

Review article:**Genetic Predisposition and Chemotherapeutic Approaches Including Oncolytic Virus for the Treatment of Prostatic Adenocarcinoma**

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Abstract:

Among the leading causes of cancer mortality, prostatic adenocarcinoma (PaC) is at second to lung carcinoma, but it is the most commonly happening non-cutaneous malignancy in elderly men in the world. Therapeutic options for PaC depend on age, growth & stage of malignancy, the desired outcomes and shortcomings of available treatment, estimated cost and patient compliance. Patients older than 60 years with a sluggish localized tumor may be placed on active surveillance, otherwise go with transurethral resection of the prostate (TURP), prostate artery embolization (PAE) and pelvic lymphadenectomy with/without radiation therapy. For metastatic PC androgen-deprivation therapy is an option with or without surgery. These agents decline the body's testosterone production or block its activity by gonadotropin-releasing hormone (GnRH) analogues including leuprolide acetate and goserelin acetate implant. The hormone's activity can be stopped by androgens antagonist such as flutamide, bicalutamide and nilutamide along with chemotherapeutic agents, such as taxanes (e.g., docetaxel, paclitaxel) but after all the disease relapses in 20-30% of patients. So, new immunological or vaccine-based therapeutic moieties have been investigated to meet the objective of providing selectivity to cancerous cells and desired therapeutic outcomes with less/no harmful effects to normal cells. The chimeric version, oncolytic poliovirus and human rhinovirus i.e. PVSRIPO is most promising feature in cancer therapeutics and activate innate immunity by neutrophils infiltration via PAMP & DAMP pathways while Sipuleucel-T expresses major histocompatibility complex (MHC) which can stimulate CD4+ helper T-cells and CD8+ cytotoxic T-cells and ultimately activate the acquired immunity against cancer cells. In this article, we have discussed the role of genetic predisposition and chemotherapeutic approaches including

oncolytic poliovirus for the treatment of PaC in order to better understanding of tumor biology and mechanisms involved in chemotherapeutic drugs based resistance.

Keywords: Docetaxel; Paclitaxel; Oncolytic Poliovirus; PVSRIPO; Sipuleucel

Introduction:

A most common cancer in elderly men is prostatic adenocarcinoma (PaC) confined to prostate gland which produce the seminal fluid, provide nutrients and helps to transport sperm. Initially, the undifferentiated growth is restrained to the prostate gland and less harmful but advanced stage is more aggressive and metastasized as shown in figure 1 and 2 (1-3). One million new cases of PaC emerge in the whole world every year and one third of them result in death. So, it's the most common and prevalent cancer in elderly men, after lung cancer and fourth leading cancer in both sexes (4). Almost 6 cases in 10 are diagnosed at the age of 65 years or later. The PaC incidence in Pakistan is 5.3 per 100,000 that is contrary to what is seen in the western world and low as compared to other Asian countries but number of cases being reported are increasing per annum. France had the highest rate in 2018 and age-standardized rate per 100,000 was 189.1 followed by Norway, Sweden, Australia and UK with 106, 103, 85 and 80 respectively (5, 6).

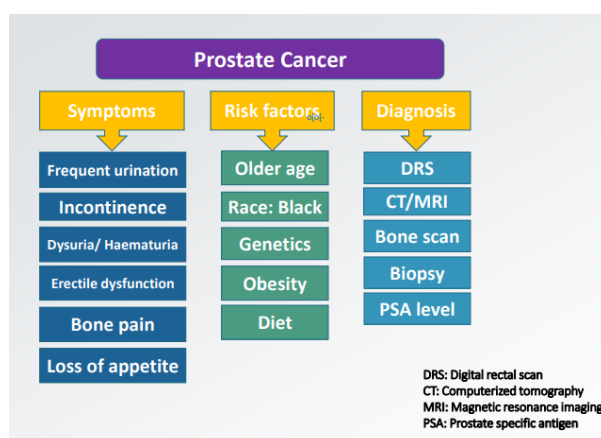


Figure 01: PaC is associated with the above mentioned symptoms, etiological risk factors which have ability to worsen the disease and all the diagnostic test used to screen the disease and classify it in 4 stages according to Gleason Pattern scale (3, 4).

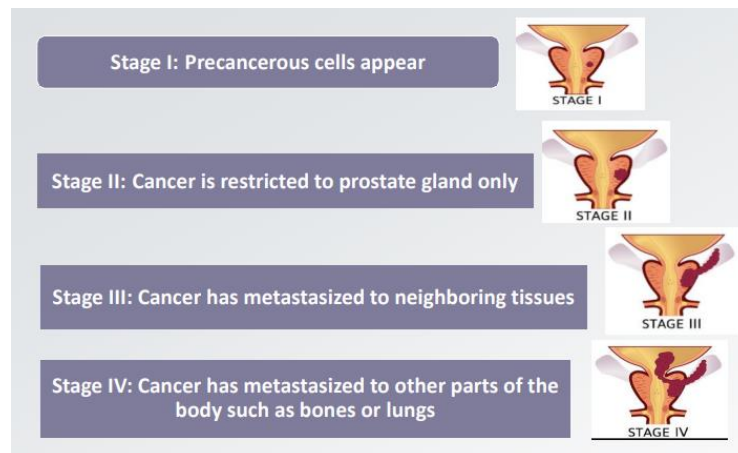


Figure 02: According to Gleason Pattern scale, lower grade (stage 1, score 1, 2) shows cancer is in initial phase, slow growing and not aggressive. From stage 2-5 and score 3-7 shows cancer is growing rapidly towards bones, lymph nodes and blood vessels (7).

If the disease is considerably alleviated or not responsive to ADT referred as Castration Sensitive Prostate Cancer and it's usually account for 3% of all PaC in men at present (8). Although in most of the patients' disease have shown significant responses to this therapy but at later stages disease ultimately progresses known as Metastatic Castration Resistant Prostate Cancer (mCRPC). A highly metastatic with aggressive stage which is associated with consecutive rise in serum prostate specific antigen (PSA) levels or/and advancement of metastatic extent in the setting of castrate heights of testosterone and all treatment modalities are shown in figure 03 (9).

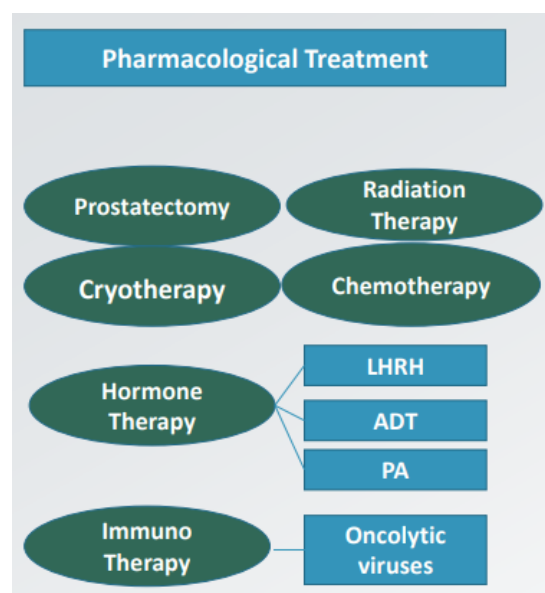


Figure 03: First step to treat disease is active surveillance. Current treatment options involves surgical resection at tumor site (prostatectomy), radiation therapy, cryotherapy therapy and/or use of systemic therapy including chemotherapy, hormonal therapy (luteinizing hormone releasing hormone antagonist: LHRH, androgen depletion therapy: ADT, pregnenolone antagonist: PA) immunotherapy (adoptive transfer of ex vivo activated T cells, natural killer cells, oncolytic viruses, cancer vaccines and administration of antibodies or recombinant proteins (3).

Genetic players in pathogenesis of PaC:

In approximately 5-10% cases PaC is inherited, which reflects a high percentage. The PaC is more aggressive in men with certain types of genetic mutations as compared to those without these mutations. Factors suggesting involvement of a genetic factor in PaC include: 1-Family history of multiple affected first degree relatives having PaC, especially if it runs in maternal or paternal family for three successive generations. 2-Early age onset of PaC ($\leq 55y$) as shown in figure 01. 3- People with family history of other cancers like breast and ovarian cancer have increased risk of developing PaC. As some genes involved in PaC are also associated with onset of ovarian and breast cancer. So there is 50% chance of passing on these genes to the off springs (10). Genetic defects associated with onset of PaC take into effect because of lower expression of tumor suppressor genes, over expression of oncogenes and oncofetal genes and due to mutations in many other cell cycle regulatory genes/ transcription factors and promoter sites.

PaC initiation and progression:

The initiation of PaC till aggressive stage development involves a series of genetic mutations in a distinct order. NKX3.1 haplo in sufficiency is the starting event in tumorigenesis of prostate, as has been proved by multiple Nkx3.1 knockout GEMMs. This mutation at chromosome 8p21 lead to consequences such as loss of basal cells, loss of markers of secretory differentiation and increase in potential to proliferate leading to prostatic intraepithelial neoplasia (early invasive cancer). Following this, deletion mutation in PTEN gene at chromosome 19q23 and homozygous deletion mutation in Rb gene at chromosome 13q14.2 results in loss of basal lamina (invasive cancer). A SNP at chromosome 17p13.1 in p53 leads to onset of mCRPC (11).

Furthermore, in the case of mCRPC, recurrent aberrations involving the AR, ERG, Tp53, RB1, SPOP, CHD1, ZBTB16/PLZF and sections of chromosome 8q gain (including the MYC locus) and 8p loss are also observed. The researcher with coworkers also stated frequent mutations in FOXA2, which translates a transcription factor expressed in tumors exhibiting neuroendocrine features i.e. metastases from 05 men exhibited hyper mutated genomes with complex structural aberrations in MSH2 and MSH6 mismatch repair genes. All metastases and the primary tumors from these men were hyper mutated, demonstrating that mismatch repair deficiency observed early in the beginning of these carcinomas as shown in figure 04 (12).

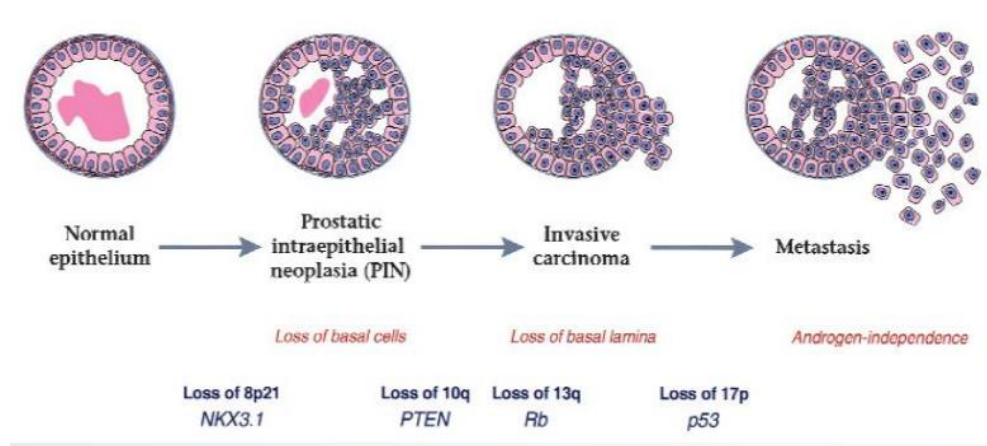


Figure 4: PaC progression pathway and each stage of progression is associated with loss of specific tumor suppressor gene and a distinct chromosomal region.

The tables 01-03 below have shown the major genetic multiplayers that contribute to normal development, initiation of PaC and progression to metastatic stage.

Table 01 Genes associated with normal prostate development.

Genes/ Location	Protein/ Product	General Function	Phenotype in mouse or human prostate	Reference
NKx3.1 Chr:8p	Homeobox transcription factor	Tumor Suppressor gene	Expresses in prostatic areas of urogenital sinus epithelium, in newly formed Prostatic buds. It is required for production of secretory proteins and normal ductal morphogenesis	13
Androgen receptor Chr: Xq11–12	Nuclear Hormone receptor	Nuclear transcription factor. Regulation of gene expression	Essential initially for formation of prostatic buds in mesenchyme and later in epithelium for production of secretory protein.	14
Shh Chr: 7q36.3	Signaling factor (Secreted)	Important role in cell growth, specialization, and in normal shaping of the body.	Expressed in urogenital sinus epithelium	15
HOX-D13 Chr: 2q31.1	Homeobox transcription factor	Role in Morphogenesis	Expressed in the developing and adult prostate cells	16
HOX-B13	Homeobox	Crucial for vertebrate embryonic development	Expressed in nuclei of ventral <i>prostate</i> luminal cells where it directs differentiation of	17

Chr: 17q21-22	transcription factor		<i>prostate</i> epithelium into a ventral <i>prostate</i> specific tissue.	
TGFβ1 Chr: 19q13.2	Secreted Protein	Regulation of cellular functions, like cell growth, proliferation, cell differentiation, and apoptosis	Associated with regulation of androgen signaling in prostate. Mutation in mice led to defects in prostatic duct formation	18
FGF10 Chr: 5p.12	Growth Factor Protein	Pivotal role in embryonic development, morphogenesis, tissue repair, cell growth, tumorigenesis and metastasis	Androgen regulated expression in prostate. It stimulates growth of prostate epithelium	19
FGF7 Chr: 15q21.2	Growth Factor protein	Role in cell growth, embryonic development, tissue repair, tumor growth and invasion.	Stimulates growth of prostate in culture	14
BMP-4 Chr:14q22-23	Secreted member of TGFβ superfamily	BMP4 stimulates differentiation of ectodermal tissue. Involved in Bone formation and neurogenesis in adults.	Defective prostate morphogenesis in heterozygous mice	20

Table 02: Genes associated with onset and progression of tumorigenesis

Genes/ Oncogenic Mutation	Protein/Product	Function	Phenotype in mouse or human PaC	References
PTEN Deletion at Chr:19q23	Tumor suppressor gene.	Protein phosphatase activity. Crucial role as tumor suppressor via cell cycle regulation by inhibiting cells from dividing or growing too rapidly	Heterozygous mice mutant develops hyperplasia and dysplasia of multiple tissues including prostate.	21
NKX3.1 Deletion at Chr:8p21	Homeodomain Transcription Factor	Tumor suppressor gene	In homozygous and heterozygous mice mutant mice, prostatic epithelial hyperplasia and dysplasia followed by PIN is seen.	13
MXI1 Mutation at Chr: 10q24	Transcription Factor	MAX Interactor 1, The protein product of MXI1 is a repressor of transcription. It acts as	Homozygous mutant mice showed relatively mild prostatic epithelial	22

		tumor suppressor gene by negatively regulating function of MYC.	hyperplasia and dysplasia.	
P16 Mutation at Chr: 9p21.3 Hypermethylation at 5' upstream promoter region	Cell cycle regulator	P16 slows cell division by reducing the progression from G1 phase to the S phase of cell cycle, therefore acts as tumor suppressor.	P16 protein expression is up-regulated in PaC	23
P27 Loss of function mutation at Chr:12p13.1	Cell cycle regulator	P27 negatively regulate cell cycle progression at the G1/S boundary, thus acts as anti-proliferative stimuli	Hyperplasia and dysplasia of multiple tissues including prostate was seen in homozygous mutant mice. In humans, loss of expression correlates with tumor grade	24
Rb Homozygous deletion mutation at Chr:13q14.2	Regulation of Cell cycle	Rb is multifunctional protein and can bind to at least 100 other proteins. Rb hinders the ability of cells to replicate DNA, it does so by hampering the progression of cell cycle from G1 (first gap phase) to S (synthesis phase) phase during cell division.	Homozygous mutant mice proved to be prone to dysplasia, Hyperplasia and carcinoma in hormone induction model and combined prostatic rescue. Human gene maps to 13q and functional studies suggest an acute role. but it is infrequently mutated	25
Myc Chromosomal amplification Mutation at Chr: 8q24.21	Transcription Factor	Overexpressed in majority of cancers. Works in synergy with RAS to induce hyperplasia in tissue recombinants	Myc is a proto-oncogene which encodes a nuclear phosphoprotein which has a crucial role in cell cycle progression, cellular transformation and apoptosis	26
FGFs Mutations in FGFR1 gene	Growth Factors	FGF receptors (FGFRs) regulates many biological functions like cell survival, migration, proliferation	Alteration in FGF function is seen to be associated with progression of TRAMP in mice.	27

<p>Chr: 8p11.23</p> <p>FGFR2 gene Chr:10q26.13</p> <p>FGFR3 gene Chr: 4p16.3</p>		<p>and differentiation. Among the signal pathways, FGFs predominantly interact with RAS/MAP kinase</p>	<p>Several FGFs member, including FGF10 and FGF7 have appeared to be implicated as regulators of prostatic growth</p>	
<p>Telomerase</p> <p>Mutation in TERT promoter at Chr:5p15.33</p>	Ribonucleoprotein	<p>Increased telomerase activity and reduced telomere length has been seen in carcinoma PIN</p>	<p>Telomerase enzymes reverses telomere shortening by extending the ends of telomere, an RNA dependent DNA polymerase</p>	28
<p>c-CAM</p> <p>Loss of function mutation at Chr: 19q13.2</p>	Cell adhesion	<p>c-CAM Expression is lost in carcinoma and reduced in PIN. In most cancers the protein product suppresses tumorigenesis</p>	<p>The encoded protein mediates cell adhesion, cellular differentiation, three dimensional arrangement of tissue structure, apoptosis, metastasis, angiogenesis, , tumor suppression, innate and adaptive immune responses modulation</p>	29
<p>C-Met</p> <p>Gene amplification mutation at Chr: 7q31.2</p>	Receptor tyrosine kinase	<p>C-Met overexpression is seen in carcinoma, metastasis and prostatic intraepithelial neoplasia (PIN)</p>	<p>MET is a tyrosine kinase receptor vital for organogenesis, embryonic development and wound healing.</p>	30
<p>Integrins</p> <p>Loss of function mutation at Chr 2,Chr10, Chr12, Chr15</p>	Cell interaction	<p>Reduced expression of certain integrin proteins is associated with cancer progression</p>	<p>Integrins facilitate adhesion of cell-extracellular matrix (ECM). Integrins, upon ligand binding they activate signal transduction pathways to mediate cellular signals like organization of the intracellular cytoskeleton regulation of the cell cycle and transport of new receptors to the cellular membrane.</p>	31

E- cadherin Deletion mutation at Chr:16q22.1	Cell adhesion	Reduced expression is associated with carcinoma and PIN, loss of expression may be associated with poor prognosis.	Cadherin plays role both as ligand and receptor. During development they assist in positioning of cells. Involved in separation of tissue layers and have important role in cell migration.	32
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Table 03: Genes involved in metastasis and advanced PaC

Genes/Oncogenic Mutation	Protein/Product	Normal Function	Phenotype in mouse or human Prostate cancer	References
Androgen receptor T878A, F876L, L702H point mutations at Chr:Xq11-12	Nuclear Hormone Receptor	Androgen receptor acts as DNA binding transcription factor, controls growth and development of prostate by regulating expression of associated genes. Mainly it is involved in development of male sexual traits.	Nominal expression even in androgen-independent cancers, it is often seen to be mutated or highly amplified in prostatic tumors.	33
Bcl2 A frequent mutation is a <i>BCL2</i> -SNP at Chr: 18q21.33 <i>BCL2</i> -938C>A	Apoptotic regulator	First apoptosis regulator found in any organism. Mediates apoptosis by either inhibiting anti-apoptotic or inducing pro-apoptotic pathways.	Main target for clinical intervention. In androgen dependent cancers, Bcl2 over expression renders resistance to apoptosis.	34
P53 Point mutation /SNP at Chr:17p13.1	Regulator of Transcription/Apoptosis	Also called tumor suppressor P53. It has major role in apoptosis and cell cycle regulation. Mutation detected in 50% of cancer patients, also called 'Guardian of genome'	In primary cancers, mutation rate is very low. In metastatic prostatic cancer P53 is frequently mutated. p53 overexpression associated with poor prognosis.	35
Ka1 (GRIK4) Translocation at Chr:11q	Putative integral membrane protein	KA1 is a kainate receptor subtype that belong to glutamate gated ion channels. Exact role in	Protein product suppress metastases. Ka1 expression is down-regulated,	36

		tumorigenesis is still unclear	though not mutated in cancer	
TGF- β 1 Mutation at Chr:19q13.2	Growth Factor	Polypeptide member of TGF β superfamily of cytokine. Have role in various cellular functions like the control of cell growth, proliferation, cell differentiation, and apoptosis.	Negatively regulates prostatic growth. In metastatic prostate cancer it shifts to autocrine regulation.	37
IGF-1 Mutation at Chr:12q23.2	Growth Factor	In addition of Insulin like effects IGF-1 has major role in systemic body growth and in regulation of cellular DNA synthesis.	Elevated levels are linked with cancer risk; it normally promotes prostate epithelium growth. Overexpression of IGF1 in TRAMP mice is linked with tumor progression	38
EGF-TGF α Mutation at Chr: 2p13.3	Growth Factor	EGF-TGF α is mitogenic polypeptide. it is activated upon binding with receptors having protein kinase activity for cell signaling TGF- α is transforming growth factor, it behaves as a ligand for epidermal growth factor receptor. It triggers signaling pathways for cell development, proliferation and differentiation	The alteration frequencies of several genes and pathways are higher in metastatic samples.	39

Hormonal implication and molecular events associated with PaC:

The androgen biosynthesis is mainly regulated by GnRH that is released by the pituitary gland and leads to the synthesis of testosterone and DHT which are androgen receptor (AR) agonists. In the case of CRPC the overstimulation of AR and a subsequent increase in PSA is observed as shown in figure 05 (40). Various therapies tend to decrease androgen production via the canonical pathway 5. However, various alternative routes tend to ensure that the concentration of endogenous

AR agonist such as DHT doesn't decrease thereby decreasing the efficacy of ADT. Moreover, undesired mutations can seriously augment the rate of biosynthesis and subsequently the tumor genesis of CRPC reported by Dai with coworkers in 2017 stated that by giving it a unique position within the steroidogenic pathway, and probably 3 β -HSD1 was a critical enzymatic gatekeeper that deliberates on tumors the ability to connect adrenal androgens (40). In fact, a gain-of-function missense in 3 β HSD1 has recently been described, which remarkably augments the capacity of this enzyme to drive conversion of DHEA to AD, thereby permitting more efficient DHT synthesis. This missense arises from a SNP at position 1245 (A to C), replacing an asparagine for threonine at amino acid position 367. The functional significance of this alteration, which can occur as either a somatic mutation or germline alternative, is an enzyme protein product that is concentrated resistant to ubiquitin mediated degradation, subsequent in intracellular accumulation.

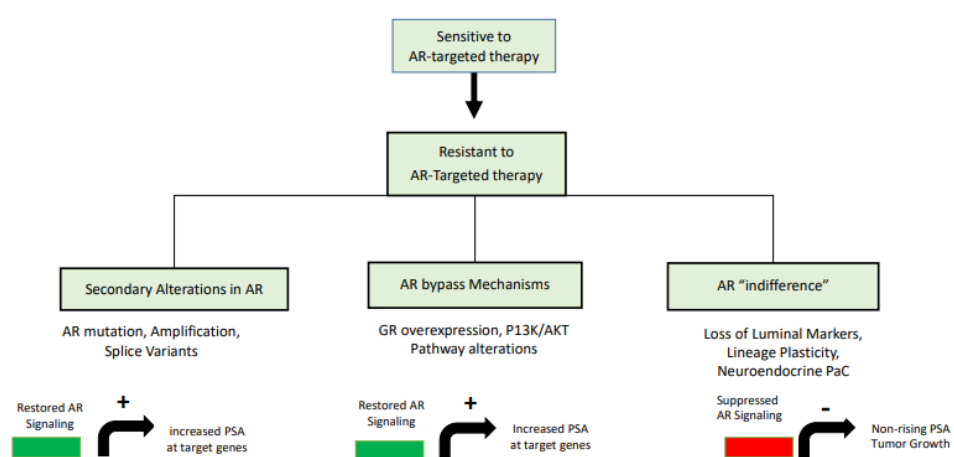


Figure 05: A number of mechanisms can elucidate the repair of competent AR signaling in CRPC. These include amplification and overexpression of AR, acquirement of constitutively active AR splice alternatives, deregulated AR coactivators/corepressors that sensitize AR in reaction to ligand binding, intracrine androgen synthesis, gain-of-function mutations and ligand-independent signaling and redundant downstream crosstalk.

Alongside aberrations in the enzymes of the biosynthesis pathways of androgens various other deleterious modifications have been observed within the Androgen/AR axis such as androgen receptor mutations/amplification loss of AR corepressor NCOR1/2 and gain of AR coactivator NCOA1/2 which leads to castration resistance. Also, conformational changes within the AR have also been noted due to genome structural changes within one third of the male population that suffers from CRPC. The abnormal expression of wide variety of AR variant species deficient in ligand-binding domain lead to persistent activation of AR signaling, such as AR variant 7 is suspected to steer disease progression (41).

Metastasis is also one of the leading pathologies associated with CRPC where the bones and lymph nodes are to be the most acutely targeted tissues. The damage to these organs and tissues leads to

prevailing co-morbidities such as leukemia as blood cells fail to undergo proper specialization with decreased immunity. Recently, it has been discovered that TNF- α has been implicated in the progression of metastasis in all those individuals that suffer from CRPC and initiates the CCR7 upregulation that leads to cell migration of tumors and cause lymphatic metastasis (42). First, human PaC was observed to express both CCR7 and TNF- α . Second, through phosphorylation of ERK, low concentrations of TNF- α was seen to induce CCR7 in PaC cells. Finally, the migration of cancerous cells through phosphorylation of the protein kinase p38 was seen to be promoted by CCL21. So, the results of Maolake and colleagues in 2018 suggested that TNF- α drive the induction of CCR7 expression and CCR7/CCL21/axis might escalate the potential of PaC to metastasize in lymph nodes (42).

Despite the fact that the mechanisms of PaC and its subsequent metastatic predispositions are not known a strong effort is underway in developing effective treatments against the disease. Both conventional and novel therapeutic strategies are being employed to cure the disease. The conventional options improve the prognosis of PaC but along with desired therapeutic effect, the side-effects are often severe to tolerate for a patient. Also, some cancers are resistant to chemo and radiotherapy or are inoperable, underlining the requirement to devise new therapeutic procedures. Oncolytic virotherapy is proving to be a promising treatment for treating cancers with least side effects in recent era (7). The idea of activating patient's immune system against cancer-cells dates back. Immuno-oncology is an uprising field of cancer treatment with the ability to manage numerous malignancies with major goal of suppression of anti-cancer immune responses of body (43). Furthermore, novel therapeutics are also under developed where gene-based modalities gaining traction in recent years.

CHEMOTHERAPY FOR PROSTATE CANCER:

Under the scope of conventional therapy comes chemotherapeutic agents which are mainly small molecule drugs. Small Molecule Drugs are chemically synthesized and have molecular weight of <900da, cheap, readily available and administered orally. Furthermore, these agents are used in placebo and in combination in order gain maximum efficacy. The impact of chemotherapy on survival of PaC patients was first determined in CRPC in 2004 and since then further studies have demarcated the role of chemotherapy in increasingly earlier scenarios in disease presentation (44).

Cyclophosphamide: It is an alkylating agent that was used as part of clinical trial study against PaC. Researchers created three branches of the study Castration Resistant (CR), Progression Resistant (PR) and Stable disease. Little to no effect was seen in the first two branches with most of the patients in the study falling under the stable category. No effect was seen using the agent but interest was relighted when the drug showed potential for angiogenesis inhibition (45).

Cisplatin is a platinum-containing compound that inhibits DNA synthesis by cross-linking and denaturing DNA strands. In 209 cases reviewed, cisplatin showed a modest antitumor activity

with a PR in 12% (95% confidential interval [CI]: 4–20% and thus was continued to be investigated as a single agent and in combination.

Carboplatin is a cisplatin derivative that results in intra- and inter-strand cross-linkage DNA damage, had been studied in earlier trials as a single agent with minimal responses. However, when combined with other chemotherapy drugs such as Paclitaxel and Estramustine, declines in serum PSA levels have been observed.

Satraplatin, the first oral 4th generation platinum analog found to be effective against cisplatin- and carboplatin-resistant cell lines held a lot of promise in castration-resistant PaC and while it showed improvement in time to pain progression, it failed to improve overall survival (OS) in the Phase III SPARC registration trials (45).

Doxorubicin is an anthracycline that interdigitate between DNA base pairs and impairs topoisomerase II function inhibiting replication and transcription. Doxorubicin has also shown only marginal responses against PaC. In the earliest trials, responses varied from a 29% response rate as reported by The NPCP results showed clinical benefit with a response rate that included stable disease reaching 84%. Subsequent trials utilizing additional Ketoconazole with Doxorubicin alternating with Vinblastine and etoposide chemotherapy showed no additional benefit to hormonal therapy alone (45).

Eight therapeutic agents have been approved from the Food and Drug Administration since 2004 for management of patients with advanced PaC. There are four androgen signaling targeted inhibitors that derail androgen-receptor (AR) function (Enzalutamide, Abiraterone, Darolutamide and Apalutamide), 1 is an autologous cell based immunotherapy, 2 are Taxane chemotherapies that repress microtubule dynamics (Cabazitaxel and Docetaxel), 1 is a bone-targeted α -emitting radiopharmaceutical agent (radium223) and vaccine for PaC (Sipuleucel-T) (46).

Docetaxel is a taxane derivative that works by binding to microtubules and preventing androgen receptor nuclear translocation and causing apoptosis through B-cell lymphoma (Bcl-2) phosphorylation (45). It inhibits microtubule disassembly and has demonstrated to downregulate AR transcriptional activity by inhibiting the translocation of the AR to the nucleus in response to both androgens and ligand-dependent signaling path-ways and known as an antimitotic agent. It also inhibits AR gene expression by acting on the gene promoter and rises the levels of Forkhead box O1 (FOXO1), a strong transcriptional repressor of AR (47). In addition, docetaxel also has anti-B-Cell lymphoma (BCL)-2 and anti-BCLX properties, thus promoting the self-eating by cell. Resistance to docetaxel may develop through several mechanisms including drug efflux, alterations in microtubule structure, activation of survival pathways, and changes in the tumor vasculature. In an effort to overcome resistance, investigators looked at combining targeted therapies with Docetaxel (48).

Cabazitaxel is a third-generation, semisynthetic tubulin-binding taxane drug and found to be as potent as docetaxel in cell lines and has antitumor activity in models resistant to paclitaxel and docetaxel (45). It prevents micro-tubule disassembly and shows antineoplastic action in cell lines with p-glycoprotein overexpression, which is also an anticipated mechanism for development of Docetaxel resistance. Moreover, Cabazitaxel has ability to penetrate the blood-brain barrier in preclinical systems and also hinder nuclear AR transport (49). It therefore, remains an option for patients with mCRPC who have failed with docetaxel. The potential advantages are: (1) the diminished affinity for P-glycoprotein, an important drug efflux pump and (2) the ability to cross the blood–brain-barrier (48).

Adverse effects of Chemotherapy:

Chemo-drugs for PaC are commonly administer through IV route while some drugs, such as Estramustine, are given through enteral route. The duration of therapy for advanced PaC depends on how well it is working and what side effects are appearing in patient's body. Possible Side effects may include: headache, fatigue, memory impairment, numbness, weakness, diarrhea, hair loss, mouth sores, emesis, anorexia and increased chances of infections (48). Some clinical manifestations are mostly specific with certain chemo drugs. For example: docetaxel associated with alopecia and bone marrow suppression but cabazitaxel causes neutropenia, anemia, thrombocytopenia, constipation, and lethargy. Estramustine have an increased risk of blood clots. Mitoxantrone rarely cause leukemia but it occurs several years later (45).

Mechanisms of Resistance to Chemotherapy

The resistance to chemotherapeutic agent after use attributes to particular mechanisms fundamental to PaC biology or broad-spectrum mechanisms as shown in table 04 given below.

Table 4: Chemotherapy resistance pathways and mechanism

Resistance pathway	Resistance Mechanism
Androgen signaling pathways	activation of AR from signal transduction pathways, cross talk between AR and HER 2/3, SRC, and translocation of AR into nucleus with the help of coactivators such as FOXO1, dynein
Anti-apoptosis	Anti-apoptosis by inhibition of BCL2, BCLX, and clusterin and up-regulation of prosurvival cellular pathways such as PI3K, mTOR, PKB, and angiogenesis by HIF, VEGF, FGF, NF-κB

Ineffective drug delivery	Ineffective drug delivery because of lack of lymphatic vessels and spherule formation by cancer cells
Epithelial - mesenchymal transition	Epithelial -mesenchymal transition mediated by TGF- β , FGF, β -catenin, and mTOR pathways.
Paracrine cytokine secretion	Paracrine cytokine secretion induced by chemotherapy alters bone microenvironment, leading to tumor proliferation.
Up-regulation of p-glycoprotein	Up-regulation of p-glycoprotein encoded by MDR1 gene and ABCB1 encoded by MDR2 gene leads to drug efflux.
Microtubule alterations	Microtubule alterations mediated by β -tubulin mutations leading to anti-apoptosis as well as chemotherapy resistance.

Upcoming Therapeutic Targets:

Despite significant advances in the treatment of PaC using chemotherapeutic agents, the cure for the disease still remains a paradox. Alongside a lack of understanding of the already known mechanisms of the disease, new pathophysiological pathways are being discovered that further add to the complexity of the disease. Challenging as they may seem, these new pathways can also serve as potential avenues for a possible cure. Poly(adenosine diphosphate-ribose) polymerase (PARP) is associated with DNA repair and latest studies have confirmed an 11.8% occurrence of germline mutations in DNA repair genes in PaC. Inhibition of PARP has verified anticancer activity. In a phase 2 trial (TOPARP), the PARP inhibitor Olaparib confirmed better results in patients with mCRPC (50). Furthermore, Maoloake et al., 2018 also state that the CCR7/CCL21 axis can serve as a “Novel” biochemical pathway that can be targeted for the inhibition of the severe Metastatic potential of mCRPC if not the cancer itself (42).

The main purpose of the chemotherapeutic drugs is to rapidly kill or slow down the proliferation rate of rapidly dividing cancer cells. However, there are also non-cancerous cells in the GIT, bone marrow and hair follicles those divide rapidly. These cells are also destroyed due to the administration of the chemotherapeutic agents that lead to adversarial effects such as cognitive deficits including change in concentration, mental speed and memory, bone density reduction and fatigue (51). PaC still a leading cause of death in elderly men worldwide despite of advances in chemotherapy, radiation and surgery. Therefore, it is advisable for the scientific community to explore more diverse and effective options for PaC treatment.

Potential Novel Therapies for PaC:

Monoclonal Antibodies including naked monoclonal antibodies (Alemtuzumab (Campath), Conjugated monoclonal antibodies including Bevacizumab (Avastin), radiolabeled antibodies including Ibritumomab tiuxetan (Zevalin), Chemo labeled antibodies including Brentuximab vedotin (Adcetris), Bispecific monoclonal antibodies including blinatumomab (Blinicyto) are in use as novel therapeutics (52, 53).

Chimeric antigen receptor (CAR) T-cell therapy is a promising new way to get immune cells called T cells to fight cancer by changing them in the lab so they can find and destroy cancer cells. Examples of CAR T-cell therapies currently approved include: Tisagenlecleucel (Kymriah), Axicabtagene ciloleucel (Yescarta), Brexucabtagene autoleucel (Tecartus) and Lisocabtagene maraleucel (Breyanzi). They cause cytokine release syndrome (CRS). Other serious side effects include neurotoxicity or changes in the brain that cause swelling, confusion, seizures, or severe headaches (54).

Immunomodulators target the immune system directly by turning down some proteins and turning up others. Thalidomide (Thalomid), lenalidomide (Revlimid) and pomalidomide (Pomalyst) are known as immunomodulating drugs (or IMiDs). These drugs can cause low blood cell counts, and neuropathy. PD-1 is a checkpoint protein, are given by IV (intravenously). Examples of drugs that target PD-1 includes the Pembrolizumab (Keytruda), Nivolumab (Opdivo) and Cemiplimab (Libtayo) and have been shown to be helpful in treating several types of cancer including prostate (Kaunitz et al., 2017). PD-L1 inhibitors includes the Atezolizumab (Tecentriq), Avelumab (Bavencio) and Durvalumab (Imfinzi). CTLA-4 is another protein to keep the immune system in check. Ipilimumab is a monoclonal antibody that attaches to CTLA-4 and stops it from working (55).

Sipuleucel-T (Provenge) is vaccines used to treat advanced PaC that is no longer being helped by hormone therapy (55). Interleukins are a group of cytokines that act as chemical signals between white blood cells such as IL-7, IL-12, and IL-21, continue to be studied against prostate cancer, both as adjuvants and as stand-alone agents (Bayer et al., 2019). IFN- α boosts the ability of certain immune cells to attack PaC cells. It may also slow the growth of cancer cells directly, as well as the blood vessels that tumors need to grow (54).

PVSRIPO stands for recombinant nonpathogenic oncolytic polio-rhinovirus chimera. This genetically modified agent was generated in part by replacing an intrinsic genetic component critical for viral protein translation (IRES element) with an equivalent component of human rhinovirus type 2. This change prohibited viral replication in normal neuronal cells, but supported replication in tumors of the central nervous system and elsewhere (51).

Some of the benefits of Oncolytic virotherapy is less invasive and debilitating; highly selective. Injections can be administered locally and uptake by tumor cells is increased. The viral machinery is manipulated to select and replicate within tumor cells only which limits the probability of infection in non-cancer cells. The large RNA size of Poliovirus makes it a favorable candidate to undergo genetic manipulations (56). Some of the risks as certain viruses and tumors require different dosage paradigms there is no standard dose for virotherapy currently. The optimization of viral production will be difficult since little information about cost is available. The

administration, transport, storage and disposal of these viral agents will be a challenge for hospitals. Although, these viruses are weakened or attenuated, they still pose a threat to immunocompromised patients (57).

PVSRIPPO may have advantage in dividing in cancer cells owing to broad phenomenon of mitogenic signaling cascade deregulation favoring cap independent translation. For example, the activation of MAPK-interacting kinase has a downstream effect of repressing serine–arginine-rich protein kinase (SRPK), which plays pivotal role in cap-dependent translation by acting on ITAFs (IRES trans-acting factor). The specific mechanism by which SRPK acts on viral translation is not known. PVSRIPPO has proved potent oncolytic activity in a broad variety of cancer cell lines derived from gliomas, glioblastoma multiform, breast cancers, melanomas, Prostate cancer and astrocytoma (7).

Recommendations:

Investigators must focus on unraveling the complete biochemistry and pathophysiology of the disease before conclusively deciding the treatment modality. There is need for greater understanding of immune modulators, oncolytic viruses and phenotypic mixing. In phenotypic mixing, the surface protein of virus B can be coated on genome of virus A. This produced chimeric virus will now infect cells based upon surface recognition properties of B virus protein coat. However, the successive progeny of virus from this infection possess a type A coat as it is encoded exclusively by its type A genetic material. A fascinating instance of phenotypic mixing is that of pseudo-types, which consist of the nucleocapsid of one virus and the envelope of another. The nucleocapsid of vesicular stomatitis virus (a rhabdovirus) and the envelope of human immunodeficiency virus (HIV; a retrovirus) are currently being used to study the immune response to HIV17. Similar “Pseudo-types” can be developed and assigned specificity to target mCRPC cell lines and check fighting against disease.

Conclusion:

The latest proven prospective of oncolytic virotherapy e.g. PVSRIPPO prove that persistent preclinical, mechanistic investigation solving all perspectives of the virus: host relationship have generated promising quantifiable outcomes in the most complex oncologic circumstances that has already become resilient to all available conventional rehabilitation approaches. However, it is important to note that the current progress of the experimental and clinical phases of PVSRIPPO therapy, the possibility exists that this recombinant virus will soon be a viable treatment option for leukemia and solid neoplasia. Patient education in factors such as rate of success, cost, pre and post treatment procedures and health risks is of supreme importance before undergoing such types of treatment.

Compliance with Ethical Standards:

Not applicable

Disclosure of potential conflicts of interest

No

Research involving human participants and/or animals

Not applicable

Informed consent

Not applicable

Funding: Not applicable

Ethical approval: This article does not contain any studies with human participants or animals performed by any of the authors.

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Figure 01: PaC is associated with the above mentioned symptoms, etiological risk factors which have ability to worsen the disease and all the diagnostic test used to screen the disease and classify it in 4 stages according to Gleason Pattern scale (3, 4).

Figure 02: According to Gleason Pattern scale, lower grade (stage 1, score 1, 2) shows cancer is in initial phase, slow growing and not aggressive. From stage 2-5 and score 3-7 shows cancer is growing rapidly towards bones, lymph nodes and blood vessels (7)

Figure 03: First step to treat disease is active surveillance. Current treatment options involves surgical resection at tumor site (prostatectomy), radiation therapy, cryotherapy therapy and/or use of systemic therapy including chemotherapy, hormonal therapy (luteinizing hormone releasing hormone antagonist: LHRH, androgen depletion therapy: ADT, pregnenolone antagonist: PA) immunotherapy (adoptive transfer of ex vivo activated T cells, natural killer cells, oncolytic viruses, cancer vaccines and administration of antibodies or recombinant proteins (3).

Figure 4: PaC progression pathway and each stage of progression is associated with loss of specific tumor suppressor gene and a distinct chromosomal region

Figure 05: A number of mechanisms can elucidate the repair of competent AR signaling in CRPC. These include amplification and overexpression of AR, acquirement of constitutively active AR splice alternatives, deregulated AR coactivators/corepressors that sensitize AR in reaction to ligand binding, intracrine androgen synthesis, gain-of-function mutations and ligand-independent signaling and redundant downstream crosstalk.

Figure 06: The flow chart has shown the 1st and 2nd line available treatment options of metastatic and nonmetastatic castration resistant prostate cancer (nmCRPC) after careful diagnostic screening