured with dendritic cells in PROVENGE® [29].In a phase III clinical trial, this treatment outperformed the placebo by 4.5 months [16].PROVENGE® was approved by the FDA following a successful second phase III trial [42].It is possible that this new medication could be used in conjunction with chemotherapy; however, additional research is needed to determine how docetaxel and PROVENGE® interact together [43].Even though all of these treatments have potential benefits, using a natural substance with anti-tumor properties would reduce the risks and side effects of treatment even more.A number of recent studies that looked at the potential antitumor effects of a methanol extract from the Ganoderma lucidum mushroom show a lot of promise and could point the way in a new direction for prostate cancer treatment.

5. GANODERIC ACIDS AS ANTI-CREATIVE THERAPIES

In Chinese culture, the Ganoderma lucidum mushroom, also known as Lingzhi, has been used as a form of herbal medicine for thousands of years [17].The ganoderic acid extracted from the Lingzhi mushroom may have tangible and wide-ranging medicinal benefits, most notably its toxicity to tumor cells with comparatively low toxicity to bystander cells, despite the fact that this mushroom was initially thought to maintain vitality and increase life expectancy.Submerged-cultured ganoderic acid extracts caused significant dose-dependent cytotoxicity in the human BEL7402 hepatoma cell line, but they did not cause significant cytotoxicity in the L02 normal human cell line [44].In addition, the study demonstrated that ganoderic acid halted the BEL7420 cell cycle at the G1-S phase, preventing the cells from progressing toward mitosis [44].

Another study demonstrated that Lewis lung carcinoma (LLC) development in a C57BL/6 mouse model was affected by ganoderic acid Me (GA-Me), which was purified from the methanol extract of G. lucidum mycelia [45].The presence of nodes in lung tissue harvested after ten days demonstrated a significant reduction in tumor growth and lung metastasis in the drug-treated mice following subcutaneous injection [45].In addition, this study demonstrated that treatment with GA-Me increased NK cell activity [45].In addition, the drug increased NF-κB protein expression and serum concentrations of the cytokines IL-2 and IFN-y [45].This led to the Th1 response characterized by the upregulation of IL-2 and IFN-y observed in the LLC model treated with GA-Me [45], which was suggested to be triggered by NF-κB upregulation.

A subsequent study expanded on the human lung cancer cell line 95-D and demonstrated an increase in Th1-mediated cytokine production to support the previous study's findings [46].The downregulation of MMP-2 and MMP-9 expression in GA-Me-treated cells also suggests its role in reducing tumor invasion and metastasis [46].Additionally, this study demonstrated that GA-Me can decrease tumor cell migration and extracellular matrix adhesion while simultaneously increasing tumor cell aggregation [46].However, 95-D cells were not significantly cytotoxic to GA-Me [46].The apoptosis induction rate was only 2.3% even at concentrations of 20 M [46].

Ganoderic acid T (GA-T), which was found to have superior cytotoxic effects on 95-D and other types of tumor cells, was the subject of another study.GA-T was significantly less toxic to normal cell types than 95-D cells, but the half maximal cytotoxicity concentration (IC50) was 27.9 g/ml [47].Similar to the study on hepatoma cells [47], the GA-T treatment prevented cell cycle progression at the G1-S checkpoint, according to the study.In addition, GA-T treatment decreased mitochondrial membrane potential, increased p53 and Bax expression, and increased cytochrome c release [47].Gano- deric acid X (GA-X) was also tested in HuH-7 hepatoma cells. There, it was found to inhibit topoisomerase production and cause apoptosis, which in turn prevented DNA synthesis in GA-X-treated cells [48].In addition, the study demonstrated that GA-X treatment decreased the anti-apoptotic protein Bcl-2 while increasing cytochrome c, ERK, and JNK kinase levels [48].

In MDA-MB-231 breast cancer cells, three additional subtypes of ganoderic acid—ganoderic acids A, F, and H (GA-A), GA-F, and GA-H—were tested, and a significant decrease in tumor growth was observed [49].In terms of how it develops, breast cancer and prostate cancer are similar.Similar to prostate cancer, breast cancer progresses from a local, treatment-responsive form to a metastatic, highly invasive form that is resistant to conventional treatments [49].AP-1 and NF-B are two factors that are frequently found to be upregulated in breast cancer [49].Osteolytic prostate tumors exploit NF-B's significant role in osteoclast development.In breast cancer, AP-1 and NF-B also upregulate urokinase-type plasminogen activator (uPA), which promotes the conversion of plasminogen to active plasminogen and promotes cell adhesion and migration [49].In the highly invasive MDA-MB-231 breast cancer cell line, GA-A and GA-H showed dose-dependent cytotoxicity, inhibiting colony formation and reducing invasiveness [49].The known activities of various glycolic acid subtypes, including both anti-proliferative

and anti-metastatic effects, are outlined in Table 1.C3-carbonyl groups are found in GA-A, GA-F, and GA-DM, C3-hydroxyl groups are found in GA-H and GA-X, and C3-acetyl groups are found in GA-T and GA-Me [49].In the molecule bay region, GA-A has two hydroxyl groups, while GA-T only has one acetyl group [47].The structure of GA-DM is the most hydrophobic and it lacks acetyl or hydroxyl side chain groups that could interfere.Ganoderic acids have been shown to have a positive effect on breast and lung cancer cell lines, but little is known about their potential use as a treatment for prostate cancer. However, one subtype of ganoderic acid DM has demonstrated promise in the treatment of advanced prostate cancer.

6. CONCLUSION

In the Western world, prostate cancer is a leading cause of death for men.Patients in the early stages of the disease benefit from current treatments and therapies, but metastatic patients do not.Utilizing the normal cellular processes of bone formation and resorption to invade and colonize bone cells, prostate cancer preferentially spreads to bone.The treatment of androgens is another focus of professional cancer therapy.The AR and 5-a-reductase both play important roles in the development of prostate cancer.5-a-reductase converts testosterone into DHT, binds to the AR, and aids in cell proliferation and survival. Research into immunotherapy, chemotherapy, and even herbal therapies is of great importance and interest because of these factors.

Although numerous immunotherapeutic and chemotherapeutic agents have been tested in clinical trials, it is still difficult to find a drug that is only moderately toxic to bystander cells while being highly toxic to tumor cells.Extracts of G. lucidum mushrooms are cytotoxic to tumor cells, and some GA subtypes are anti-metastatic.The effects of GA subtypes on prostate cancer are less clear, despite extensive research using them in breast and lung cancer.Because GA-DM treatment has demonstrated cytotoxicity in prostate cancer cells regardless of their dependence on androgens, studies involving GA-DM are particularly interesting. It has been demonstrated that GA-DM inhibits DHT's competitive binding to the androgen receptor and limits testosterone's conversion to DHT.

The inhibition of osteoclastogenesis, a process utilized by some prostate cancer cells to promote bone metastasis, has also been linked to GA-DM. The introduction of GA-DM-infused nanoparticles with targeted delivery to malignant cells could be an alternative strategy for combating advanced prostate cancer, even though GA-DM remains promising. This review suggests that treating advanced metastatic prostate cancer with GA-DM may be beneficial.

7. REFERENCES

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