UJEMI PEARLS

Towards the Long-Term Protection for Prostate Cancer

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SUMMARY Worldwide, prostate cancer (PC) is the second most commonly diagnosed cancer in men, and the second leading cause of cancer death in the developed world [1-4]. Approximately 11% of all men in the United States are diagnosed with PC over their lifetime, with the incidence increasing with age [3]. Current treatment options for PC depend on PC stage and may include radical prostatectomy, radiation therapy, androgen deprivation therapy, and chemotherapy [4-6]. However, despite advances in PC screening and the wide availability of treatment options available for PC, the prognosis of metastatic PC remains grim with a 5-year survival rate of 28% for metastatic disease [3, 5, 7]. Furthermore, current treatment options for PC present a wide variety of undesirable side effects or complications [8-10]. One such type of therapy includes the use of androgen deprivation therapy, which has been associated with loss of bone density, vasomotor symptoms, and sexual dysfunction with or without a change in mental state [11-16]. The development of oncolytic viral therapy may provide a novel treatment option for the treatment of PC by direct killing of tumor cells and enhancement of the immune response against the tumor [1, 2, 17-19]. In addition, this novel therapy could be utilized in tandem with other currently approved treatment options for a potential synergistic treatment of PC. This article will provide an overview of the current research in oncolytic viral therapy, compare the potential utility of oncolytic viral therapy in PC in comparison to current treatment regimens, and suggest an optimal oncolytic viral therapy schedule for PC patients. Understanding the benefits of oncolytic viral therapy provide us with a greater diversity of treatment options that may be used or combined for PC, particularly for castration-resistant PC tumors or metastases, as well as other cancers with few treatment options.

INTRODUCTION

Prostate cancer (PC) is the most prevalent malignancy in men worldwide [1-4, 20, 21]. In North America alone, PC is the second most diagnosed cancer among men within North America, with an estimated incidence rate of 21% [3]. It is also the second leading cause of cancer-related death in North America [3]. The causes of PC are many, including key associative factors of age - an average age of diagnosis being 66 years old [22, 23]. Other key factors include genetic factors, lifestyle, and diet [22, 23]. Individuals with a family history of PC have an increased relative risk of two to five times higher than those with no prior history [23]. PC is also ethnicity-related, as African Americans make up 44.2% of patient, Caucasian Americans 19.1%, and Asian Americans 9.1% [22].

Despite the high annual incidence rate and high mortality rate of PC, the survival rate within 5 years of diagnosis is up to 95%, at least within North America [21]. This is mainly due to the awareness of the general public, along with the development of advanced screening and diagnostic tools, such as prostate-specific antigen (PSA) concentration screenings and transrectal ultrasound-guided biopsy. However, when considering the global scale of PC, countries like South America and Japan have very poor outcomes with such diagnosis [1, 3, 20]. This is not only due to the limited diagnostic tools and treatments, but also the lack of awareness and low prevalence [1, 20].

PC is usually diagnosed after clinical exams, such as the abnormal prostate findings during a digital rectal exam and/or elevated PSA during blood workups. Symptoms are usually rare, but patients may in some cases present with nonspecific urinary symptoms, hematuria, or hematospermia [24]. Clinical symptom manifestations are usually associated

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with advanced PC.

Current treatment of PC after diagnosis revolves around three main approaches depending on the cancer grade – localized, advanced, or distant metastatic PC. For patients with localized PC, the treatment options include either surgical removal of the prostate or radiation therapy, usually followed by close active monitoring of the patient's PSA levels [4]. In the case of advanced PC, the first line of treatment usually involves surgery, followed by radiation treatments. Patients with distant metastatic PC usually range from surgical interventions and radiation, to androgen deprivation therapy (ADT) and chemotherapy [4]. As a last line of defense, patients may be suggested to undergo alternative treatment options such as newly FDA approved treatments and/or clinical trials, along with palliative care [4].

Despite the numerous current treatment options, the 5-year survival rate for individuals with progressive PC is in the single digits – approximately 7%, with up to 40% of patients eventually experiencing disease progression and/or relapse within 12 to 18 months [1]. Furthermore, the second and last lines of treatment have met with limited success, with 70% of high risk patients with metastasis dying within 5 years of diagnosis [1, 25]. Due to these issues, a new therapeutic option is greatly needed, such as oncolytic viral therapy (OVT).

OVT is a new promising strategy against cancer, due to the fact that oncolytic viruses (OVs) mediate antitumor effects in several ways [Figure 1]. An OVs is defined as a genetically engineered or natural-occurring virus with the ability to selectively replicate in oncolytic cells; the replication in tumor cells allows for the killing of such cells, all while propagating and infecting other tumor cells [1]. These engineered viruses have already been used as pre-clinical treatment for cancers like melanoma, lymphoma, multiple myeloma, and acute myelogenous leukemia, utilizing various viruses like the herpes simplex virus and reovirus [26-29]. Primary effects include the efficient infection of cancers and propagations via lysis, alongside preferential infections of cancer cells over normal cells. Aside from this, OVs are able to stimulate and activate the immune system, overcoming the immune-suppressive environment created and maintained by cancerous cells. This in turn can facilitate a strong and robust response of both innate and adaptive immunity against the tumor itself, leading to the development of anti-tumor antigens and facilitating long-term immunological memory.

The utilization of OVT for PC is especially attractive, due to the location of the tumor and immediate benefit. Since PCs are easily accessible via the perineum, OVs would be allowed to directly affect the tumor site. This is particularly important, as OVs can be recognized by the immune system as pathogens and the consequent anti-viral response could minimize effectiveness. Furthermore, due to the fact that PC patients with distant metastasis have a survival rate of less than 29%, any potential benefits, whether prolongation of patient life or increase of patient quality of life, would be advantageous [5, 7]. In addition, these successful clinical trials of OVT for PC would promote more research into OVT and other subsequent clinical trials against different type of cancers.

RESEARCH QUESTIONS

Patients with local PCs have a 95% chance of survival, and patients with advanced PC also have a 95% survival rate [3, 7, 21]. However, patients with distant metastatic PC have a survival rate of less than 29% with current treatments[3, 5, 7]. Due to this issue, OVT would provide a novel avenue of treatment that could curb the mortality rate of distant metastatic PC patients, thereby prolonging the patient's life and increasing the patient's quality of life. In this context, this article will examine three key areas. First, it will examine the population of PC patients that have low survival rates, and what key factors are involved. Following this, it is important to assess the current treatment options for these PC patients and their limited effectiveness, in comparison to OVT. Lastly, this article will explain why PC is a excellent candidate for OVT, explore which viruses would be the best candidate for OVT, and discuss how this novel therapy should be integrated with current avenues of treatment.

PROJECT NARRATIVE

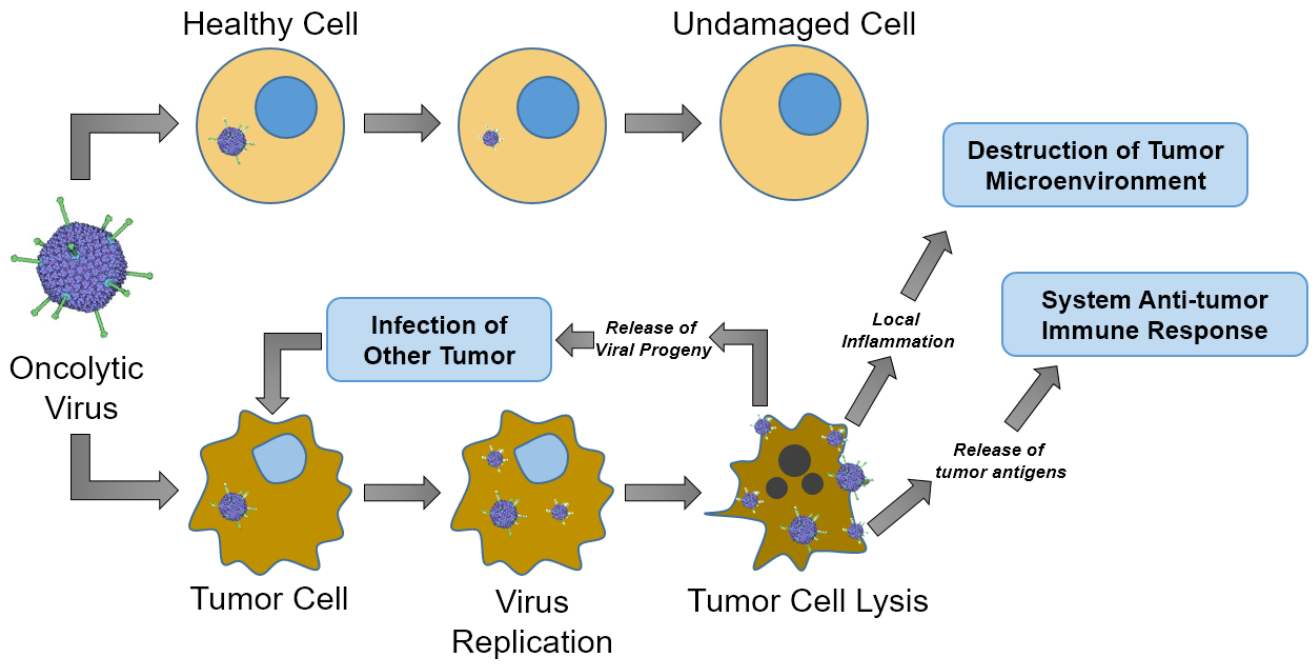
What population of PC patients have poor survival rates? The development of sensitive diagnostic tools for early diagnosis of patients with PC has been correlated with a high survival rate, as early detection of PC translates to better prognosis. This is further correlated

with the development of the current myriad of effective treatment options. Despite this, on average 4,300 men die from PC in Canada, which represents 10% of all cancer deaths in men in 2017 [23]. The questions remains as to why some patients, despite early diagnosis, still have poor survival rates. Even with the most current and novel treatment strategies, there are limitations to the effectiveness of the treatment in a subset of patients. Due to this, most options for metastatic PC, aside from aggressive forms of treatment, usually prescribe palliative measures to maximize the patient's quality of life. As a result, there is no cure for metastatic PC, as the majority of therapies involve in palliative care. Currently, there are two main groups of patients that represent the majority of PC-related deaths [Figure 2]. They are: i) hormone-sensitive PC (HSPC); and ii) castration resistant PC (CRPC) [30-33].

Patients with HSPC are individuals who have PCs that are sensitive and respond well to ADT. Up to 75% of metastatic cases are hormone sensitive, although there are issues of developing resistance to ADT [33].Within this group there are 2 subsets of patients. Individuals who have undergone a prostatectomy or radiation therapy for localized PC but still have an increasing PSA level are categorized as a biochemical reoccurrence (BCR) [21]. BCR represents 30% to 50% of all PC patients in Canada [21, 34, 35]. BCR is particularly dangerous as patients diagnosed are still at risk of developing metastasis in 35% of cases [34]. The other subset of individuals are the metastatic hormone-sensitive PC (mHSPC) patients [33, 35]. In the case that a patient does develop androgen resistance, these patients are considered to have castration-resistant PCs (CRPC), which includes both non-metastatic and metastatic cancers [35]. Of all the patients with advanced or metastatic PC, the prognosis of CPRC is the grimmest.

Research question #2: How do current PC treatments compare to oncolytic viral therapy for treatment-resistant PC patients? Although the majority of cases of PC are diagnosed and treated while the PC is localized, some men have an elevated risk or have evidence of developing a disseminating disease after their intervention treatments (e.g., hormone therapy, radiation therapy), and others have evidence of a metastatic PC. Current research has led to the development of multiple treatment modalities for men with advanced

FIG. 1 Mechanisms of action of oncolytic virus therapy. Local infection of tumor cells via oncolytic viruses induces lysis, releasing viral progeny that infect other tumor cells. Lysis also leads to local inflammation and release of tumor antigens, leading to stimulation of innate and adaptive immunity through the presentation of tumor antigens and shifting the local tumor microenvironment towards a pro-inflammatory state.



or distant metastatic PC. The choice of treatment depends on a variety of factors, such as the stage and size of the tumor, overall health and age, and personal preference. The management of these patients mainly relies on the goals of prolonging survival, minimizing complications, and maintaining/increasing quality of life.

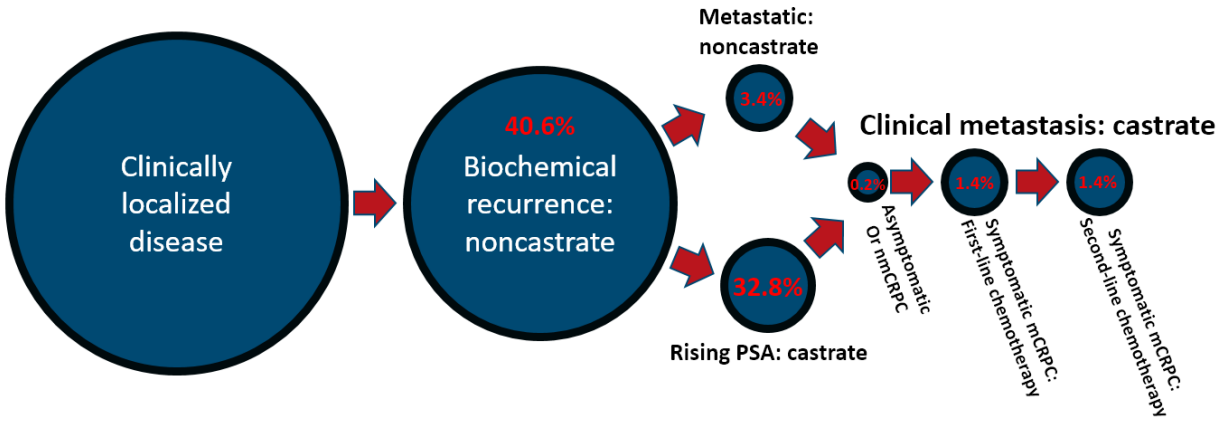
PCs that continue to have increased levels or rising levels of PSA despite a definitive treatment are diagnosed as BCR PC. The therapeutic options for these patients are focused towards the management of the PSA, with either 2 years of hormonal therapy with an androgen blocker (e.g., bicalutamide) or 6 months of testosterone suppression with standard ADT [21, 36]. In addition, the patient's serum PSA is closely monitored in order to inform any further changes that may be needed [36].

The initial approach for treatment of patients with disseminating PC usually includes ADT. ADT can be achieved either with a bilateral orchiectomy (i.e., surgical castration) or a medical orchiectomy [37]. The former is a simple, cost-effective treatment in order to stem or decrease the elevated/rising serum PSA. It is especially useful in cases where immediate decrease of testosterone is necessary or when cost/adherence is an issue. The latter utilizes the hypothalamic-pituitary axis, in order to deceases the testicular production of testosterone. However, ADT is associated with a wide range of side effects that can significantly impair the quality of life. This includes side effects associated with lack of testosterone (e.g., osteoporosis, muscle loss), sexual dysfunction, vasomotor instability, fatigue, and neurological and cardiovascular abnormalities. To improve the effectiveness of the treatment, ADT is usually combined with either docetaxel, a microtubule inhibitor, or abiraterone acetate, an antiandrogen medication [5]. However, these additional treatments are not without side effects. Patients may have complications, such as nausea, emesis, and muscle/joint pain.

For patients with evidence of metastatic PC, treatments options tend to differ, as the majority of patients develop androgen resistance, negating ADT - the most commonly used treatment for PC [21, 38]. Despite this, ADT treatments (i.e., medical orchiectomy) are usually continued, along with additional therapies and palliative care [39]. In the case of additional therapies, this includes immunotherapy and chemotherapy [40-42]. For palliative care, this usually refers to the utilization of pain-relief and/or Radium-223, which is especially used for patients with bone metastasis [39].

The main issue with the treatment of BRC, HSPC, and non-metastatic/metastatic CRPC (nm/mCRPC) are that these forms of treatment focus on the goal of preserving/prolonging a patient's life rather than treating the disease. This is further compounded by the fact that the optimal timing for initiating systemic therapies is uncertain, and varies depending on the experience and knowledge of the physician. Hormone therapy for disseminated PC is not curative, and immediate therapy has not been shown to prolong survival compared with delayed therapy [6, 43]. Furthermore, treatment-related side effects can adversely affect a

FIG. 2 A proportional prostate cancer clinical states model. The circles represent the corresponding prostate cancer disease state, along with the prevalence rate. Adapted from the prostate cancer clinical states model and the prostate cancer clinical states prevalence model [52, 53]. nmCPRC = non-metastatic castration-resistant prostate cancer; mCRPC = metastatic castration-resistant prostate cancer; PSA = prostate-specific antigen.



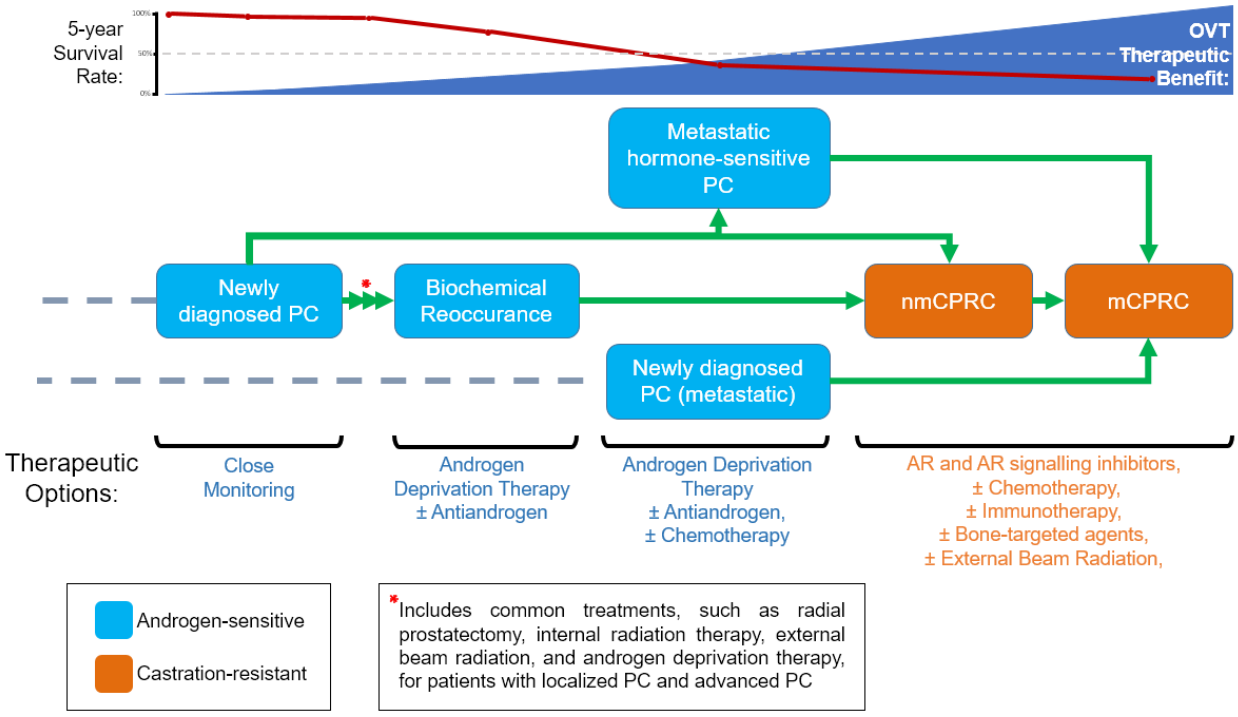
patient's quality of life [10].

Due to this, OVT provides an alternative treatment avenue that not only is potentially curative, but could also provide increased quality of life and survival in patients with disseminating/disseminated PC. This is because viral infections have an intrinsic cytopathic property in inducing cell death and cellular dysfunction. In addition, the viral genome can easily accommodate modifications that could increase viral tropism to neoplastic cells, enhance selective viral replication and lytic capacity, alter viral pathogenicity, and induce host antitumor immunity. These features are the foundation for the use of viruses in cancer therapeutics. The ability to generate virions rapidly and genetically engineer additional genes that promote antitumor immunity, increase tumor cell susceptibility to ionizing radiation or cytotoxic chemotherapy, and increase patient safety, are all major advantages of OVs.

Research question #3: How beneficial is OVT for PC, which viruses should be utilized for PC, and what would be an optimal strategy/therapy? PC is an excellent candidate for OVT, primarily due to two reasons. The first is that there are no effective treatments readily available for patients with distant metastasis or relapse. This is evident as patients diagnosed with metastatic PC have a 5-year survival rate of 28% [3, 5, 7]. Due to the low survival rate of PC, as any increase in survival rate in patients with distant metastasis or relapse would prolong the patient's life. The second reason that PC would benefit from OVT is the route of administration. As the PC is easily accessible with current surgical and radiation treatments via the perineal muscle or transrectal route, administration of OV are ideal due to the location.

OVT for PC would involve the injection of OV directly into the tumor and surrounding area. Similar to how a prostate biopsy would function, physicians would inject the viral particles transrectally with transrectal ultrasound guidance to aid the placement of the injection. Pre-clinical and clinical phase I/II trials of OVT for PC have shown promising results with minimal traditional side effects, such as erectile dysfunction and incontinence [44]. Although there are multiple viruses that can be utilized for OVT in patients, such as herpes simplex virus and reovirus, the most beneficial virus for distant metastatic PC would

FIG. 3 Prostate cancer disease progression model, depicting patient transitions between distinct prostate cancer clinical states. Based on clinical data from [54, 55]. The model highlights movement towards clinical states that have a lower 5-year survival rate, depicting higher mortality rates. In addition, current therapeutic options are shown below, along with the potential therapeutic benefit of oncolytic viral therapy in each clinical state. PC = prostate cancer; nmCPRC = non-metastatic castration-resistant prostate cancer; mCRPC = metastatic castration-resistant prostate cancer.



be adenovirus. The first reason is that adenovirus has been widely and thoroughly studied since its first identification in 1953 [45]. The second reason is that adenovirus has broad tropism for a variety of tissues, allowing for wide-spread infection of tumors throughout an individual [46]. This is particularly useful in patients with distant metastasis, as the circulation of the OVs would help with affecting secondary sites as well. The third reason is that OVs can contain small molecules (e.g., 5-FC), which could increase the effectiveness of the cancer-killing [46, 47].

The development of an optimal strategy for patients with disseminating or distant metastatic PC would utilize a multi-disciplinary approach integrating both current and novel methods. The inclusion of OVT to current treatment plans of both androgen-sensitive and castration-resistant PC would be the most effective in both minimizing disease progression and potential side effects.

ADT provides excellent management of the proliferation of PC cells, as the majority of these cancer cells have greater amounts of androgen receptors (AR) and/or a lower threshold of ligand needed to activate the receptor [48]. Thus inhibiting circulating levels of androgens would mediate inhibition of the transcription of target genes that modulate growth and differentiation of prostate epithelial cells. Subsequent treatments of abiraterone acetate and docetaxel would further inhibit the proliferation of PC cells by inhibiting circulating androgens and inhibiting PC cell division via microtubular depolymerization, respectively. OVT would provide another therapeutic avenue that would not only lyse PC cells within the primary tumor sites, but also circulating and secondary sites of metastasis. In addition, adenovirus OVs are able to package additional genes that could encode for pro-drugs or proteins, enhancing antitumor efficacy and augmenting antitumor immunity induction. This is particular evident in the clinical trials done by Freytag *et al.* in which they engineered an oncolytic virus, using an adenovirus that packaged and genetically expressed 5-fluorocytosine (5-FC), a chemotherapy drug that inhibits synthesis of DNA and RNA [47]. They observed a decrease of at least 25% in the PSA levels in 60% of patients that utilized this OV [47]. Another target molecule for PC to consider could be a Pace4 inhibitor, an inhibitor of the proprotein convertase that is overexpressed in the majority of PC cells and has been implicated in the upregulation of growth factors leading to sustained cancer progression [49].

CONCLUSIONS

Over the last 30 years, there have been incredible achievements in PC research, from the discovery of PSA to the development of Pace4 inhibitors. This is supported by the nearly 100% survival rate of localized PC patients and the sensitive diagnostic platforms available. In addition, the current treatments provide not only management of the disease and prolongation of patient life, but are also able to cure patients of their PC. However, despite these recent scientific advancements (e.g., antiandrogen and chemotherapy drugs), 10% of all PC patients die [3]. Due to this, OVT is promising for its effectiveness in especially distant metastatic PC patients [Figure 3].

Current and past clinical trials show promising results, especially to patients with alternative forms of treatment combined with OVT. Many clinical trials have shown that a monotherapy of OV is generally well-tolerated in a variety of patients with varying progression of PC [1, 2, 17, 18]. Of these clinical trials with patients with no alternative option in decreasing PSA levels, many have shown a significant decrease in PSA levels with the use of OVT [1, 2, 17, 18]. Further synergistic effects in the treatment of PC could be potentially achieved through a combined treatment plan, utilizing OVT, ADT, antiandrogen, and chemotherapy. This would maximize the effectiveness by targeting PC by different mechanisms, all while decreasing the likelihood of developing androgen resistance. This is particularly an issue as all patient undergoing ADT therapy develop androgen resistance through the manipulation of the nontraditional pathways involving androgenic ligands and receptors [50]. Thus, a multiprong therapy would both minimize treatment durations and maximize tumor cell death, leading to decreased development of androgen resistant PC.

Although OVT for PC is promising, there is still a long way to go. One major obstacle is the ethical concern of using a live virulent strain of virus in a patient. Other major obstacles for this form of therapy are: i) the host range of the virus (i.e., the virus' function to successfully adsorb and/or enter target cells); ii) safety risks involved in using modified

viruses (e.g., vulnerability to elderly or immunocompromised, non-specific targeting, and elimination of OVs from host); and, iii) the varying mutation rates associated with viruses (e.g., low mutations with adenovirus, high mutations rates with Newcastle virus). The biggest constraint with OVT is the host's adaptive immune response, as many hosts develop working immunological protection to the OV, reducing its effectiveness after one dose. However, several strategies and solutions already exist to minimize or circumvent many of these limitations, supporting OVT as a viable option and powerful tool in the fight against cancer. OVT may play an emerging role in the PC in limiting not only developed countries, but also developing countries, but more research and clinical trials will have to be done [2, 51].

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