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Research Article

Immunotherapy in the Scenario of Prostate Cancer an Update

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Abstract

Over the last few years, immunotherapy had become an important cancer treatment option, and even though the principles of immunotherapy had evolved over many decades, the FDA approvals of sipuleucel-T and ipilimumab had commenced a new wave in immuno-oncology. Despite the current enthusiasm, it is unlikely that any of the immunotherapy treatments alone could dramatically change the outcomes of prostate cancer; nevertheless, combination therapeutic strategies had been more promising and they do provide a reason for optimism. Many completed and ongoing studies have demonstrated that the combination of cancer vaccines or checkpoint inhibitors with different immunotherapy agents, hormonal therapy (enzalutamide), radiotherapy (radium 223), DNA-damaging agents (olaparib), or chemotherapy (docetaxel) could enhance immune responses and induce more dramatic, long-lasting clinical responses without significant toxicity. The goal of prostate cancer immunotherapy does not have to be complete eradication of advanced disease, but instead the return to an immunological equilibrium with an indolent disease state. Further to determining the optimal combination of therapy regimens, efforts are also being made to ascertain to discover biomarkers of immune response. With such concerted efforts, it is expected that the future of immunotherapy in prostate cancer would be brighter in the future than earlier.

Keywords: prostate cancer; immunotherapy; sipuleucil-t; ipilimad; combination treatment; immune profile; promising

Introduction

Immunotherapy encompasses a wide variety of treatments to engage the immune system to target malignancies. Over recent years, immunotherapy has made a major impact upon therapy of metastatic cancer and has changed the standard of care for many types of neoplasms. Nevertheless, predicting and understanding of responses across tumour types has been a challenge. While some metastatic cancers have demonstrated dramatic responses to immunotherapy, such as melanoma, lung cancer, and renal cell carcinoma, prostate cancer in Prostate Cancer. [1] Nevertheless, small series of prostate cancer patients have demonstrated impressive responses to cellular and immunotherapy. [1,2] Maselli et al. [2] made the ensuing iterations:

- Prostate cancer (PC) is the most common type of malignant neoplasm in men.
- In the early stage of the PC disease, it is sensitive to androgen deprivation therapy.
- In patients with metastatic castration-sensitive prostate cancer (mHSPC), chemotherapy and second-generation androgen receptor therapy had led to increased survival.
- Nevertheless, despite advances in the management of mHSPC, castration resistance is unavoidable and many patients do develop metastatic castration-resistant disease (mCRPC).
- Over the recent past few decades, immunotherapy had dramatically changed the oncology landscape and had increased the survival rate of many types of cancer. Nevertheless, immunotherapy in prostate cancer had not yet given the revolutionary results it had in other types of tumours.
- Research into new treatments is very important for patients with mCRPC because of its poor prognosis.

The ensuing article contains an update on immunotherapy in malignant neoplasm of the prostate gland including adenocarcinoma of the prostate gland and other cell types of prostate cancer.

Aim

To provide an update on immunotherapy of prostate cancer.

Methods

Internet databases were searched including Google, Google Scholar, Yahoo, and PUBMED. The search words that were used included: Immunotherapy of prostate cancer; immunotherapy of carcinoma of the prostate gland, immunotherapy of malignant neoplasm of the prostate gland; immunotherapy of prostatic malignant tumour; and immunotherapy of prostatic cancer. One hundred and ten (110) references

were identified which were used to write the article which has been divided into two parts: (A) Overview, and (B) Miscellaneous narrations and discussions from some case reports, case series, and studies related to immunotherapy of prostate cancer.

Results

[A] Overview

Definition / General Statements

- Immunotherapy or biological therapy is the terminology which is used for the treatment of disease by the activation of or suppression of the immune system. [3].
- It has been iterated that immunotherapy is designed to elicit or amplify an immune response which are classified as activation immunotherapies, while immunotherapies which reduce or suppress are classified as suppression immunotherapies. [3]
- It had been pointed out that immunotherapy is under preliminary research for its potential to treat various forms of malignant neoplasms. [3,4,5,6,7]
- Cell-based immunotherapies had been documented to be effective for some cancers. [8,9]
- Immune effector cells such as lymphocytes, macrophages, dendritic cells, natural killer cells, and cytotoxic lymphocyte had been iterated to work together to defend the body against cancer by targeting abnormal antigens which are expressed upon the surface of tumour cells. [3]
- Vaccine-induced immunity to COVID-19 is stated to rely mostly upon an immunomodulatory T-cell response.[3,10]
- Treatments including granulocyte colony-stimulating factor (G-CSF), interferons, imiquimod and cellular membrane fractions from bacteria had been documented to be licensed for medical use. [3]
- Others including IL-2, IL-7, IL-12, various chemokines, synthetic cytosine phosphate-guanosine (CpG) oligodeoxynucleotides and glucans had been iterated to be involved in clinical and preclinical studies. [3]

Immunomodulators

- It has been iterated that the terminology immunomodulators refers to the active agents of immunotherapy. [3]
- It has been pointed out that immunomodulators are a diverse array of recombinant, synthetic, and natural preparations. [3,11]

The ensuing summations had been made regarding the class of immunomodulators and their examples: [3]

Class	Example agents
Interleukin	IL-2, IL-7, IL-12.
Cytokines	Interferons, G-CSF.
Chemokines	CCL3, CCL26, CXCL7
Immunomodulatory imide drugs (ImiDs)	Thalidomide and its analogues (lenalidomide, pomalidomide, and apremilast), BCG vaccine, [12,13] as well as Covid vaccines [3,12,14,15]
Others	Cytosine phosphate-guanosine, oligodeoxynucleotides, glucans

Activation immunotherapies – also exist for utilization.

History of Cancer Immunotherapy

- It had been pointed out that previously the treatment of cancer had been focused upon the killing or removal of cancer cells and tumours, by the undertaking of chemotherapy or surgery or radiotherapy. [3]
- In 2018 the Nobel Prize in Physiology or Medicine was awarded to James P Allison and Tasuku Honjo "for their discovery of cancer treatment by inhibition of negative immune regulation." [3]
- Cancer immunotherapy does attempt to stimulate the immune system in order to destroy tumours. [3]
- Various types of immunotherapy strategies are being utilised or are undergoing research and testing. [3]
- Randomized controlled studies in different cancers emanating in significant increase in survival and disease free period had been documented [3,5] and its efficacy has been enhanced by 20% to 30% when cell-based immunotherapy is combined with conventional treatment methods. [3,5]
- It has been pointed out that one of the oldest forms of cancer immunotherapy is utilization of Bacillus Calmette Guerin (BCG) vaccine, which was originally used to vaccinate against tuberculosis and subsequently was found to be useful in the treatment of urinary bladder cancer. [3,16]
- BCG immunotherapy does induce both local and systemic immune responses.
- The mechanisms by which BCG immunotherapy mediates tumour immunity had been widely studied, but they had still not been completely understood.[3,17]
- It had been pointed out that utilization of monoclonal antibodies in cancer therapy was first introduced in 1997 with rituximab which is an anti-CD20 antibody for treatment of B cell lymphoma. [3,18] Pursuant to that many monoclonal antibodies had been approved for treatment of a variety of haematology malignancies as well as for solid tumours. [3,19,20]
- Some types of immunotherapies entail the extraction of G-CSF lymphocytes from the blood and expanding in vitro against a tumour antigen preceding reinjecting of the cells with appropriate stimulatory cytokines. The cells then destroy the tumour cells that express the antigen. [3,21]
- Topical immunotherapy utilises an immune enhancement cream (imiquimod) which produces interferon that causes the recipient's killer T cells to destroy warts, [3,22] actinic keratoses, basal cell cancer, vaginal intraepithelial neoplasia, [3,23] squamous cell cancer, [3,24,25] cutaneous lymphoma, [3,26] and superficial malignant melanoma. [3,27] Injection immunotherapy ("intra-lesional" or "intra-tumoral") uses

mumps, candida, the HPV vaccine [3,28,29] or trichophytin antigen injections to treat warts (HPV induced tumours).

- It had been iterated that adoptive cell transfer had been tested on the lung [3,30] and other cancers, with greatest success achieved in melanoma.

Dendritic cell-based pump-priming or vaccination

- It has been iterated that dendritic cells (DCs) could be stimulated to activate a cytotoxic response towards an antigen. [3]
- Dendritic cells, which are a type of antigen-presenting cells, are harvested from the person needing the immunotherapy. These cells are then either pulsed with an antigen or tumour lysate or they are transfected with a viral vector, which causes them to display the antigen. Upon transfusion into the person, these activated cells present the antigen to the effector lymphocytes (CD4+ helper T cells, cytotoxic CD8+ T cells as well as B cells). This initiates a cytotoxic response against tumour cells that express the antigen (against which the adaptive response has now been primed). The first FDA-approved cell-based immunotherapy, [3,31] the cancer vaccine Sipuleucel-T is stated to be one example of this approach. [3,32]
- The Immune Response Corporation [3,33] (IRC) developed this immunotherapy and licensed the technology to Dendreon, which obtained FDA clearance.

The current approaches for DC-based vaccination have been mainly based upon antigen loading on in vitro-generated DCs from **monocytes** or **CD34**+ cells, then activating them with different **TLR** ligands, **cytokine** combinations, and then injecting them back to the patients. The in vivo targeting approaches do comprise of administering specific cytokines (for example, **Flt3L, GM-CSF**) and THEN targeting the DCs with antibodies to C-type lectin receptors or agonistic antibodies (for example, anti-CD40) which are then conjugated with antigen of interest. Multiple, next-generation anti-CD40 platforms are being actively developed. [3,34] Future approach might target DC subsets based upon their specifically expressed **C-type lectin receptors** or **chemokine-receptors**. Another potential approach is stated to be the generation of genetically engineered DCs from induced pluripotent stem cells and utilisation of **neo-antigen**-loaded DCs for the induction of better clinical outcome. [3,35]

T-cell adoptive transfer

- It has been iterated that Adoptive cell transfer in vitro does cultivate autologous, extracted T cells for later transfusion. [3,36]
- It had also been stated that alternatively, **Genetically-engineered T cells** are created by harvesting T cells and then infecting the T cells with a **retrovirus** which contains a copy of a **T cell receptor** (TCR) gene which is specialised to recognise tumour antigens. [3] The virus integrates the receptor into the T cells' **genome**. [3] The cells are then expanded non-specifically and/or stimulated. The cells are then reinfused and produce an immune response against the tumour cells. [3,37] The technique has been tested on refractory stage IV metastatic melanomas. [3,36] and advanced **skin (cutaneous) cancer**. [3,38,39,40] The first FDA-approved CAR-T drug, Kymriah, used this approach. It has been stated that in order to obtain the clinical and commercial supply of this CAR-T, Novartis had purchased the manufacturing plant, the distribution system and hired the production team that produced Sipuleucel-T developed by Dendreon and the Immune Response Corporation. [3,41]
- It had been pointed out that whether T cells are genetically engineered or not, before re-infusion, lympho-depletion of the recipient is required to eliminate regulatory T cells as well as unmodified, endogenous lymphocytes which compete with the transferred cells for homeostatic cytokines. [3,36,42-44] It had also been stated that lymphodepletion might be achieved by **myeloablative** chemotherapy, to which total body radiotherapy might be added for greater effect. [3,45] Transferred cells that are multiplied in vivo and had persisted within peripheral blood in many people, sometimes representing levels of 75% of all $CD8^+$ T cells at 6 months to 12 months after infusion. [3,46] It was stated that as of 2012, clinical trials for metastatic melanoma were ongoing at many sites. [3,47] Clinical responses to adoptive transfer of T cells were observed in patients with metastatic melanoma resistant to multiple immunotherapies. [3,48]

Checkpoint inhibitors

- It has been pointed out that **Anti-PD-1 / PD-L1** and anti-CTLA-4 antibodies are the two types of checkpoint inhibitors which had been currently available to patients.
- It has been iterated that the approval of anti-cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) as well as anti-programmed cell death protein 1 (PD1) antibodies for human use had already resulted in significant improvements in disease outcomes for various cancers. [3,49]
- It has been documented that even though these molecules were originally discovered as molecules playing a role in **T cell activation** or **apoptosis**, subsequent preclinical research had demonstrated their important role in the maintenance of peripheral immune tolerance. [3,50]
- It has been pointed out that immune checkpoint inhibitors had been approved to treat some patients with a variety of cancer types, including: **melanoma,** breast cancer, urinary bladder cancer, cervical cancer, colon cancer, lung cancer, head and neck cancer, or Hodgkin lymphoma. [3,51,52]
- It had also been stated that these treatments had revolutionized **cancer immunotherapy** as they had been shown for the first time in many years of research in metastatic **melanoma**, which is regarded as one of the most **immunogenic** human cancers, an improvement in overall survival, with an increasing group of patients benefiting long-term from these treatments, although caution remains needed for specific subgroups. [3,50,53,54]
- It had been pointed out that the next generation of checkpoint inhibitors targets other receptors such as lymphocyte-activation gene 3 (**LAG-3**), T-cell immunoglobulin and mucin-domain containing-3 (**TIM3**), and T cell immunoreceptor with Ig and ITIM domains (**TIGIT**). It had also been documented that: antibodies against these receptors had been evaluated in clinical studies, but had not yet been approved for widespread utilisation. [3,55]

Immune enhancement therapy

- It had been explained that **autologous immune enhancement treatments** use a person's own peripheral blood-derived **natural killer cells**, cytotoxic T lymphocytes, epithelial cells and other relevant immune cells are expanded in vitro and then re-infused. [3,56] It has also been pointed out that the treatment had been tested against **hepatitis C**, [3,57,58,59] **chronic fatigue syndrome,** [3,60,61] and **HHV6** infection. [3,62]

Suppression immunotherapies

It had been iterated that **immune suppression** does dampen an **abnormal immune response** in **autoimmune diseases**, or reduces a **normal immune response** to prevent **rejection** of **transplanted** organs or cells. [3]

Immunosuppressive drugs

- It has been pointed out that immunosuppressive drugs can be utilised to control the immune system with organ transplantation and with autoimmune disease. Immune responses depend on lymphocyte proliferation.
- Lymphocyte proliferation is stated to be the multiplication of lymphocyte cells that are used to fight and remember foreign invaders. [3,63]
- Cytostatic medicaments are a type of immunosuppressive drug which aids in slowing down the growth of rapidly dividing cells.
- Another example of an immunosuppressive medicament is stated to be Glucocorticoids that are more specific inhibitors of lymphocyte activation. [3] Glucocorticoids are stated to work by emulating actions of natural actions of the body's adrenal glands in order to help suppress the immune system, which is helpful with autoimmune diseases|, [3,64]
- Alternatively, inhibitors of immunophilins more specifically target T lymphocyte activation, the process by which T-lymphocytes stimulate and commence to respond to a specific antigen, [3,65]
- There are also immunosuppressive antibodies that target steps in the immune response so as to prevent the body from attacking its tissues, which is a problem with autoimmune diseases, [3,66]
- There are many other medicaments that modulate immune responses and could be utilised to induce immune regulation. It was ascertained in a pre-clinical trial that regulation of the immune system by small immunosuppressive molecules such as vitamin D, dexamethasone, and curcumin could be helpful in the prevention of or treatment of chronic inflation. Given that the molecules are administered under a low-dose regimen and subcutaneously. A study had been stated to provide a promising preclinical demonstration of the effectiveness and ease of preparation of Valrubicin-loaded immunoliposomes (Val-ILs) as a novel nanoparticle technology to target immunosuppressive cells. Val-ILs do have the potential to be used as a precise and effective treatment based upon targeted vesicle-mediated cell death of immunosuppressive cells. [3,67]

Immune tolerance

- It had been pointed out that the body naturally does not launch an immune system attack on its own tissues.
- Models generally identify **CD4+ T-cells** at the centre of the **autoimmune response**. [3] Loss of T-cell tolerance then unleashes B-cells and other immune effector cells on to the target tissue. [3] The ideal **tolerogenic therapy or treatment** would target the specific T-cell clones co-ordinating the autoimmune attack. [3,68]
- It had been stated that **immune tolerance therapies or treatments** are stated to seek to reset the immune system so that the body stops mistakenly attacking its own organs or cells in **autoimmune disease** or accepts foreign tissue in **organ transplantation**. [3,69] A recent therapeutic or treatment approach is stated to be the infusion of **regulatory immune cells** into transplant recipients [3]. The transfer of regulatory immune cells is stated to have the potential to inhibit the activity of effector. [3,70,71]
- Creating immune tolerance is stated to reduce or eliminate the need for lifelong immunosuppression and attendant side effects. [3] It had been tested upon transplantations, **rheumatoid arthritis**, **type 1 diabetes mellitus** and other **autoimmune disorders**. [3]

Approaches to therapeutic tolerance induction [3,68,72,73]

	Modality	Details	
Non-antigen specific	Monoclonal Antibodies	Depleting: • Anti-**CD52** • Anti-**CD4** • Anti-**LFA-2**	Non-depleting: • Anti-CD4 • Anti-**CD3** • **Anti-LFA-1** • **CTLA4-Ig** • Anti-**CD25**
•	Haematopoietic stem cell transplantation	Non-myeloablative	Myeloablative
	Mesenchymal stem cell transplantation		
	Regulatory T cell therapy	Non-antigen specific	Antigen-specific
	Low dose **IL-2** to expand regulatory T cells		
	Microbiome manipulation		
Antigen specific	Peptide therapy	Subcutaneous, intradermal, transmucosal (oral, inhaled) Tolerogenic dendritic cells, liposomes and nanoparticles	
	Altered peptide ligands		

Allergen immunotherapy

- It has been stated that immunotherapy could also be utilised to treat **allergies**. [3]
- While allergy treatments (such as **antihistamines** or **corticosteroids**) are used treat allergic symptoms, it has been pointed out that immunotherapy could reduce sensitivity to **allergens**, which lessens its severity. [3]

- It has been pointed out that allergen immunotherapy could also be referred to as allergen desensitization or hypo-sensitization. [3,74]
- It had also been stated that immunotherapy might produce long-term benefits. [3,75]
- Immunotherapy is stated to be partly effective in some people and ineffective in other people, but immunotherapy offers people with allergies a chance to reduce or stop their symptoms.[3]
- It has been documented that subcutaneous allergen immunotherapy was first introduced in 1911 through the postulate that people with hay fever were sensitive to pollen from grass. A process was developed to create an extract by drawing out timothy pollen in distilled water and then boiling it. This was injected into patients in increasing doses to help alleviate symptoms. [3,76]
- Allergen Immunotherapy is stated to be indicated for people who are extremely allergic or who cannot avoid specific **allergens** and when there is evidence of an IgE-mediated reaction which correlates with allergen symptoms. [3] These IgE-mediated reactions could be identified through a blood IgE test or skin testing. [3]
- It had been pointed out that if a specific IgE antibody is negative, there is no evidence that allergen immunotherapy would be effective for that patient. Nevertheless, there are risks associated with allergen immunotherapy as it is the administration of an agent the patient is known to be highly allergic to. It has been pointed out that patients are at increased risk of fatal anaphylaxis, local reaction at the site of injection, or life-threatening systemic allergic reactions. [3,74]
- A promising approach to the treatment of food allergies is stated to be the use of **oral immunotherapy** (OIT). OIT is stated to consist of a gradual exposure to increasing amounts of allergen which could lead to the majority of subjects tolerating doses of food sufficient to prevent reaction on accidental exposure. [3,77] Dosages of **oral immunotherapies** increase over time, as the person becomes desensitized. This technique has been tested on infants to prevent peanut allergies. [3,78]

Helminthic therapies

- It had been pointed out that **Whipworm ova** (Trichuris suis) and **hookworm** (Necator americanus) had been tested for immunological diseases and allergies, and had proved beneficial on multiple fronts, yet it is not entirely understood. [3]
- It had also been stated that scientists had found that the immune response that is triggered by the burrowing of hookworm larvae to pass through the lungs and blood so the production of mast cells and specific antibodies are now present. They also reduce inflammation or responses ties to autoimmune diseases, but despite this, the hookworm's effects are considered to be negative typically. [3,79]
- It had been stated that helminthic treatment had been investigated as a treatment for relapsing remitting **multiple sclerosis**, [3,80] Crohn's disease, [3,81,82,83] allergies and asthma. [3,84]
- It had also been stated that whilst there is much to be learned about this, many researchers had the opinion that the change in the immune response is thanks to the parasites shifting to a more anti-inflammatory or regulatory system, that would in turn decrease inflammation and self-inflicted immune damage as seen in Crohn's and multiple sclerosis. [3] It had also been documented that specifically: MS patients saw lower relapse rates and calmer symptoms in some cases when experimenting with helminthic therapy. [3,85] Hypothesized mechanisms had been documented to include: re-polarisation of the T_h1 / T_h2 response [3,86] and modulation of dendritic cell function.[3,87,88] The helminths downregulate the pro-inflammatory T_h1 cytokines, **interleukin-12** (IL-12), **interferon-gamma** (IFN-γ) and **tumour necrosis factor-alpha** (TNF-α), while promoting the production of regulatory T_h2 cytokines such as **IL-10**, **IL-4, IL-5** and **IL-13**. [3,86,89]
- It had been iterated that co-evolution with helminths had shaped some of the genes that are associated with **interleukin** expression and immunological disorders, such **Crohn's disease**, **ulcerative colitis** and **celiac disease**. [3] It has been advised that: Helminths' relationship to humans as hosts should be classified as mutualistic or **symbiotic**. [3,90] It had been explained that in some ways, the relationship is symbiotic because the worms themselves need the host (humans) for survival, because this body supplies them with nutrients and a home. [3] It had also been pointed out that from another perspective, it could be reasoned that it is mutualistic, being that the above information about benefits in autoimmune disorders continues to remain true and supported. [3] Also, some authors had said that the worms could regulate gut bacteria. [3,91] Another possibility is stated to be one of this being a parasitic relationship, arguing that the possible risks of anaemia and other disorders outweighs the benefits, yet this is significantly less supported, with the research alluding to the mutualistic and symbiotic approach being much more likely. [3]

Other reported studies related to immunotherapy can be found in: [91-98].

[B] Miscellaneous Narrations And Discussions From Some Case Reports, Case Series, And Studies Related To Immunotherapy Of Prrostate Cancer.

Chen et al. [99] made the ensuing iterations:

- Incidences of rectal infiltration by prostate cancer (PCa) are reported to afflict up to 12% of patients studied.
- PCa invading the rectum is prone to cause difficulty in defecation, bloody stool and pain, emanating in a decline in patients' quality of life.
- Unfortunately, the prognosis for these patients has tended to be poor and the survival period is short.
- Total pelvic exenteration (TPE) has been shown to mitigate pain and improve symptoms such as defecation difficulty, dysuria, and haematuria. Nevertheless, majority of patients still harbour residual tumour and fail to exhibit any improvement in long-term survival.

Chen et al. [99] reported a case of PCa invading the rectum with focal neuroendocrine differentiation, which was characterized by clinical presentations of defecation difficulties and rectal bleeding. A TPE procedure was undertaken, with a whole exome sequencing (WES) assay indicating that the patient had exhibited a high tumour mutation burden (TMB) and high microsatellite instability (MSI-H). Subsequently, the patient received androgen deprivation therapy (ADT) which was combined with adjuvant immunotherapy following the procedure. At his subsequent six-year follow-up, no local or systemic recurrence was observed, and his serum prostate-specific antigen (PSA) level had remained undetectable. Chen et al. [99] made the ensuing conclusions:

- This disease entity remains relatively rare in the prognosis.

- It is of utmost importance to establish an accurate differential diagnosis, which necessitates the collaboration of multiple disciplinary teams and the performance of requisite tests, including immunohistochemistry staining studies and genetic testing.

Shi et al. [100] made the ensuing iterations:

- Cytotoxic T lymphocyte (CTL) immunotherapy is an autologous cellular immune therapy which had been approved for treating patients with malignant tumours.
- Nevertheless, there is still limited information regarding the impact of CTL on metastatic prostate cancer (PC) patients with bone metastatic lesions.

Shi et al. [100] reported an 82-year-old male patient, who had manifested with interrupted micturition, dysuria, and significant dysuria on November 24, 2014. He underwent trans-urethral resection of the prostate (TURP) and postoperative pathological examination of the prostatic chips showed prostatic adenocarcinoma, and he underwent a SPECT/CT scan which demonstrated multiple bone metastases. In addition, his serum prostate specific antigen (PSA) and free PSA (FPSA) levels were 54.54 μg/mL and 2.63 μg/mL, respectively, at the beginning of his treatment. His main diagnosis was adenocarcinoma of prostate gland and multiple bone metastases. He received 30 cycles of alloreactive CTL (ACTL) immunotherapy regularly. Over the course of his 2-year treatment, he exhibited diminished bone metastasis which was accompanied by a marked reduction of serum PSA and FPSA from 54.54 and 2.63 μg/ml to 0.003 and <0.006 μg/ml, respectively. Shi et al. [] concluded that:

- Their clinical observations had demonstrated that CTL immunotherapy is a viable treatment option for PC patients, particularly those with bone metastatic lesions and high serum levels of PSA and FPSA.

Idossa et al. [101] made the ensuing iterations:

- High-grade treatment-emergent neuroendocrine prostate cancer (T-NEPC) is a rare sub-type of prostate cancer which has limited therapeutic options and which is associated with poor prognosis.
- Understanding biomarkers that influence the efficacy of immune checkpoint inhibitors (IO) is vital to form a better therapeutic arsenal for these patients.

Idossa et al. [101] reported an impressive response to IO combination immunotherapy with ipilimumab plus nivolumab (Ipi/nivo) in a patient who had T-NEPC who had failed standard treatment approaches. The patient was manifesting signs of a rapid decline in quality of life despite his serum prostate-specific antigen (PSA) levels remaining undetectable and he had no previous response to standard therapies. The results of the next-generation sequencing DNA analysis demonstrated the presence of intermediary tumour burden, an ATM mutation and a rare SF3B1 (G742D) mutation, and had served as rational for IO therapy in the patient. Idossa et al. [101] concluded that:

- Their reported case had highlighted the genetic profile of tumour with a rare combination of ATM and SF3B1 mutations that could be further explored as biomarkers for IO therapy in T-NEPC and other tumour types.

Sharan et al. [102] made the ensuing iterations:

- Prostate cancer along with colorectal and lung cancers accounts for 42% of cancer cases in men globally.
- It is the first cancer indication for which utilization of active immunotherapy, Sipuleucel-T (Provenge) was granted by the FDA in 2010.
- They had presented a case of prostate carcinoma and the tumour remission which was observed after administration of a personalised Dendritic cell vaccine (APCEDEN).

Sharan et al. [102] reported a 58 years old Caucasian male, who was diagnosed with prostate carcinoma with GLEASON score 8. The patient had previously been diagnosed with Renal Cell Carcinoma (RCC) in 1996 and he had undergone nephrectomy of the right kidney. He had PET CT scan, which demonstrated multiple intensely PSMA avid lesions which were identified in both lobes of the prostate gland with SUVmax -28.3 and the prostate gland measuring 3.2 × 3.2 cm displaying maximum dimensions. Pathology examination of his prostate biopsy specimens which were obtained by FNAC followed by PETCT confirmed CA Prostate and the diagnosis was further supported by his increased serum PSA level. He underwent personalised Dendritic Cell Immunotherapy APCEDEN regimen of six doses biweekly, in a time frame of 3 months were given both via intravenous and intradermal route. Six months pursuant to completion of APCEDEN, the patient was administered 6 booster shots for 6 months. Progressive remission of carcinoma was observed together with reduction in his PSA and Testosterone levels. He had PET CT scan which demonstrated decline in PSMA avidity by 50% with SUVmax -14.0 and normal size and shape of prostate gland. Sharan et al. [102] made the ensuing discussions, declaration of lessons to learn and conclusions:

- Carcinoma of the prostate gland is the second most common cancer in men with majority of them exhibiting locally advanced disease.
- Apparently 20% to 30% of them are categorized as relapsed cases after various treatment interventions.
- Modulating immune system is an emerging treatment which is termed as Immunotherapy and potentiates the killing cancer cells via immune activation.
- Interestingly, prostate cancer is slow growing and it does provide the scope and time to mount an anti-tumour response that makes it an attractive target for immunotherapy.
- Their reported case had demonstrated the efficacy of APCEDEN Immunotherapy regimen resulting in a significant disease remission benefiting the patient

Reed-Perino et al. [103] made the ensuing iterations:

- While checkpoint inhibitor therapy had revolutionized the therapy landscape of some solid tumours, it has demonstrated limited efficacy in metastatic castration-resistant prostate cancers (mCRPC).
- A small (about 3% to 5%) but clinically distinct subset of mCRPC tumours have a DNA mismatch repair deficiency (dMMR) and develop a hypermutation phenotype with elevated tumour mutational burden and high microsatellite instability (MSI-H).
- Retrospective analyses had demonstrated dMMR/MSI-H status to be a predictive biomarker for response to pembrolizumab in prostate tumours.

Reed-Perino et al. [103] reported a case of a patient with mCRPC harbouring a somatic dMMR who had progressed on pembrolizumab after an initial response. He enrolled on a clinical trial with JNJ-081, a prostate-specific membrane antigen-CD3 bispecific T-cell engager antibody and had experienced a partial response with the course complicated by cytokine release syndrome. On progression, he was re-initiated on pembrolizumab and he experienced an exceptional second response, with his prostate-specific antigen falling from a high level of 20.01 to undetectable level after 6 weeks and his serum PSA LEVEL HAD

remained undetectable for more than (>)11 months. Reed-Perino et al. [103] concluded that:

- To their knowledge, their reported case represented the first reported case of bispecific T-cell engager-mediated re-sensitization to checkpoint inhibitor therapy in any cancer.

Cabel et al. [104] made the ensuing iterations:

- Prostate cancer is one of the most common cancers in men and the fourth leading cause of cancer mortality in the world.
- Even though major progress had been achieved over the last years for patients with metastatic castrate-resistant prostate cancer (mCRPC), thanks to next-generation androgen receptor axis targeted drugs, taxanes, and bone-targeted agents, immunotherapy had not been widely approved and utilised for the treatment of prostate cancer.
- Two large studies with ipilimumab, an anti-CTLA-4 (cytotoxic T-lymphocyte antigen 4) antibody had reported improved progression-free survival, but not statistically improved overall survival at the primary analysis (CA184 043 and CA184 095).

Cabel et al. [104] reported on two patients who had received ipilimumab in these trials and who were still in long-term complete remission with a follow-up of 64 months and 52 months respectively after the commencement of ipilimumab. Immunohistochemical staining for hMLH1, hMSH2, hMSH6 and PMS2 was undertaken on archival prostate biopsy samples from one of the two patients; they exhibited normal protein expression. Interestingly for this patient, a high CD3+ and CD8+ T cell infiltration was identified on archival prostate biopsies as well as Treg FoxP3+ T cells. Cabel et al. [104] concluded that:

- Ipilimumab produces clinical activity in patients with CRPC, including very long responders with no detectable residual disease.

Ashraf et al. [105] made the ensuing iterations:

- Prostate cancer (PCa) is the second leading cause of cancer-causing death in the United States of America (USA).
- As the most common malignancy in men, it is pertinent to explore whether novel immunotherapies might improve the quality of life and overall survival (OS) of patient populations.
- They had undertaken a systematic review and post hoc analysis curates of a patient-by-patient pool of evidence adhering to PRISMA Statement 2020 guidelines.

Ashraf et al. [105] reported their findings as follows:

- In total, 24 patients were analysed for treatment history and associated variables including serum prostate-specific antigen (PSA) levels at the time of diagnosis and post-treatment, Gleason score, secondary tumour locations, success/failure of therapy, and post-immunotherapy outcomes including OS.
- In total, 10 types of immunotherapies were identified with Pembrolizumab (among 8 patients) followed by IMM-101 (among 6 patients) being the most commonly administered.
- The mean overall survival (OS) for all patients was 27.8 months (24 patients) with the relatively highest mean OS reported with IMM-101 (56 months) followed by tumour-infiltrating lymphocytes (30 months).

Ashraf et al. [105] concluded that:

Their research article had provided critical insights into the evolving landscape of immunotherapies being tested for PCa and had addressed gaps in oncological research to advance the understanding of PCa.

Schirrmacher et al. [106] reported the case of a patient with hormone-refractory metastatic prostate cancer who had failed standard treatment, but then achieved complete remission ensuing combined therapy with local hyperthermia (LHT), Newcastle disease virus and dendritic cell (DC) vaccination, which was an unusual combination. In August 2005, the patient had undergone a radical prostatectomy. Despite standard treatment, the patient subsequently developed progressive bone metastases and had stopped conventional therapy in June 2007. Commencing in October 2007, he was treated with LHT, oncolytic virotherapy and DC vaccination. His serum prostate-specific antigen (PSA)-levels, with the highest level of 233.8 ng/ml in January 2008, had decreased to 0.8 ng/ml in late February 2008. In March 2008, a reduction in his bone metastases could be identified by positron emission tomography/computed tomography. Since then, his PSA levels had remained low and the patient was doing well. The treatment had induced a long-lasting antitumor memory T-cell response. This possibly had explained the long-term effectiveness of this novel experimental combined treatment approach.

Ferreira Bruzzi Porto et al. [107] made the ensuing iterations:

- High-grade treatment-emergent neuroendocrine prostate cancer (T-NEPC) is a rare subtype of prostate cancer with limited therapeutic options and poor prognosis.
- Understanding of biomarkers which influence the efficacy of immune checkpoint inhibitors (IO) is vital to form a better therapeutic arsenal for these patients.

Ferreira Bruzzi Porto et al. [107] described an impressive response to IO combination immunotherapy with ipilimumab plus nivolumab (Ipi/nivo) in a patient who had T-NEPC and who had failed standard treatment approaches. The patient was demonstrating signs of a rapid decline in quality of life despite his serum prostate-specific antigen levels remaining undetectable and he had no previous response to standard therapies. The results of his next-generation sequencing DNA analysis had demonstrated the presence of intermediary tumour burden, an ATM mutation and a rare SF3B1 (G742D) mutation, and served as rational for IO therapy in this patient. Ferreira Bruzzi Porto et al. [107] concluded that:

- Their reported case had highlighted the genetic profile of tumour with a rare combination of ATM and SF3B1 mutations that could be further explored as biomarkers for IO therapy in T-NEPC and other tumour types.

Zhang et al. [108] made the ensuing iteration:

- Epithelioid hemangioendothelioma is a rare vascular malignancy, and currently, there is no standard treatment regimen for this disease and existing treatment options do have limited efficacy.

Zhang et al. [108] reported a patient with lung and lymph node metastases from prostate epithelioid hemangioendothelioma who had achieved a significant partial response. This was accomplished via alternating nivolumab therapy with ipilimumab and liposomal doxorubicin, resulting in a progression-free-survival more than 6 months up to the time of the report of his case. The treatment was well-tolerated throughout. Zhang et al. [108] made the ensuing conclusions:

- Their report had suggested that dual immunotherapy alternating with anti-PD-1antibody plus doxorubicin might be a potential treatment modality for epithelioid hemangioendothelioma.
- Nevertheless, larger sample studies are necessary to ascertain the effectiveness of this treatment strategy and it is pivotal to continue monitoring this patient in order to sustain progression-free survival and overall survival.

Fei et al. [109] made the ensuing iterations:

- Primary small cell neuroendocrine carcinoma of the prostate is very rare, highly aggressive, and has a very poor prognosis, with an overall survival typically not exceeding one year.
- Standard treatment is generally based upon the regimen for small cell lung cancer (SCLC), with guidelines recommending etoposide combined with cisplatin (EP regimen) as the first-line treatment.
- Nevertheless, their therapeutic effects are limited.
- For primary small cell neuroendocrine carcinoma of the prostate gland which has failed the EP regimen treatment, there is currently a lack of relevant treatment methods.

Fei et al. [109] reported a case of small cell neuroendocrine carcinoma of the prostate gland with multiple metastases, whose disease had rapidly progressed despite receiving EP and second-line systemic chemotherapy. The patient was then administered a combination of anlotinib and tislelizumab. Following this treatment, the patient's symptoms were controlled, his tumour marker levels had decreased, and his radiology-imaging showed significant improvement. The patient had a progression-free survival time of more than 22 months and he had continued to receive treatment. Fei et al. [109] concluded that:

- Their reported case had presented the first report of utilisation of anlotinib combined with tislelizumab for the treatment of primary small cell neuroendocrine carcinoma of the prostate, providing a new therapeutic option for patients with this disease.

Rehman et al. [110] made the ensuing iterations:

- Prostate cancer is the most commonly diagnosed cancer in men globally, making up 21% of all cancer cases.
- With 345,000 deaths per year owing to the disease, there is an urgent need to optimize prostate cancer care.

Rehman et al. [110] undertook a systematic review which collated and synthesized findings of completed Phase III clinical trials administering immunotherapy; a current clinical trial index (2022) of all ongoing Phase I–III clinical trial records that were also formulated. Rehman et al. [110] summarized their discussions as follows:

- A total of four Phase III clinical trials with 3588 participants were included administering DCVAC, ipilimumab, personalized peptide vaccine, and the PROSTVAC vaccine.
- In this original research article, promising results were seen for ipilimumab intervention, with improved overall survival trends.
- A total of 68 ongoing trial records pooling in 7923 participants were included, spanning completion until June 2028.
- Immunotherapy is an emerging option for patients with prostate cancer, with immune checkpoint inhibitors and adjuvant therapies forming a large part of the emerging landscape.
- With a variety of ongoing trials, the characteristics and premises of the prospective findings would be key in improving outcomes in the future.

Conclusions

- The immune microenvironment of prostate cancer and the various strategies are currently being developed to promote immunotherapy of prostate cancer.
- By means of immune checkpoint blockade, induction of tumour cell ICD, reversal of the immunosuppressive TME, tumour vaccine therapy, immune adjuvants, CAR-T therapy, and overcoming penetration barriers, it has been found that there is a potential to sensitize prostate cancer to immunotherapy, transforming it from an immunosuppressive "cold" tumour to an immune-responsive "hot" tumour.
- Understanding the connections between treatment of prostate cancer outcomes and antigen presentation, the activation of $CD8^+$ T lymphocytes, the maintenance of cytotoxic function, and the release of related pro-inflammatory cytokines provides necessary insights for the design of novel immunotherapy approaches for prostate cancer.
- Despite some progress which had been made in prostate cancer immunotherapy over the recent years, there are still many challenges in enhancing clinical immunotherapy outcomes.
- irAEs are a significant concern in immunotherapy.
- Uncontrolled activation of immune cells could lead to excessive inflammatory responses, resulting in damage and inflammation of normal tissues, such as in hepatitis, colitis, and pneumonitis, potentially affecting any organ or system.
- The severity of irAEs is based on the type and dose of ICIs administered, and combination with other therapies has a higher incidence rate.
- Guidelines recommend the discontinuation of treatment upon the occurrence of irAEs (grade ≥2), which can be handled and treated according to the guidelines.
- Further research and clinical trials are required to validate the safety and efficacy of these new methods and materials. Nevertheless, during the treatment process, it is important to take into consideration the heterogeneity of patients and to adopt a combination of multiple treatment options to promote immunotherapy for prostate cancer, thereby offering favourable treatment outcomes for patients with advanced or metastatic tumours
- Immunotherapy in combination with other therapies had been demonstrated to be effective in the management of some cases of adenocarcinoma of the prostate gland as well as in other cell-types of prostate cancer. Nevertheless, in some reported cases of metastatic or advanced prostate cancer, immunotherapy had been found not to be effective.

Conflict Of Interest - NIL

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