Review

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Contemporaneous and upcoming trends in immunotherapy for prostate cancer: review

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Abstract

Prostate cancer (PCa) is the most common cancer in men worldwide. It affects more than 1.4 million men worldwide and kills up to 37 5000 people. PCa is routinely managed with chemotherapy and androgen deprivation therapy, but the success rate of these treatments is unsatisfactory. Immunotherapy is a novel method of treating different types of cancers, and it utilizes the body's own immune system to fight cancer. Different types of cancer respond differently to immunotherapy, with some showing excellent responses, while others do not show very satisfactory responses. PCa is known to be an immunologically cold tumor, such that conventional immunotherapy does not work as effectively as it works in other cancers. In the past decade, multiple studies and trials have been conducted to test different types of therapies, ranging from immune checkpoint inhibitors to anticancer vaccines to anticancer cytokines. Even after many studies, there is still a drug to be discovered that can completely cure any stage of PCa. Recent immunotherapeutic drug trials have started using immunotherapy in conjunction with chemotherapy and radiotherapy and have shown promising results. In this paper, the authors present a comprehensive overview of the currently used immunotherapeutic drugs as well as emerging immunotherapies, including modalities of combination immunotherapy with radiotherapy and chemotherapy. This review can help readers gain the latest knowledge about emerging trends in the current immunotherapy landscape for the treatment of PCa, as well as a general overview of the already used immunotherapy drugs for PCa.

Keywords: castration-resistant, immunization, immunotherapy, prostatic neoplasms, radioimmunotherapy

Introduction

Prostate cancer (PCa) is the most common genitourinary tumor in men worldwide, with cases exceeding 1.4 million and more than 375 000 deaths. Despite anticancer treatment, patients with a high International Society of Urological Pathology grade show progression and metastasis, with a poor prognosis[1]. Androgen deprivation therapy (ADT), consisting of luteinizing hormone-releasing hormone agonists or antagonists, is usually administered to patients with metastatic or recurrent disease[1]. Although effective in suppressing androgen signals, many PCa patients eventually develop castration-resistant PCa (CRPCa), with a high rate of metastatic disease and a poor prognosis[2].

HIGHLIGHTS

- Prostate cancer is the world's most common cancer in men. It affects more than 1.4 million men worldwide and kills up to 37 5000 people worldwide.
- Chemotherapy as well as immunotherapy play an evolving role in the management of Prostate cancer.
- Prostate carcinoma lacks neoantigens as opposed to other cancers and has an immunologically cold tumor microenvironment making it hard for immunotherapeutic drugs to mount an effective immune response against it.
- CAR-T cell therapy can be used to genetically engineer the antigens of our choice, which can help fight cancer.

Chemotherapy and immunotherapy have evolved in their roles in PCa management. Since 2004, the chemotherapy drug docetaxel has been the standard therapy but has shown minimal survival benefit[3]. Recent data from two landmark trials (STAMPEDE and CHAARTED) showed that if docetaxel is combined with ADT in patients who have not received ADT previously, there is more than a year of survival benefit when compared to conventional ADT alone[4,5].

Immunotherapy was introduced for men with metastatic castration-resistant PCa (mCRPC) earlier because of the limited therapeutic options available for PCa patients[6]. Immunotherapy refers to a treatment that uses the human immune system to fight neoplastic cells. The outcomes of immunotherapy in the

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treatment of PCa have been optimistic, but not revolutionary. One major reason for the lack of success of immunotherapy in PCa is that it is a 'cold' tumor, meaning the immune system is not sufficiently activated against it to eradicate it. This may be due to an imbalance between the killer cells (cytotoxic T cells) of the immune system and immune response 'turn-off switch' (T regulatory) cells infiltrating the cancer cell environment, such that the majority of cells suppress the immune response more than those killing the tumor[7].

PCa cells also express an overwhelmingly large amount of 'don't eat me' antigens (PD-1 and CTLA-4) on their surface, which exhaust immune cells like the cytotoxic and antigen-presenting dendritic cells (DC), making them ineffective in the battle against cancer. There is also a preponderance of CD4 + T lymphocytes and M2 macrophages in the immune system against PCa to secrete suppressive cytokines, which further suppresses the antitumor response of the immune system and helps the tumor gain access to more nutrients by favoring its angiogenesis. Studies have shown that the more advanced the tumor becomes, the colder it becomes, evading the immune system and making it harder to treat[7].

Grand research efforts have been ongoing in the field of immunotherapy for PCa over the past decade, with efforts to stimulate a patient's immune system to fight cancer. There are current and emerging trends in the field of PCa immunotherapy, as discussed by some of the most recent clinical trials. Researchers have attempted to use immunotherapy in conjunction with hormonal therapy, combining a cocktail of immunotherapeutics to work in harmony and eradicate PCa. Synthesizing vaccines specifically designed to do this is another method by which researchers have attempted to control and eradicate PCa.

Methods

Literature search strategy

A comprehensive literature search was conducted using electronic databases, including PubMed, Scopus, and Web of Science, to identify studies published between January 2000 and February 2023 on the use of immunotherapy in PCa. The following search terms were used: 'immunotherapy', 'prostate cancer', 'immune checkpoint inhibitors', 'CAR-T cell therapy', 'vaccine therapy', 'prostate-specific antigen', 'androgen receptor', and 'cytokines'. The search was limited to studies published in the English language.

Inclusion criteria

Studies were included if they met the following criteria: focused on the use of immunotherapy in PCa, included human subjects, published in peer-reviewed journals, reported on clinical trials or observational studies, and provided relevant outcomes related to the use of immunotherapy in PCa.

Data extraction

Two reviewers independently screened articles based on their titles and abstracts to identify potentially relevant studies. The full texts of potentially relevant articles were then reviewed to determine whether they met the inclusion criteria. Data were extracted from each included study, including the study design, sample size, patient characteristics, intervention(s), and relevant outcomes.

Data synthesis

A narrative synthesis approach was used to summarize the findings of the included studies. Data were synthesized by examining similarities and differences in study design, patient characteristics, interventions, and outcomes across studies. The results were presented descriptively and organized according to the intervention type.

The preferred reporting items for systematic reviews and meta-analyses (PRISMA)[8] flowchart is displayed in Figure 1.

Results

The review of the literature revealed that immunotherapy, including checkpoint inhibitors, cytokines, and therapeutic cancer vaccines, holds promise as a potential therapeutic strategy for PCa. Immunotherapy has emerged as a promising approach for the treatment of PCa, offering potential improvements in therapeutic strategies and patient outcomes. The classification of immunotherapies into checkpoint inhibitors, cytokines, and therapeutic cancer vaccines has provided a framework for their application. Clinical trials and studies on various malignancies have shown positive results with immunotherapy, indicating its potential efficacy in PCa. Understanding the complex interactions between tumor cells and the tumor microenvironment, particularly with infiltrating macrophages and lymphocytes, is crucial for successful management of mCRPCa. Resistance mechanisms developed by PCa cells, such as evasion of immune surveillance and blocking of immune checkpoints, can be targeted by immunotherapeutic agents. The autologous vaccine Sipuleucel-T, targeting prostatic acid phosphatase (PAP), has demonstrated promising outcomes in mCRPCa patients, including improved overall survival (OS) and reduced mortality rates. Although costly, Sipuleucel-T has gained approval from the Food and Drug Administration, which highlights the importance of early screening and accurate diagnosis in optimizing its benefits. Monoclonal antibodies, such as ipilimumab, have also shown potential in PCa immunotherapy by blocking CTLA-4 and enhancing immune responses. Manipulation of cytokines has been explored to stimulate robust antitumor immune responses. Further research and clinical trials are warranted to harness the full potential of immunotherapy in PCa treatment. Immunotherapy holds promise as a potential therapeutic strategy for PCa, with several emerging approaches being investigated. Combination therapies, such as the use of chemotherapy drugs and immune checkpoint inhibitors, have shown efficacy in managing mCRPCa while minimizing toxicity. Genetic engineering techniques, such as CAR-T cells targeting specific receptors on PCa cells, have also shown promising results. Additionally, the use of immune checkpoint inhibitors in combination with other immunotherapeutic drugs or radiotherapy has demonstrated potential in increasing disease control rates (DCR). Vaccines and personalized DC therapies have also been explored for their ability to induce immune responses and reduce the risk of disease recurrence. Further research and clinical trials are warranted to evaluate the safety and efficacy of these emerging immunotherapeutic strategies for PCa treatment.

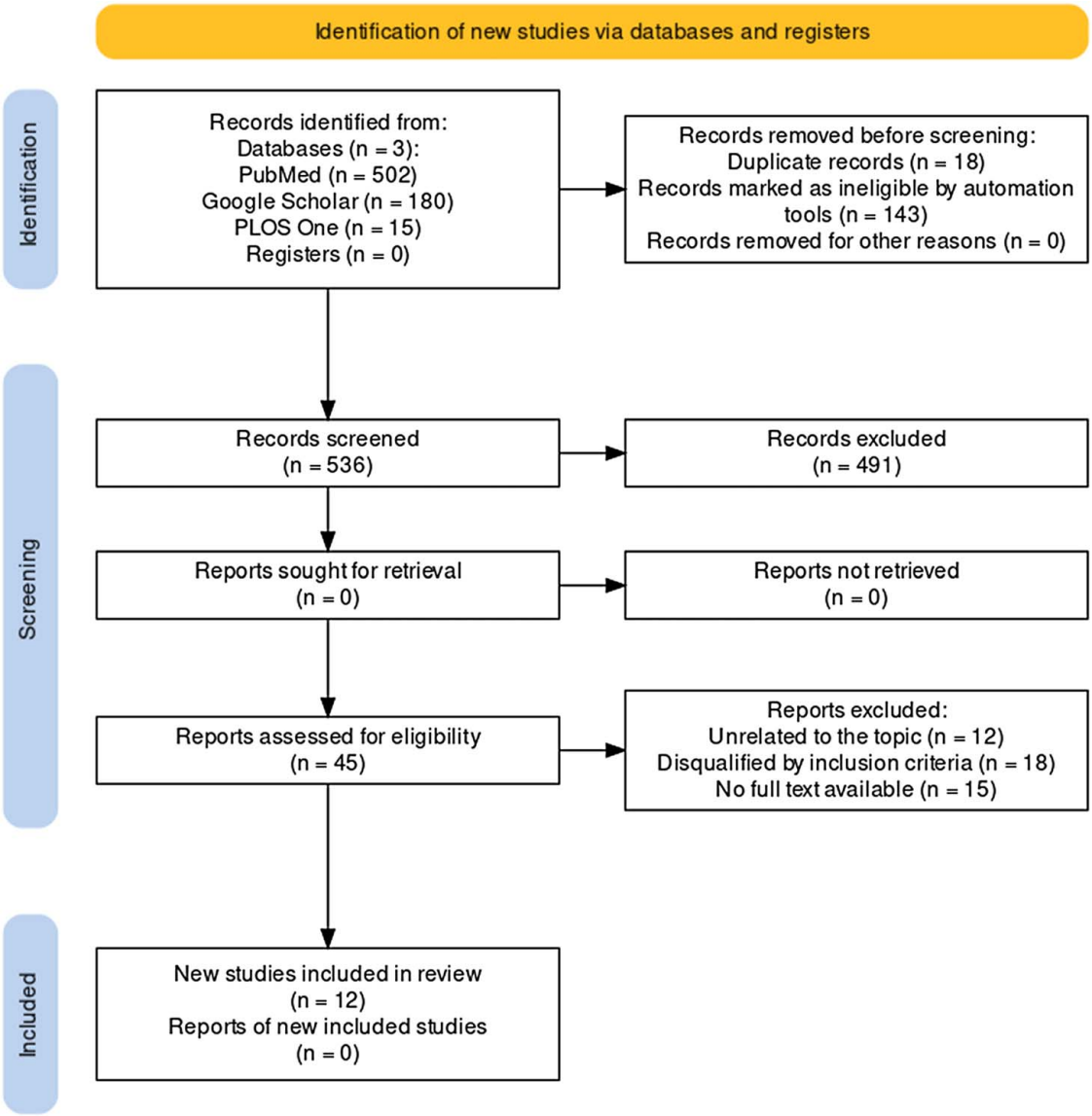

Figure 1. Preferred reporting items for systematic reviews and meta-analysis (PRISMA) flowchart.

Discussion

Currently used immunotherapy

Immunotherapy has shown promising results and will likely improve therapeutic strategies for patients with PCa. This will undoubtedly lead to increased quality and quantity of life.

Immunotherapies are generally classified into one of three categories: checkpoint inhibitors, cytokines, or therapeutic cancer vaccines[9] from review of the literature. We already know that immunotherapy has been used in clinical trials with positive outcomes for other malignant neoplasms such as colon, lung, metastatic melanoma, and kidney cancer[10]. Prompt and successful management of mCRPCa can be achieved if we better understand the complexity of tumor cells and their interactions with the surrounding tumor microenvironment, particularly with infiltrating macrophages and lymphocytes[11]. As the cancer grows and progresses, the cancer cells develop a mechanism of evading the immune system by developing resistance to proapoptotic signals. This may be in the form of blocking the immune checkpoints in the PD-1, PD-L1, PD-L2, and CTLA-4 axes. PCa is a slow growing tumor that provides ample time for an immune response to be elicited even in patients with advanced disease. Therefore, PCa is an ideal target for cancer vaccines[12]. The Sipuleucel-T is an autologous vaccine. The patient's blood was collected and mononuclear cells were separated by leukapheresis[13]. The target of sipuleucel is the PAP. PAP is a glycoprotein enzyme that is synthesized in the prostate epithelium and increases significantly as cancer progresses to become more advanced in its course. PAP is also elevated in patients with PCa and bone metastasis and correlates with a poor prognosis. The immunotherapy for prostate adenocarcinoma treatment trial showed that treatment with sipuleucel-T resulted in a 4.1-month OS benefit. It also caused a 22% relative risk reduction of mortality in patients who had mCRPCa[14]. The data from immunotherapy for prostate adenocarcinoma treatment reveals

that the benefit is highest in patients who receive the vaccine while having a lower disease burden[12,15]. This indicates the importance of early screening and an appropriate diagnosis of PCa. A figure depicting the OS rates of patients using Sipuleucel-T and ipilimumab is shown in Figure 2.

Sipuleucel-T is approved by the Food and Drug Administration but it is highly costly with an incremental cost-utility ratio of US $283 000 per quality-adjusted life-year[16]. It was also observed that despite the survival benefits, only minimal antineoplastic responses were observed when patients received the vaccine. PCa responds differently to melanoma in response to anticancer vaccines. This is because vaccines seem to have minimal effects on the immunological microenvironment of tumors. Monoclonal antibodies also play an important role in PCa immunotherapy. The first monoclonal antibody (ipilimumab, Yervoy) was approved for melanoma treatment to improve survival and increase the antitumor efficacy of the immune system. It was directed against the control molecule, CTLA-4[17]. CTLA-4 is a protein receptor found on the membranes of T lymphocytes that downregulates the immune response. When CTLA-4 is activated by antigens, it decreases the immune response. Ipilimumab is a fully human monoclonal antibody that prevents this receptor to be activated and hence, prevents the downregulation of the immune response, which results in a more enhanced anticancer immunity, which plays a role in the context of PCa[18]. Kwon *et al.*[19] concluded that ipilimumab can prolong median OS in a select subset of patient's metastatic castration-resistant PCa lacking visceral disease and with favorable laboratory values. It has been shown that stimulation of the immune system by affecting the cytokines can produce strong antitumor immune responses[20]. For illustration purposes, a list of the latest Phase 3 clinical trials is shown in Table 1. This

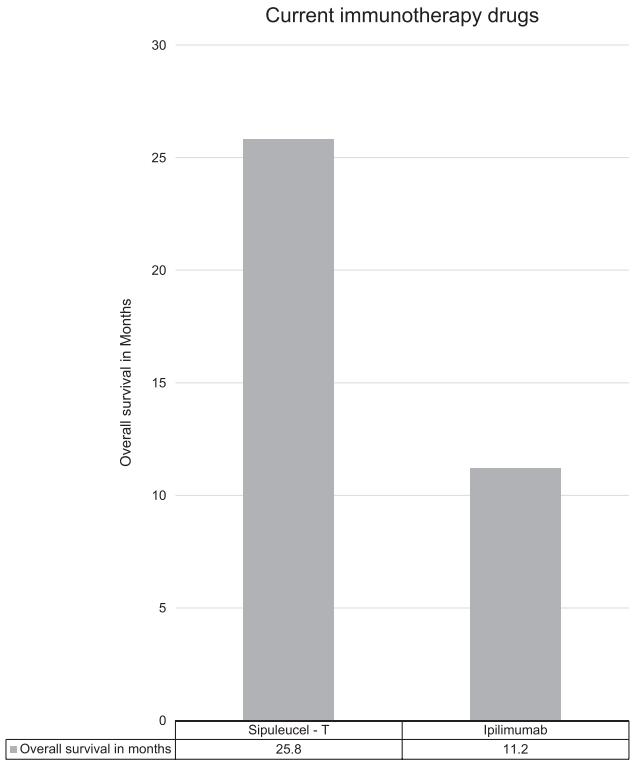

Figure 2. Overall survival due to currently used immunotherapy drugs.

Table 1
Phase 3 trials

Study	Trial name	Phase and status	Patient criteria	Number of patients	Drug	Primary endpoint	Outcome
Kantoff[14]	Sipuleucel-T immunotherapy for castration-resistant prostate cancer	Phase 3, completed	Men with mCRPC	512	Sipuleucel-T	Overall survival	Relative reduction of 22% in the risk of death as compared with the placebo group (hazard ratio, 0.78; 95% CI, 0.61–0.98; $P = 0.03$).
Kwon[19]	Ipilimumab versus placebo after radiotherapy in patients with metastatic castration-resistant prostate cancer that had progressed after docetaxel chemotherapy (CA184-043).	Phase 3, completed	Men with mCRPC	799	Ipilimumab	Overall survival	Median overall survival was 11·2 months (95% CI 9·5–12·7) with ipilimumab and 10·0 months (8·3–11·0) with placebo (hazard ratio [HR] 0·85, 0·72–1·00; $P = 0·053$). However, the assessment of the proportional hazard assumption showed that it was violated ($P = 0·0031$). A piecewise hazard model showed that the HR changed over time: the HR for 0-5 months was 1·46 (95% CI 1·10–1·95), for 5–12 months was 0·65 (0·50–0·85), and beyond 12 months was 0·60 (0·43–0·86).

narrative review can provide readers with up-to-date information on new trends in the present immunotherapy landscape for the treatment of PCa, as well as a detailed overview of currently available immunotherapy medications for PCa Figure 3.

Trials of emerging immunotherapeutics

Combination therapies can be efficacious for the treatment of PCa. They also have lower toxicity and in light of this Agarwal *et al.*[21] used a combination of a chemotherapy drug cabozatenib and an immune checkpoint inhibitor atezolizumab combination in patients who had mCRPCa. Patients with mCRPCa have very limited options of therapy after failing novel hormonal therapy; therefore, they carried out this study in those patients and achieved an objective response rate of 23% (95% CI 17–32; 31 of 132 patients), which is encouraging and makes it a safe combination to use. Genetic engineering can also be used to treat patients with PCa. CAR-T cells are genetically engineered cells of the immune system that can be used to target specific receptors on the target of choice[22]. Narayan *et al*[23] used CAR-T cells in the treatment of mCRPCa. CAR-T cells have not been successful in solid cancers because of the tumor microenvironment, which does not allow these cells to effectively mount an immune response against cancer. Solid cancers such as PCa secrete high levels of the immune 'switch-off' molecule TGF-β. When immune cells enter the cancer environment, TGF-β binds to the receptor on the immune cells, signaling it to switch-off and thus inhibit their function. Using this information, they created genetically modified T cells that lacked the TGF-β receptor and targeted the prostate-specific membrane receptor (PSMA), which is heavily expressed in PCa cells. They found that this therapy caused greater than 98% reduction in prostate-specific antigen (PSA) and only five of the 13 patients developed grade greater than or equal to 2 cytokine release syndrome, which is a promising and encouraging result. CAR-T cells also activate the patient's immune system against the tumor, increasing the antitumor response, making it a safe and feasible therapy. Other combinations have also been investigated. Another method to treat PCa is to combine different immunotherapeutic drugs. Lymphocyte-activation gene 3 is a T cell receptor that negatively regulates T cell activation. Spartalizumab is an immune checkpoint inhibitor. Schöffski *et al*[24] enrolled patients with mCRPCa and subjected them to ieramilimab with spartalizumab therapy. Antitumor activity was observed in the combination arm, and ineramilimab was well-tolerated as monotherapy and in combination with spartalizumab. The toxicity profile of ieramilimab in combination with spartalizumab was comparable to that when only spartalizumab was used alone, but with the combination, the antitumor activity was modestly increased. Yu *et al*[25] in a Phase 1/2 trial reported that a combination of a glucocorticoid with an immune checkpoint inhibitor and chemotherapy showed

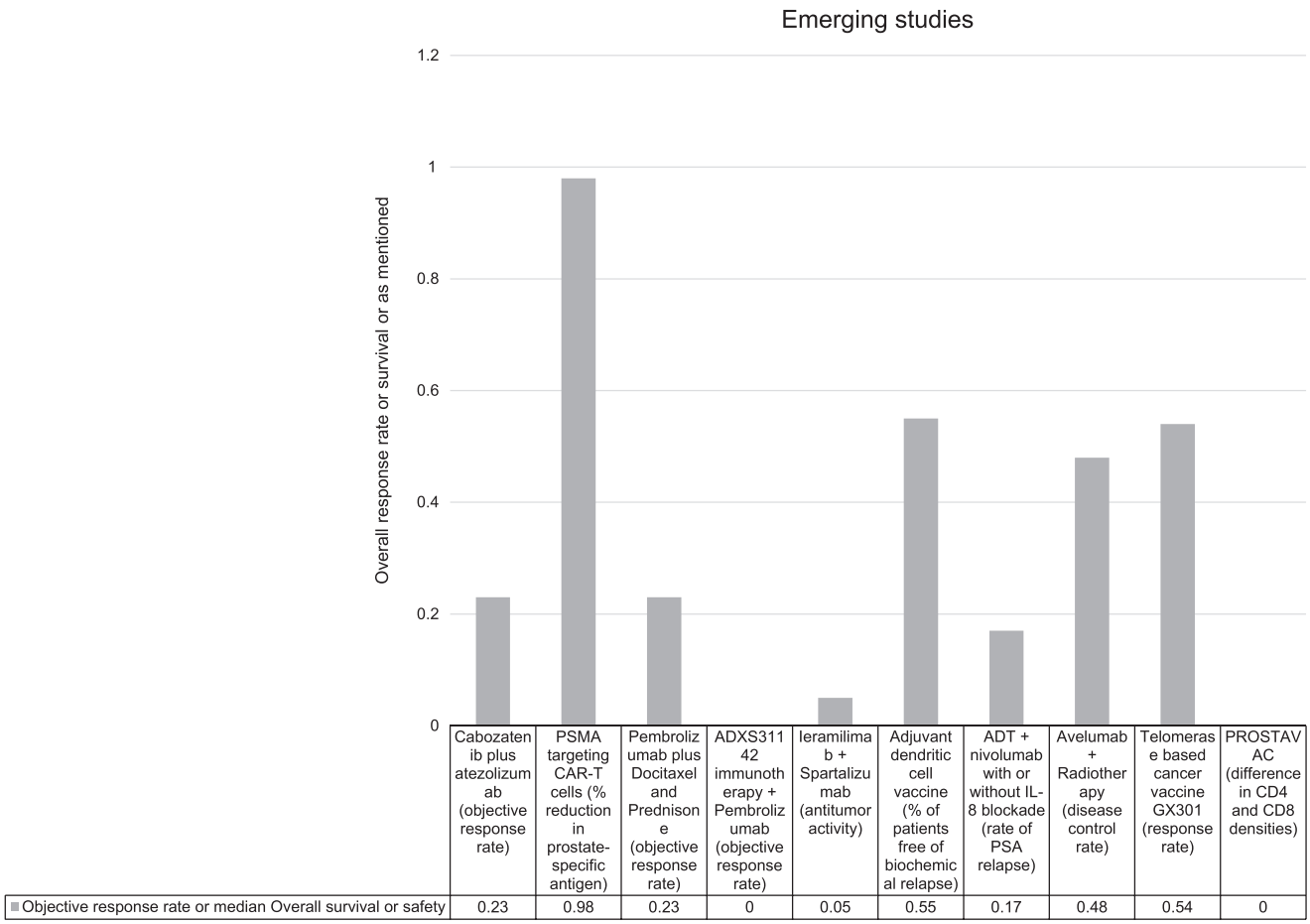

Figure 3. Emerging studies.

antitumor activity and manageable safety in patients with mCRPCa who failed conventional chemotherapy. Immense approaches have been used in vaccine-based immunotherapy for PCa treatment in the last decade. ADXS31-142 is an attenuated Listeria monocytogene-based immunotherapy. It targets PSA. It is being evaluated as a monotherapy and in combination with pembrolizumab for mCRPCa. Stein *et al.*[26] enrolled men with mCRPCa who have progressed after 2 or fewer prior systemic treatment regimens in the metastatic setting. Promising OS benefit was observed in combination-treated patients who had received prior docetaxel (16.0 months, 95% CI:6.4–34.6; $n=20$) and those with visceral metastasis (16.4 months, 95% CI 4.0-not evaluable; $n=11$). Combining ADXS31-142 with pembrolizumab was safe and well-tolerated, warranting further research on this combination therapy. It is well known that patients with high-risk PCa can experience biochemical relapse (BCR) of PCa even after surgery and develop incurable PCa, so Tryggestad *et al.*[27] did a study aimed to reduce the risk of BCR with a personalized DC vaccine, given as adjuvant therapy, after robot-assisted laparoscopic prostatectomy. It was observed that patients diagnosed with extraprostatic extension and International Society of Urological Pathology grade 5 PCa were at a particularly high-risk of developing postsurgical BCR, and when the vaccine was used in this subgroup, the vaccine response was related to a reduced BCR incidence. In addition, the vaccine was safe without side effects. In general, immunotherapy has low efficacy in CRPCa. When ADT is used to treat PCa, it recruits both anticancer and immunomodulatory effects, but also carries with it the side effect of recruiting myeloid cells that suppress the immune system in such a way that favors the cancer cells to thrive. This by increasing interleukin-8 (IL-8). It is hypothesized that if ADT is used in combination with an inhibitor like anti-PD-1 nivolumab or anti-IL-8 that inhibits the immunosuppressive side effect of ADT, it could lead to better treatment of PCa and decrease disease progression. Dallos *et al.*[28] conducted a phase Ib/II clinical trial of immunotherapy plus ADT in men with recurrent castration-sensitive PCa. They reported that a short course of ADT plus nivolumab may decrease the rate of PSA relapse and lead to durable long-term responses after recovery of testosterone in a subset of patients with PCa. They also reported that the addition of anti-IL-8 to the ADT + nivolumab regimen didn't significantly decrease the rate of PSA relapse, but it had another benefit in that it significantly decreased the toxicity associated with ADT + nivolumab if it was administered. High-dose radiotherapy is also a modality to treat PCa, especially when it is metastatic in nature.

It was hypothesized that if radiotherapy is used in synergy with checkpoint inhibitors, it could increase the DCR. Kwan *et al.*[29] evaluated the efficacy and safety of the PD-L1 inhibitor avelumab with stereotactic ablative body radiotherapy in mCRPCa and found out that the DCR was 48% (15/31; 95% CI 30–67%), which means that the combination resulted in nearly half of patients experiencing cancer control for 6 months or longer.

Moreover, it was also reported that it was a safe combination to use. There is huge debate over whether more or less dosages of vaccinations should be given to patients, with higher doses of vaccinations causing more benefit in

Table 2
Phase 1 trials

Study	Trial name	Phase and status	Patient criteria	Number of patients	Drug	Primary endpoint	Outcome
Agarwal[21]	Cabozantinib in combination with atezolizumab in patients with metastatic castration-resistant prostate cancer: results from an expansion cohort of a multicentre, open-label, phase 1b trial (COSMIC-021)[21].	Phase 1b/2, active, not recruiting.	mCRPC with radiographic soft tissue progression following treatment with either enzalutamide or abiraterone, or both; measurable soft tissue disease per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1; and an Eastern Cooperative Oncology Group performance status of 0 or 1.	132	Cabozatenib + atezolizumab	Objective response rate per RECIST version 1.1 as assessed by the investigator.	Objective response rate was 23% (95% CI 17–32; 31 of 132 patients), with three (2%) confirmed complete responses and 28 (21%) confirmed partial responses.
Narayan[23]	PSMA-targeting TGFβ-insensitive armored CAR-T cells in metastatic castration-resistant prostate cancer: a phase 1 trial[23].	Phase 1, active, recruiting.	Metastatic castrate resistant prostate cancer with ≥ 10% tumor cells expressing PSMA as demonstrated by immunohistochemistry analysis on biopsied tissue. Radiographic evidence of osseous metastatic disease and/or measurable, nonosseous metastatic disease (nodal or visceral).	18	Biological: CAR-T-PSMA-TGFβRDN cells.	safety and feasibility	> 98% reduction in prostate-specific antigen (PSA) and safe.

Table 3

Phase 1/2 trials.

Study	Trial name	Phase and status	Patient criteria	Number of patients	Drug	Primary endpoint	Outcome
Yu[25]	Pembrolizumab Plus Docetaxel and Prednisone in Patients with Metastatic Castration-resistant Prostate Cancer: Long-term Results from the Phase 1b/2 KEYNOTE-365 Cohort B Study[25].	1b/2, Recruiting.	Patients with mCRPC who were chemotherapy naïve and who experienced failure of or were intolerant to ≥ 4 week of abiraterone or enzalutamide for mCRPC with progressive disease within 6 months of screening.	104	Pembrolizumab Plus Docetaxel and Prednisone.	Safety, the prostate-specific antigen (PSA) response rate, and the objective response rate (ORR).	The confirmed PSA response rate was 34% and the confirmed ORR (RECIST v1.1) was 23%.
Stein[26]	ADXS31-142 Immunotherapy ± Pembrolizumab Treatment for Metastatic Castration-Resistant Prostate Cancer: Open-Label Phase I/II KEYNOTE-046 Study[26].	Phase I/II	Men with mCRPC who have progressed after 2 or fewer prior systemic treatment regimens in the metastatic setting.	50	ADXS31-142 Immunotherapy ± Pembrolizumab.	Safety, overall response rate, progression-free survival (PFS), overall survival (OS), and immunogenicity.	Median OS was 7.8 months (95% CI: 4.4–18.5) and 33.7 months (95% CI: 15.4–not evaluable), respectively.
Schöffski[24]	Phase I/II study of the LAG-3 inhibitor ieramilimab (LAG525) ± anti-PD-1 spartalizumab (PDR001) in patients with advanced malignancies[24].	Phase I/II	Advanced/metastatic solid tumors and progressed after, or were unsuitable for, standard-of-care therapy, including checkpoint inhibitors in some cases.	255	LAG-3 inhibitor ieramilimab (LAG525) ± anti-PD-1 spartalizumab (PDR001).	To assess the maximum tolerated dose (MTD) or recommended phase II dose (RP2D).	Antitumor activity was observed in the combination arm, with 3 (2%) complete responses and 10 (8%) partial responses in a mixed population of tumor types. In the combination arm, eight patients (6.6%) experienced stable disease for 6 months or longer versus six patients (4.5%) in the single-agent arm.
Tryggestad[27]	Long-term first-in-man Phase I/II study of an adjuvant dendritic cell vaccine in patients with high-risk prostate cancer after radical prostatectomy[27].	Phase I/II	Patients with high-risk prostate cancer (PC) after robot-assisted laparoscopic prostatectomy (RALP).	20	adjuvant dendritic cell vaccine.	Reduce the risk of biochemical relapse with a personalized dendritic cell (DC) vaccine, given as adjuvant therapy, after robot-assisted laparoscopic prostatectomy (RALP).	Among 20 patients, 11 were BCR-free over a median of 96 months (range: 84–99.
Dallos[28]	A randomized phase Ib/II study of intermittent androgen deprivation therapy plus nivolumab with or without interleukin-8 blockade in men with hormone-sensitive prostate cancer (MAGIC-8)[28].	Phase Ib/II	Men with recurrent castration-sensitive prostate cancer (CSPC).	59	Patients were randomized 1:2 to nivolumab + degarelix (Arm A) versus nivolumab + BMS-986253 (2400mg Q2W) + degarelix (Arm B).	PSA recurrence at 10 months following randomization and safety.	Patients treated on Arm A had a significantly lower rate of PSA relapse (17.39%) at 10 mos compared to historical controls ($P = <$ 0.001) and safe.

Table 4

Phase 2 trials

Study	Trial name	Phase and status	Patient criteria	Number of patients	Drug	Primary endpoint	Outcome
Kwan[29]	Avelumab Combined with Stereotactic Ablative Body Radiotherapy in Metastatic Castration-resistant Prostate Cancer: The Phase 2 ICE-PAC Clinical Trial[29].	2	Progressive mCRPC after at least one prior androgen receptor-directed therapy.	31	Avelumab Combined with Stereotactic Ablative Body Radiotherapy.	Disease control rate (DCR)	The DCR was 48% (15/31; 95% CI 30–67%).
Filaci[30]	Telomerase-based GX301 cancer vaccine in patients with metastatic castration-resistant prostate cancer: a randomized phase II trial[30].	2	mCRPC patients with response/disease stability after docetaxel chemotherapy.	Ninety-eight patients were randomized to receive either eight (regimen 1), four (regimen 2) or two (regimen 3) vaccine administrations.	GX301 -telomerase-based cancer vaccine.	To comparatively analyze safety and immunological response to three GX301 regimens.	A 54% overall immune responder rate was observed with 95% of patients showing at least one vaccine-specific immune response.
Parsons[31]	Immunotherapy to prevent progression on active surveillance study (IPASS): a phase II, randomized, double-blind, controlled trial of PROSTVAC in prostate cancer patients who are candidates for active surveillance Immunotherapy to prevent progression on active surveillance study (IPASS): a phase II, randomized, double-blind, controlled trial of PROSTVAC in prostate cancer patients who are candidates for active surveillance[31].	2	Patients with clinically localized, low- or favorable intermediate-risk prostate cancer.	154	Seven doses of subcutaneous PROSTVAC or placebo (empty fowlpox vector) over 140 days.	Change from baseline to post-vaccination in CD4 and CD8 T cell infiltration in biopsy tumor tissue.	There were no differences in CD4 and CD8 densities (count of cells/mm2) in post-treatment biopsy tumor tissue between groups ($P = 0.63$ and $P = 0.75$, respectively).

controlling or sometimes preventing cancer but with the side effect of exhausting immune cells that mount an antitumor immune response. To add further data to this hypothesis, Filaci *et al.*[30] did a study whose main objective was to comparatively analyze the safety and immunological response to three GX301 regimens (telomerase-based cancer vaccine) in mCRPCa patients with response/disease stability after docetaxel chemotherapy. A 54% immune response rate was observed with 95% of patients showing at least one vaccine-specific immune response. It was also reported that the rate of immunological responders and number of immunizations were proportionally related. This indicates that GX301 cancer vaccine is safe and immunogenic in metastatic CRPCa patients. It is thought that immunotherapy can not only be used reactively in response to PCa but can also be used proactively to prevent the progression of early PCa to advanced mCRPCa. Parsons *et al*[31] evaluated the clinical effects of PROSTVAC, a vaccinia/fowlpox viral vector-based immunotherapy that contains PSA and three T cell costimulatory molecules, in patients with localized PCa to find out whether there was a change in baseline CD4 and CD8 T cell infiltration into the tumor tissue and results showed that although compared to placebo, patients did not elicit significant T cell infiltration but those who did receive the PROSTVAC vaccine were less likely to demonstrate disease progression. A figure depicting major emerging studies is shown in Figure 2. A detailed list of the latest emerging studies including Phase 1, Phase ½, and Phase 2 in Tables 2, 3 and 4.

Limitations

Although immune checkpoint blockade has achieved some success, there are still differences in the way that various tumor types respond to treatment. Prostate tumors are particularly challenging because of their complex immunophenotypes, which can significantly impact the effectiveness of immunotherapy. To improve outcomes, it's critical to identify biomarkers that can help predict which patients are most likely to benefit from a specific immunotherapy. Additionally, clinicians need reliable ways to monitor patient responses, which can be complicated by phenomena such as pseudo-progressions. Researchers are exploring genomic and transcriptomic data to identify patient immune profiles that can be used to predict responders and develop personalized immune therapies[32–34]. For example, genomic profiling could help identify candidate cancer-associated neoantigens that can be targeted using approaches such as peptide vaccines or CAR-T treatments in conjunction with immune checkpoint blockade[35].

Conclusion

PCa is the most frequent genitourinary malignancy in males globally, accounting for more than 1.4 million cases and killing over 375 000 people. Chemotherapy and immunotherapy are both used to treat PCa. Because PCa lacks neoantigens like other cancers and has an immunologically cold tumor microenvironment, it has been difficult and challenging to develop a landmark immunotherapy for it. Because it is a slow growing tumor, anticancer vaccines can be used to control it. Furthermore, as discussed in this paper, there are many new studies that point out novel ways to circumvent the hostile tumor microenvironment by using combination immunotherapies. Additionally, CAR- T cell therapy can be used to genetically engineer the antigens of our choice, which can aid in the fight against cancer. Radiation therapy can be combined with immunotherapy to improve the treatment of PCa.

Ethics approval and consent to participate

None.

Consent for publication

None.

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Author contribution

S.S.: conceptualization, data curation, formal analysis, methodology, and writing the original draft of the paper; A.B.R., S.S, and A.V.V.: data curation, writing, and formal analysis; H.M., M.S., and A.B.: conceptualization, writing, supervision, and methodology; A.A. and S.N.S.: data curation, methodology, and analysis, methodology, and analysis.

Conflicts of interest disclosure

All authors of this research paper declare that they have no financial or personal relationships that could potentially influence the content of the paper.

Availability of data

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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