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Sipuleucel T: The Potential Arrival in the Field of Immunotherapy for Prostate Cancer

Megha Bajaj, Amit Sharma, Nikita Khera, Bintoo Sharma, Harsh Tyagi and Teena Chhabra*

ISF College Of Pharmacy, Moga, Punjab, India

***Corresponding author:** Teena Chhabra, ISF College Of Pharmacy, Moga, Punjab, India

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ABSTRACT

Sipuleucel-T represents a novel immunotherapeutic compound designed to stimulate an immune response against metastatic castration-resistant prostate cancer (mCRPC). It is a personalized therapeutic vaccine in which individual patient-specific immune cells are used. It works by focusing on prostate cancer by triggering the patient's own immune system. There are three doses total in a typical sipuleucel-T therapy regimen. The RCTs or randomized controlled trials, that provided FDA approval were done to evaluate the efficiency and safety of sipuleucel-T. An early double-blind trial (IMPACT) showed the life-prolonging effect of the treatment. There was an approximate 22% reduction in risk of death in Sipuleucel-T patients, compared with those in the placebo group and survival benefit of 4.1 months was noted with sipuleucel-T. Sipuleucel-T is now being used in the clinic for patients with a lower disease burden. Specifically, a few of the problems with advanced prostate cancer treatment, research and development, rational combinations of sipuleucel-T with other approved agents and how could they change/modify the issue of prostate cancer clinical care, are brought up. Current and future areas of investigation that are being explored in relation to sipuleucel-T are investigated.

Keywords: Prostate Cancer; Sipuleucel-T; Immunotherapy; Metastatic Castration-Resistant Prostate Cancer; Therapeutic Cancer Vaccine

Abbreviations: PSA: Prostate Specific Antigen; ADT: Androgen-Deprivation Therapy; mCRPC: Metastatic Castrate-Resistant Prostate Cancer; FDA: Food and Drug Administration; OS: Overall Survival; PAP: Prostatic Acid Phosphatase; GM-CSF: Granulocyte-Macrophage Colony-Stimulating Factor; TILs: Tumor-Infiltrating Lymphocytes; APCs: Antigen Presenting Cells; TPP: Time to Progression; BF: Biochemical Failure

Background

Prostate cancer being the most prevalent non-cutaneous malignancy, is second most common cause of worldwide mortality of men due to cancer [1], even though mortality rates have been trending downwards since the early 1990s [2]. The patient's age, rate of disease growth and additional prognostic criteria will all play a role in determining the initial prostate cancer therapy. Surgery or radiation therapy can usually cure individuals with localized cancer when active surveillance is not an option; however, up to 30% of patients will experience disease recurrence, which is normally detected by a progressive increase in serum prostate specific antigen [PSA] [3]. At the time of diagnosis, 15% or so of prostate cancer patients had metastatic illness. Androgen-deprivation therapy [ADT] is the backbone of treatment for these groups. Although the administration of ADT typically results in an early and good PSA response, there are severe side effects, therefore most men eventually develop castrate-resistant prostate cancer [CRPC] [2]. There is presently no cure for metastatic castrate-resistant prostate cancer [mCRPC] and the prognosis is generally poor [4]. Androgen receptor and androgen synthesis inhibitors, chemotherapy, radiopharmaceuticals, and immunotherapy are still some of the approved treatments [5].

The United States Food and Drug Administration [USFDA] approved Mitoxantrone as the first chemotherapeutic agent for individuals with castrate-resistant, metastatic illness; nevertheless, it was not discovered to increase overall survival [OS] in males [6-8]. Docetaxel, after proving to have a survival benefit, was given approval in 2004,

however it has considerable side effects [9]. The FDA authorized the use of cabazitaxel and abiraterone acetate as treatments following prior docetaxel therapy in 2010 and 2011 and in patients with bone metastasis, denosumab has been approved for the prevention of skeletal-related events [10]. More recently, radium-223 and enzalutamide both improved OS in patients with metastatic CRPC [10,11] and the latter was approved in 2012. The development of tumor-targeted antibodies, immune checkpoint inhibition and cancer vaccines in recent years have had a significant impact on the treatment of solid tumors [4]. Sipuleucel-T is the only immunotherapy with a proven OS benefit for mCRPC among these newly developed innovative treatments [12]. The first therapeutic vaccination sipuleucel-T received FDA approval in April 2010 for the treatment of patients.

Main Text

Sipuleucel T- A Cancer Vaccine

Sipuleucel-T [Provenge; Dendreon] is an autologous cellular immunotherapy used to treat individuals with metastatic castration-resistant prostate cancer [mCRPC] who are asymptomatic or just mildly symptomatic. It is an individually tailored therapeutic vaccine designed to elicit an immune response against prostate cancer cells [13]. Prostate cancer has shown some promise for cancer vaccines that train the immune system to detect tumor-associated antigens and activate a T cell response. Typically, vaccines contain a target protein or peptide that is known to be related with the cancer. Prostate cancer expresses tumor-associated antigens including PSA, PSMA and prostatic acid phosphatase [PAP], which is a desirable target for immunotherapy using vaccines [14]. It has recently been recognized that sipuleucel-T also elicits humoral immune responses against non-target [non-PAP] tumor antigens via antigen expansion in addition to stimulating an anti-tumor immune response against PAP, which is expressed in over 95% of prostate Adenocarcinoma [15]. The therapeutic effectiveness of sipuleucel-T in extending overall survival may be influenced by the expansion of the immune response [16,17]. Prior to prostatectomy, sipuleucel-T induces T-cell and B-cell trafficking to the tumor margin in men with locally advanced prostate cancer and it elicits long-lasting immune responses in men with mCRPC [5]. The antigen is presented by APC in a way that T cells can detect it. MHC class II and class I molecules, which can activate CD4+ T-helper cells and CD8+ T cytotoxic cells, respectively, are frequently expressed by these cells. When the T cell and the antigen match, the T cell is excited and begins to generate various cytokines and other chemical messengers, such as interleukin-12, GM-CSF and tumor necrosis factor-alpha [TNF-α] [18].

Tumor Microenvironment

Many times, prostate cancer is portrayed as a "cold" tumor with an immunosuppressive microenvironment [19]. The tumor microenvironment, which is a hostile environment where a developing tumor deposit is shielded from immune rejection, is one of the numerous potential obstacles to success. Overcoming these obstacles must become a requirement and be considered while developing cancer vaccines and choosing patients. The high interstitial pressure and hypoxia linked to big tumor masses are additional physical and immunological variables that hinder the diffusion of molecules like antibodies and effector T cells into the tumor environment. Adaptive antitumor immunity is what vaccines are intended to promote in cancer patients [20]. By preventing T-effector cell function, tumor-infiltrating lymphocytes [TILs] may aid in the growth of prostate cancer. TILs with a leaning tendency toward T-regulatory and T helper 17 phenotypes, which decrease auto-reactive T cells and antitumor immune responses, have been discovered in prostate cancer biopsy tissues [19]. Antigen-presenting cells called dendritic cells [DCs] are crucial for activating CD8+ T lymphocytes, which then kill tumors [21]. ADT has been observed to briefly reduce T cell tolerance and increase T cell priming to prostatic antigens [22-24]. Withholding androgen increases thymocyte proliferation and differentiation, which can reverse thymic involution. It can also encourage T-cell infiltration in malignancies. The stroma of CRPC is highly reactive and is characterized by an enhanced T-cell infiltration that is predominately composed of populations of regulatory T cells that inhibit the immune system [25]. Numerous studies have demonstrated that the nature of the gut microbiota may influence immunotherapy responses and that antibiotics may reduce treatment response [26,27]. Removal of the tumor bulk, in situ tumor killing with tools like oncolytic viruses, production of immune-stimulating cytokines and a range of pharmaceutical treatments can all help combat the deleterious effects of the tumor microenvironment [28]. Figure 1 illustrates the logistics of administration of sipuleucel-T.

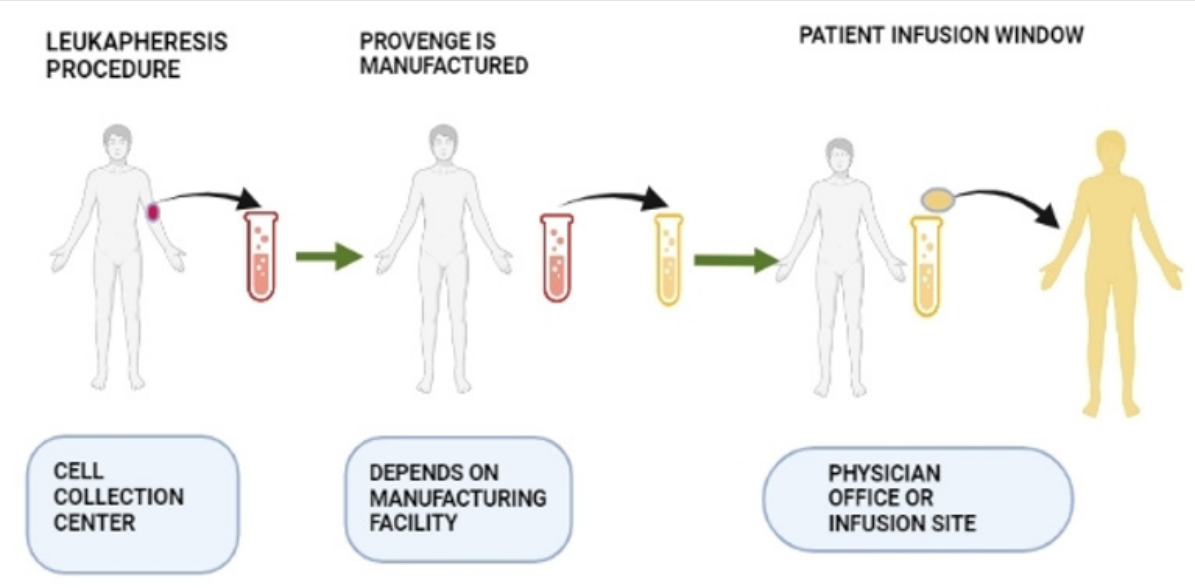

Figure 1: Logistics of administration of sipuleucel-T.

Mechanism of Action

Even though sipuleucel-T is frequently referred to as a "vaccine," a conventional vaccination differs from combining of *ex vivo* and *in vivo* leukocyte activation. In the conventional, an antigen or an adjuvant/antigen combination is directly administered to the patient. Here, effector cell development and physical antigen presentation occur only inside the host. Sipuleucel-T can also be called as an "autologous cellular immunotherapy," however this term does not consider the extensive ex vivo processing of the cells, that creates an environment distinct from the likely immunosuppressor cytokine and cellular milieu existing within a patient with continuous disease progression [29,30]. Although the sipuleucel-T's exact mode of action is not yet fully understood, it principally requires the development of a T-cell response against PAP. The targeting and recognition of PAP-expressing prostate cancer cells by T lymphocytes may not be the only part of the system. T cells need to meet cognate antigen on an active APC in order to function [31]. The activated APCs enable *in vivo* priming of T cells following infusion and ex vivo priming of T cells during culture. After the first dose is given, there is a noticeable increase in APC and T-cell activation markers in the PBMCs of treated individuals, as well as a rise in the ex vivo generation of T-cell activation-related cytokines. As a result, patients receive progressively activated APCs and T lymphocytes [32].

In most patients, sipuleucel-T prolonged survival but failed to clearly demonstrate measurable PAP-specific immunity. The attempt to link outcome to PAP immunity was hampered by the vaccine's apparent benefit in patients without measurable immune responses. Very little protein-based free PAP is injected into patients due to washing process. Peripheral blood may not accurately depict T-cell reactions at tumor deposition locations. It's likely that most patients did not have significant numbers of PAP-specific T cells activated, meaning that the observed therapeutic benefit was not reliant on inducing PAP-specific immune responses. Prostate cancer patients frequently experience dominating discomfort and cachexia. Many cytokines, including TNF-α, IL-1, IL-6, and IL-8, are increased in prostate cancer patients and may contribute to cachexia. Without significantly influencing size or growth of tumor, the infusion of activated APCs and T cells, which are sipuleucel-T components, may have significantly disturbed the type and circulating cytokine level [33,34]. Figure 2 demonstrates the mechanism of action of sipuleucel-T.

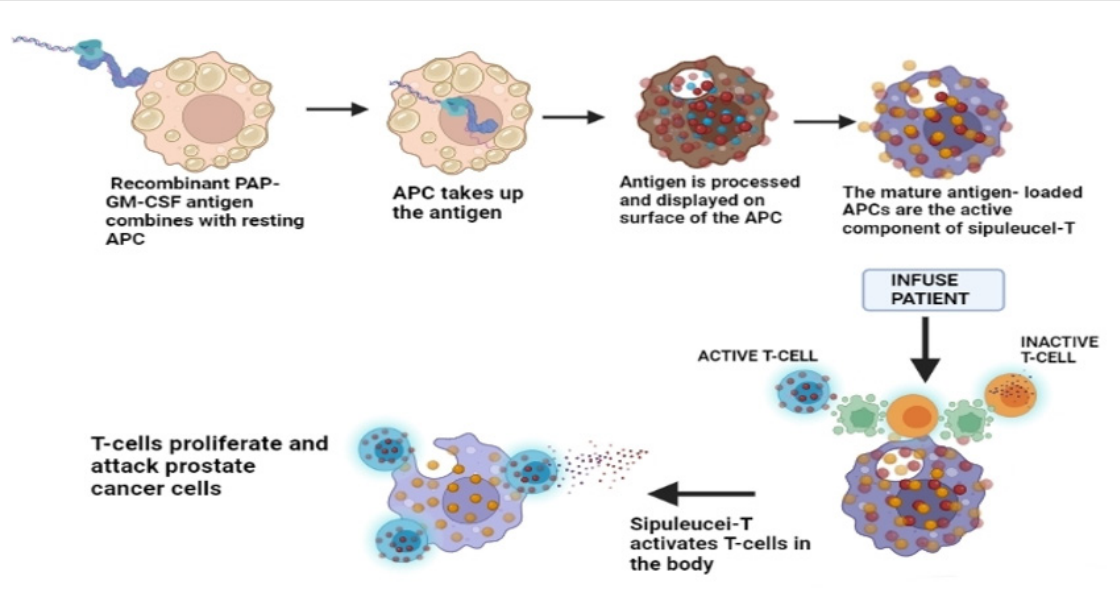

Figure 2: Mechanism of action of sipuleucel-T.

Clinical Evidence

Clinical trials were performed on men with mCRPC to evaluate the efficiency and safety of sipuleucel-T. Utilizing measures of tumor response, slowed disease progression and decreased blood PSA levels, these studies' efficacy was evaluated. Whether serum PSA is a trustworthy predictor of clinical benefit and responsiveness in prostate cancer is up for debate. However, a PSA reduction of at least 50% has been recognized as an efficient screening indicator for anticancer effectiveness [35]. Although survival is the most objective and important result, no published studies have been constructed to examine it as a primary endpoint to date [36].

Phase 1 and 2 Trials: Consecutive phase 1 and phase 2 studies assessed the PAP vaccine's safety and its capacity to overcome immunological tolerance to PAP [37,38]. In the phase 1 experiment, increased doses of sipuleucel-T were administered to the patients. A total of their leukapheresis product, prepared as sipuleucel-T, was administered to those on the phase 2 regimen. Time to progression[TTP] and immunological response to PAP were both associated [39].

a) In 1997, Burch and associates at the Mayo Clinic carried out the sipuleucel-T's initial Phase 1 clinical trial. 13 patients with mCRPC participated in the study. They received three monthly subcutaneous injections of PA2024 alone at one of three dosage levels [0.3, 0.6, or 1.0 mg/injection] after receiving two infusions of sipuleucel-T spaced one month apart. All patients assessed for immunological response at the study's conclusion had produced T cells that were specific to an antigen. Three patients experienced a 50% or greater decrease in serum PSA levels. Analysis of the trial's antibody response also indicated that additional injections of the soluble antigen PA2024, beyond the three infusions of activated dendritic cells, did not contribute to a rise in antibody titer [37]. At the University of California, San Francisco, sipuleucel-T was the subject of another Phase 1 clinical investigation. Leukapheresis was performed on the study subjects at weeks 0, 4, and 8 to remove CD54+ precursor cells that would later be infused ex vivo with antigen and given intravenously. Patients who had stable or better conditions received a fourth dose in week 24. Six patients received the maximal dose of sipuleucel-T, which was administered to 12 individuals in a dose-escalation way at 0.2 × 109, 0.6 × 109, 1.2 × 109 or 2.0 × 109 nucleated cells/m2. Prior to enrolling in the trial, nearly all the patients have had chemotherapy and second-line hormonal therapy. Peak T cell proliferation responses to the PA2024 were reached after two or three infusions of sipuleucel-T and all patients displayed immunological response to it. It typically took 12 weeks for the condition to progress.

b) Following that, Small et al. extended their Phase 1 clinical trial into Phase II, enrolling 19 more CRPC patients [38]. The maximum manufacturing dose of sipuleucel-T was administered to each patient. Seven individuals had not progressed by the conclusion of the expected 1-year follow-up period, which was observed to be the average progression time for the Phase 2 patients at 29 weeks. The formation of T-cell proliferation responses following sipuleucel-T infusion were observed in all 31 patients when the data from both Phases 1 and 2 clinical trials were merged for analysis. 20 individuals experienced an immunological response to PAP following therapy, whether in the form of T-cell proliferation or antibody production and their average time to disease progression was much greater than that of the other patients [34

weeks versus 13 weeks]. Burch et al. started a Phase 2 trial of sipuleucel-T for castrate-resistant prostate cancer before their Phase 1 findings showing the safety of sipuleucel-T and PA2024 were published [39]. At weeks 0 and 2, sipuleucel-T was injected intravenously into 21 qualified patients. At weeks 4, 8, and 12, they additionally got three 1.0 mg subcutaneous injections of PA2024. 13 out of the 15 individuals who had their immune responses assessed had antibodies that were specific for PA2024. It's interesting to note that two patients' serum PSA levels dropped by 50% while they were receiving treatment. The average time to disease progression was 14.5 weeks. Another Phase 2 experiment conducted at the University of California, San Francisco examined the PSA-modulating effects of sipuleucel-T. Patients who previously received radiation therapy or definitive surgery and then saw rising PSA levels between 0.4 and 6.0 ng/ml were included in the trial. Without further subcutaneous injections, sipuleucel-T was infused three times as scheduled. 13 patients showed average prolongation of PSA doubling time of 62% [4.9 months before treatment versus 7.9 months after treatment]. Only grade 1 toxicity was found [40].

Phase 3 Trials: Sipuleucel-T FDA's approval was based on three crucial phase 3 trials. Across numerous subgroups, the OS rates remained constant. Sipuleucel-T was found to significantly extend survival in two early phase 3 randomized double-blind placebo-controlled trials [trials D9901 and D9902A] in men with asymptomatic mCRPC as compared with placebo. However, these smaller initial trials were combined for an initial FDA filing which led to initiate a larger randomized, double-blind, placebo-controlled phase clinical registration trial known as IMPACT study [Immunotherapy for Prostate Adenocarcinoma Treatment] [D9902B].

D9901 study: A randomized Phase 3 clinical trial of sipuleucel-T [D9901] [NCT00005947] was started in 1999 based on positive Phases 1 and 2 studies' findings. In the first phase 3 clinical experiment to be reported, conducted by Small and colleagues, immune response data from men with androgen-independent prostate cancer were gathered in a double-blind, placebo-controlled clinical trial. Sipuleucel-T [n = 82] or a placebo [n = 45] were administered every two weeks to a total of 127 participants in a 2:1 ratio. Patients on placebo who were seen to be developing illness were transferred to sipuleucel-T. All patients' survival was monitored for 36 months. 115 patients were identified to have progressing illness at the time of data analysis. Compared to 10 weeks for the placebo, the median TTP for sipuleucel-T was 11.7 weeks [P = 0.052]. The ninety five percent confidence interval [CI] for the hazard ratio [HR] ranged from 0.99 to 2.11. TTP was not significantly delayed for the sipuleucel-T group as a whole, although patients with a Gleason grade of 7 or fewer experienced a substantial change in TTP. The difference in average survival between sipuleucel-T [25.9 months] and placebo [21.4 months] was 4.5 months, making a significant difference [P=0.01]. When compared to the placebo group, the sipuleucel-T patients' T-cell proliferation was eight times higher [16.9 vs. 1.99; P = 0.001]. A remarkable threefold increase in overall survival fraction was observed at 36 months, with 34% of sipuleucel-T patients still alive compared to 11% of placebo patients [41].

D9902A Study: Initially planned to be a companion trial to D9901, the D9902A trial [NCT01133704] had a similar research design and the same end goal of integrating data with D9901, specifically with relation to time to pain progression criteria. Three infusion of sipuleucel-T or a placebo were given to the men at random. The study was terminated after 98 patients were enrolled because sipuleucel-T did not show a statistically significant advantage over placebo in TTP in the prior study [D9901] [P = 0.033]. The study was underpowered to achieve its main goal of improved TTP; the estimated TTP was 10.9 months in the sipuleucel-T arm and 9.9 months in the placebo arm [HR = 1.09, p = 0.719]. Patients receiving sipuleucel-T had a median OS of 19.0 months compared to 15.7 months in the placebo group [HR = 1.27; p = 0.331]. A subgroup of patients with a Gleason score of 7 or below, though, showed positive results. The initial phase of the investigation was given the code D9902A. In order to concentrate on patients with a Gleason score of seven or fewer, the trial protocol was modified and kept as D9902B. 225 individuals were randomly randomized to receive sipuleucel-T [n = 147] or a placebo [n = 78] in an integrated analysis of D9901 and D9902A. A significant 33% decrease in the risk of death was observed in the treated patients [P = 0.011], compared to a reduction of 15% in the placebo group and this resulted in a median OS benefit of 4.3 months [23.2 months vs. 18.9 months; HR = 1.50; p = 0.011]. The probability of the disease progressing was also decreased by 21% as a result of the treatment [P = 0.111]. Prostate-specific antigen [PSA] levels were reduced by 25% or more in just seven out of 147 individuals receiving sipuleucel-T, compared to none of the 78 patients receiving placebo. According to the study, sipuleucel-T has a favorable risk-benefit ratio [16].

Impact Study: The largest prospective, third randomized [2:1], double-blind, global Phase 3 trial D9902B [Immunotherapy for Prostate Adenocarcinoma Treatment; IMPACT, NCT0065442] was conducted to establish sipuleucel- T advantages in long-term survival. 512 men with metastatic, hormone-refractory prostate cancer participated in placebo-controlled research. Initially, patients with a Gleason score of 7 or fewer were the ones who were targeted. Later, this standard was modified to take into account individuals with Gleason scores greater than 7. Three sipuleucel-T doses [n = 341] or a placebo [n = 171] were given to patients at intervals of two weeks. At 36 months, sipuleucel-T showed a survival advantage of 4.1 months; median survival was 25.8 months with sipuleucel-T and 21.7 months with placebo. At the time of the cutoff, patients who took sipuleucel-T had significantly longer overall survival [P = 0.032; HR = 0.775]. In numerous patient groups, the outcomes were consistent. After 349 patients died at an estimated follow-up of 36.5 months, an updated

analysis revealed that sipuleucel-therapeutic T's effect was still present and significant [HR = 0.751; P = 0.012]. Importantly, attaining titers of PAP or PA2024-specific antibodies was associated with enhanced survival; however, no difference in survival was found based on T cell proliferation to PAP or PA2024. These findings led to the US FDA's approval of sipuleucel-T on April 29, 2010 [4].

Protect study: Beer and associates conducted the PROTECT [PROvenge Treatment and Early Cancer Treatment] randomized controlled, double-blind, multicenter trial to ascertain the biological processes of sipuleucel-T in CSPC [castration sensitive prostate cancer] [42]. Men with non-metastatic, androgen-dependent prostate cancer were included in the phase 3 research P-11 [PROTECT] [43]. Following radical prostatectomy, 176 patients with prostate cancer underwent androgen suppression therapy for 3–4 months before being randomly assigned in a 2:1 ratio to receive sipuleucel-T. Biochemical failure [BF], which was the main endpoint, was determined as a serum PSA level more than or equivalent to 3.0 ng/ml. The average time to BF was 18 months in the sipuleucel-T group and 15.4 months for the placebo group, a difference which was not statistically significant [HR, 0.936; p = 0.737]. The PSA doubling time [PSADT] was also assessed and this difference between groups was statistically significant. After testosterone levels returned to normal, patients who got sipuleucel-T experienced a 48% increase in PSADT [155 versus 105 days; p = 0.038] [42]. There was no apparent change in quality of life seen between sipuleucel-T arm and the placebo arm, according to a second examination of the same patient cohort [44]. A follow-up study is currently being conducted to analyze the effectiveness and safety of PROTECT patients who will proceed to receive three more sipuleucel-T booster infusions. Sipuleucel-T induced immune response, as assessed by antigen-specific T-cell responses, interferon-gamma enzyme linked immune spot [ELISPOT] assay and antigen-specific humoral immune responses, is the main result of this experiment [NCT01338012] [45].

Safety and Toxicity

Sipuleucel-T is generally very well tolerated. Following the onset of the disease and every 6 months or less after that, patients were monitored for treatment-related side effects and survival [4]. Four randomized phase 3 studies were used to check the safety of sipuleucel-T. Three of the studies [IMPACT, D9901 and D9902A] involved patients with metastatic CRPC, while the fourth involved patients with androgen-dependent prostate cancer. In total, 601 patients were treated with sipuleucel-T and 303 received a control treatment in the four studies [PROTECT] [46]. There was no proof that leukapheresis resulted in immune system suppression [43]. With a 22% decrease in death risk and a 4.1-month median survival benefit, the IMPACT trial's findings showed an OS benefit. When applied to a patient population with survival rates of less than two years, this survival extension has clinical significance [4,16]. Numerous subgroups, including those based on age, race, ECOG performance status, number of bone metastases and prior chemotherapy use, all responded favorably to treatment [47]. Overall, no differences existed between patients receiving sipuleucel-T [23.8%] and those receiving a placebo [22.4%] in terms of the percentage of major adverse events [48].

The majority of reported adverse events [AEs] are infusion-related, self-limited and well managed with acetaminophen and diphenhydramine [49]. An integrated safety analysis of Phase 3 trials recognized the adverse events that were more frequently observed with sipuleucel-T [at a rate at least twice that of control], including chills [53.1%], pyrexia [31.3%], headache [18.1%], myalgia [11.8%], influenza-like sickness [9.7%] and excessive sweating [5.0%]. The majorities of reported adverse effects [AEs] were mild to moderate in intensity [Grade 1 or 2] and disappeared within 1 to 2 days. These incidents often happened within 1 day of infusion [4]. There was no evidence of a difference in the occurrence of non-neurologic arterial [1.0% vs. 0.7%; sipuleucel-T vs. control] or venous [2.8% vs. 4.0%] vascular events, in the incidence of cerebrovascular events, which was reported to be 3.5% for sipuleucel-T individuals and 2.6% for control subjects [50]. Chills, exhaustion, back discomfort, hypertension, hyperkalemia and muscular weakness were G3 events that were recorded for at least one patient at least one day following the sipuleucel-T infusion. 6.7% of sipuleucel-T individuals and 2.3% of control subjects suffered grade 3 adverse events within one day of infusion and one G4 incident was documented [intravenous catheter associated bacteremia] [51].

Combination Therapy

It is becoming more recognized that combination therapy is the best approach for treating cancer. In preclinical and early-phase settings, logical combinations combining immunotherapeutic methods with a variety of therapy modalities are being investigated for prostate cancer [52]. The combination therapy and a wide range of medicines that either function as immune stimulants/adjutants or blockers of immune regulatory cells in conjunction with cancer vaccines is possible and are currently used. All have been verified in preclinical and several have offered early clinical benefit data [53].

Conventional Combination Therapy: When two or more chemotherapeutic drugs are combined with a target therapy each drug functions independently to produce additive antitumor effects. This has been demonstrated in various preclinical models that combine chemotherapy drugs and vaccinations. Immune responses to vaccinations have not been negatively impacted when given along with specific chemotherapeutic agents, such as 5-fluorouracil and docetaxel, in patients, even though vaccines are less effective in those who have received extensive pretreatment with chemotherapy [54,55]. For instance, it has even been demonstrated in preclinical investigations that the COX-2 inhibitor celecoxib did not negatively impact immune responses to vaccination and functioned effectively in combination with vaccination to increase anticancer effects [56]. Preclinical investigations have demonstrated that chemotherapy [docetaxel] increases the expression of the tumor antigen and the major histocompatibility

complex 1 [MHC-1] [26,57,58]. One more research has demonstrated that the chemotherapy drug Cytoxan [Cyclophosphamide] can improve the effectiveness of vaccines. It diminishes the functionality and quantity of regulatory T cells [59-61].

Vaccine and Androgen Deprivation Therapy: Given that hormone suppression may have immunostimulatory effects, it is logical to combine sipuleucel-T with it. Two studies are currently evaluating such combinations: one with leuprolide acetate [NCT01431391] and the other with abiraterone acetate [NCT01487863]. Androgen restriction therapy has been demonstrated to increase the overall survival of individuals with high-risk metastatic prostate cancer, despite some debate [62]. ADT is a physiological treatment that affects men's androgen signaling in one of two ways. One strategy is to limit the release of FSH and LH at the pituitary level with a GNRH super-agonist, such as leuprolide acetate. Using androgen receptor blockers like bicalutamide, nilutamide or flutamide is another technique to stop the androgen axis from working. The tissues' androgen receptors are bound by these substances, making normal levels of androgen inactive [63]. Androgen signaling is necessary for the majority of prostate epithelial cells to survive. Thus, ADT causes both normal and malignant prostate tissues to rapidly undergo apoptosis, which encourages the influx of immune cells to the prostate [23,64,65].

The requirement of low-dose corticosteroids in the case of abiraterone acetate led to concerns about whether this would diminish any immunological response produced by sipuleucel-T. Recently, a randomized, open-label, Phase 2 study of sipuleucel-T given either before beginning abiraterone and prednisone [5 mg orally twice daily] or concurrently with them in men with mCRPC was published [NCT010487863]. According to CD54 expression, ex vivo APC activation was the same regardless of when abiraterone plus prednisone was administered and it increased after the second and third infusions of sipuleucel-T in both arms, indicating an efficient immune prime-boost action. Additionally, the peripheral immune responses and sipuleucel-T product characteristic profiles in both arms were similar with previously reported Phase 3 results, indicating that sipuleucel-T's immunological action was neither blunted or altered [66]. In conclusion, androgen restriction therapy reduces immunological response, boosts naive T cell thymic production, encourages T cell migration to the prostate and improves tolerance, all of which give a strong case for working with immunotherapy [22,23,67-70].

Vaccine and Cytokine Combination Therapy: Combining vaccine with cytokine therapy is one potential therapeutic strategy because of the comparatively low efficiency of vaccine monotherapy in prostate cancer to date. It is well documented that cytokines can improve immune response. Both IL-15 and IL-7 have the potential to be helpful in boosting memory T-cell responses in combination with vaccination [71] IL-7 is a homeostatic growth factor for T cells that can promote proliferation, maintain T cell responsiveness and prevent and reverse T cell energy depletion [72]. Patients with asymptomatic or minimally symptomatic mCRPC were randomized to receive CYT107, a recombinant glycosylated human interleukin-7, after receiving regular sipuleucel-T in a phase 2 randomized, controlled clinical trials [NCT01881867]. Compared to controls [no CYT107], patients got CYT107 therapy 3–7 days after finishing sipuleucel-T therapy. The accrual phase of this trial is complete and preliminary findings demonstrate that CYT107 can significantly increase T cell growth as compared to controls [73].

Vaccine and Check Point Inhibitors: Studies are being conducted to evaluate the interaction of sipuleucel-T with the PD-L1 inhibitor atezolizumab [NCT03024216] and the CTLA-4 inhibitor ipilimumab [NCT01804465] [74]. Under normal conditions, checkpoints protect the host from autoimmune disease and an overactive immune system. In the case of cancer, antibody blocking therapy of these checkpoints may aid in breaking tolerance, aid in improving the initial reaction when primed by a DC vaccination and aid in maintaining a high-quality long-lasting T-cell response. CTLA-4 was the first T-cell immunological checkpoint that was made a target for antibody blockage. The inhibitory molecule CTLA-4 is being up regulated and delivered to the surface during the early phases of activation. The level of CTLA-4 expression at the cell surface increases with the strength of the T-cell receptor stimulation. To be able to compete with CD28's co-stimulatory function, CTLA-4 has a higher affinity for binding CD80 and CD86 than CD28 [another inhibitory molecule] [75,76]. Sipuleucel-T and ipilimumab were combined in a preliminary phase 1 research [NCT01832870] with nine participants and the results showed possible synergistic benefits, with elevated amounts of PAP and PA2024-specific antibody levels than would have been anticipated with sipuleucel-T alone [74]. In other studies, tumor vaccination and antibody blocking were combined and put up against either no treatment or both as a monotherapy. Blockade and vaccination together improved survival accelerated tumor remission and boosted IFN-gamma production [77].

Programmed Cell Death-1 [PD-1] is a different monoclonal antibody that is currently undergoing clinical testing. A Phase 1 trial analyzed human anti-PD-1[MDX-1106] in patients with metastatic solid tumors [78]. This experiment showed a very low rate of adverse events, with only a few exceptional grade III toxicities. more effective and more tolerated than conventional cancer therapies [79-97].

Conclusion

A new oncology therapeutic paradigm is being introduced by sipuleucel-T, the first autologous cellular immunotherapy to receive approval and show an improvement in overall survival. Immunotherapy has been a standard of care with an influence on survival since the US FDA approved sipuleucel-T in April 2010 as a novel treatment for metastatic CRPC that is asymptomatic or very minimally symptomatic. Many clinical trials were done and data from the phase 3 randomized IMPACT trial showed improved median overall survival by four

months. A fusion protein containing a prostate-specific tissue antigen linked to GM-CSF is utilized to activate autologous PBMC ex vivo to produce sipuleucel-T. In addition to promoting PAP uptake, processing and presentation, the fusion protein PA2024 also supports cell survival. Treatment with sipuleucel-T is associated with easily manageable side effects, which are usually mild. Numerous other clinical studies have shown it to be potentially helpful in the early phases of disease and pairing it with other treatments may increase its effectiveness. Sipuleucel-T has laid the groundwork on which additional strategies can be implemented to facilitate the control of this disease. Moving forward, the central challenge for physicians will be to determine the optimal strategy for integrating sipuleucel-T into the management of men with advanced prostate cancer, both in terms of optimal sequencing and combination of sipuleucel-T with other available agents. We anticipate that the development of sipuleucel-T for the treatment of prostate cancer will pave the way for the successful application of other immune therapies that rely on more antigens as well as for the strategic coordination of immunologically unrelated therapies.

Declarations

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Ethics Approval and Consent to Participate

Not applicable

Consent for Publication

All the six authors agreed for the publication of the article in this journal.

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Authors' Contributions

Ms. Megha Bajaj and Dr. Teena Chhabra collected literature for this review article and writing the manuscript. Dr. Amit Sharma, Ms. Megha, Dr. Teena Chhabra, and Ms. Nikita are major contributor in writing, analyzing, drafting and referencing the manuscript. Dr. Amit Sharma, Mr. Bintoo Sharma, Mr. Harsh Tyagi are the major contributors in reading and approval of the final manuscript.

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