**[Sipuleucel-T: A success in vaccine-based cancer therapy]**

Department of Microbiology and Molecular Genetics, Oklahoma State University, Stillwater, OK 74078, USA 

Sipuleucel-T is an immunotherapy treatment for castration-resistant prostate cancer (mCRPC). The therapy was approved by the FDC in 2009, the use of this vaccine-based treatment shows promising results in increasing life expectancy for men diagnosed with mCRPC. Immunotherapies aim to improve immune responses against cancer cells. The goal of Sipuleucel-T is to improve immune responses and increase the overall survival rate (OS). 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. The researchers determined overall survival and adjusted for base levels of serum prostate specific antigen (PSA) as well as lactate dehydrogenase. Sipuleucel-T patients also reported more adverse events (chills, fever, headache) compared to the placebo group. In the years following the approval of this therapy, data collected in PROCEED, a registry of men with mCRPC, support these original findings. The OS rate did decrease compared to the original trial study; this can be attributed to the differences in criteria used to find eligible patients for the trial and the broader types of patients added to the registry. Another study (2015) concluded that Sipuleucel-T could be administered alongside abiraterone acetate (AA) without altering immune parameters that correlate with Sipuleucel-T’s clinical benefit. Each of these findings support the use of Sipuleucel-T as a life-prolonging therapy for men with mCRPC. In combination with other forms of cancer treatment, Sipuleucel-T seems to provide a safe and effective increase in immune cell responses. As this field grows, our understanding of the relationships between immune-based vaccines and the other treatment methods should be further studied.

**Introduction**

Immunotherapy is a biological cancer treatment that works to aid the immune system in fighting cancer. Cancer cells can evade immune system responses, and immunotherapy aims to increase the body’s ability to detect and destroy cancer cells. There are multiple different types of immunotherapies, including immune checkpoint inhibitors, t-cell transfer therapy, treatment vaccines, immune system modulators, etc (3). Sipuleucel-T is a vaccine-based immunotherapy designed to treat metastatic castration-resistant prostate cancer (mCRPC), Prostate cancer is the second leading cause of death from cancer among men in the United States. For men with mCRPC, the median survival has ranged between 12.2 to 21.7 months (4). There are multiple new treatments for mCRPC, including androgen signaling inhibitors, radiopharmaceuticals, and cytotoxic chemotherapies (5). Considering the number of available therapies, it is important to understand how they can work together to inhibit mCRPC progression. Sipuleucel-T is a cellular immunotherapy, a therapeutic cancer vaccine, containing autologous peripheral-blood mononuclear cells (PMBCs) as well as antigen presenting cells (APCs) activated with recombinant fusion protein (PA2024). PA2024 contains a prostatic acid phosphatase fused to an immune cell activator, as well as a PSA (4). The vaccine increases overall humoral immunity (1), and it has been used in conjunction with Abiraterone Acetate, a hormone based chemotherapy (5). Combinations of treatments can potentially increase life expectantly and improve quality of life for men with mCRPC. Since Sipuleucel-T is a relatively new therapy it is important to understand the long term impact of this treatment. The PROCEED registry tracks patients who have undergone this treatment, and it has shed light on the effects of Sipuleucel-T in a non-trial setting (2). This vaccine treatment is showing promising results in treating mCRPC.

**Recent Progress**

In the 12 years since the FDA approval of Sipuleucel-T, our understanding of the treatment’s effectiveness has deepened. Multiple studies have supported the initial finding that Sipuleucel-T increases OS and can be used alongside other treatments: abiraterone acetate, enzalutamine, cabazitaxal, and radium 223 (5). The PROCEED registry is a resource that tracks the effect of Sipuleucel-T in patients with mCRPC (2). The goal now is to understand long-term effects of Sipuleucel-T and how it can work with other treatments and methods to maximize OS. In terms of progress in general immunotherapy research, research is being focused on reducing side effects of immunotherapies, decreasing resistance to immunotherapies, and better predicting immune responses (3).

**Discussion**

Several studies have been conducted in the last decade to determine the success rate of Sipuleucel-T. The results of the initial research process were promising. A double-blind trial involving 512 patients, called Immunotherapy for Prostate Adenocarcinoma Treatment (IMPACT), aimed to confirm survival findings by calculating overall survival (OS). This study evaluated the effectiveness of Sipuleucel-T in reducing risk of death in men with mCRPC. This original trial was a placebo-controlled, multicenter phase III trial with 512 participants. There was a 2:1 ratio of sipuleucel-T to placebo patients. Patients were given infusions (sipuleucel-T or placebo) every two weeks, totaling 3 infusions. Eligible men had mCRPC and an expected survival of 6+ months. The trial included patients with any Gleason score (a score that determines the prognosis for men with prostate cancer) after an earlier trial showed positive results (4). The study found a 4.1-month improvement in median survival, and the 36-month survival probability was 31.7% in the trial group versus 23.0% in the placebo group. Adverse events, fever, chills, and headache, were reported more frequently in the sipuleucel-T group than in the placebo group. A subgroup of patients was monitored for immune functions at 6, 14, and 24 weeks. No survival difference was detected between patients in the Sipuleucel-T group who had T-cell responses to PA2024 or prostatic acid phosphatase and those who didn’t (4). This original study determined that Sipuleucel-T was safe for use and that it improved OS. The next step was to monitor the effects Sipuleucel-T had on specific immune system cellular responses.

As part of the IMPACT phase III study, the connection between the antitumor response of immunotherapies, like Sipuleucel-T, and the immune responses to secondary tumor antigens was studies closely. A sample of participants in the IMPACT study were used to assess humoral immunity responses (1). Serum samples from IMPACT patients were taken and assessed using multivariate Cox models, also adjusting for baseline PSA and lactate dehydrogenase (1). The results showed that IgG levels against PSA, as well as other secondary antigens, were elevated after Sipuleucel-T treatments. IgG responses increased approximately two weeks after infusions, and could persist up to six months later (1). Additionally, IgG responses to LGALS3 and PSA both were associated with increased OS. This study concluded that increased IgG responses increased overall OS. This assessment showed the successfulness of the vaccine and demonstrated the connection between improved immune response and OS. These particular methods and findings could help in future assessments of immunotherapies (1). Immunotherapies are used to treat many types of cancer and many of these treatments are being studied and improved. The hope is to create vaccines that can improve immune responses significantly without degrading quality of life.

Another trial combined use of Sipuleucel-T with abiraterone acetate. This study displays the methods in which we can determine the effectiveness and safety in combining immunotherapies with other forms of cancer treatment. This phase II trial assessed the differences of concurrent or sequential administration of abiraterone acetate plus prednisone (AA + P) on Sipuleucel-T immune responses and manufacture (5). Men with mCRPC were either treated with Sipuleucel-T followed by AA + P concurrent (once) or sequential (10 weeks after the infusion). Treatment with AA + P continued for the following 26 weeks. The goal of this treatment was increased antigen presenting cell (APC) activation, as well as to test the safety of this combined treatment. Overall, 69 mCRPC patients were enrolled with 35 and 34 patients split into two groups, concurrent and sequential respectively. APC activation was greater at the second and third infusions compared to the baseline APC activation. Antigen spread was also observed similarly to previous studies and was consistent with the other endpoints (5). There was also no indication that the combined treatment impacted the overall safety of either treatment. This trial concluded that AA + P alongside Sipuleucel-T is a safe and effective treatment for mCRPC. The combination of immunotherapy and other forms cancer treatments is common, and it is important to understand how combining therapies affects the effectiveness and safety of the treatment. Vaccine therapies have inconsistent effects on the immune response and improving our ability to predict responses is also an important task.

Since the approval of Sipuleucel-T in 2009, the monitoring of patients has improved out understanding of the effectiveness of the vaccine. The PROVENGE Registry for the Observation, Collection, and Evaluation of Experience Data (PROCEED) evaluated the effectiveness of Sipuleucel-T for mCRPC (2). PROCEED (2011-2017) tracked patients receiving 3 biweekly Sipuleucel-T infusions and assessed for overall survival, cerebrovascular events, serious adverse events, and anticancer interventions. Patients were followed up at 3+ years or until death or withdrawal from study.

This study found that although PROCEED patients had a good overall performance status (2). However, in comparison with those from the original IMPACT trial, the results showed a smaller increase in OS. This can be explained by several reasons, the PROCEED trials were larger and because randomized clinical trials like IMPACT have more stringent criteria for eligibility. Despite the lower overall results, the overall survival was higher for the PROCEED study, 30.7 months compared to 25.8 months. The PROCEED study took place during a period of significant progress in mCRPC management. Four new life-extending therapies were made available: abiraterone acetate, enzalutamine, cabazitaxal, and radium 223. These therapies used in tandem with Sipuleucel-T increased overall survival rates (2). The registry provided in vivo results and did conclude that Sipuleucel-T would increase OS. Each study determined that Sipuleucel-T was safe for use as well.

These studies each contribute the conclusion that Sipuleucel-T is an effective treatment for mCRPC. The available combinations of treatments for mCRPC are plentiful and can be tailored to each patient. Sipuleucel-T has the ability to increase survival for patients, buying them invaluable time. Future studies should focus on finding ways to predict immune reponses to Sipuleucel-T. As well as determining how Sipuleucel-T works in tandem with other types of cancer treatments. Although there is more to understand about this particular immunotherapy, these studies indicate a promising future for the treatment of cancer with vaccine-based cancer therapies. Personalized treatments show promising results and the field of immunotherapy research is growing. The better we can understand the mechanisms of cancer cells and the ways in which they interact with the immune system the better we can treat patients.

**References**

1. GuhaThakurta, D., Sheikh, N. A., Fan, L., Kandadi, H., Meagher, T. C., Hall, S. J., . . . Drake, C. G. (2015). Humoral Immune Response against Nontargeted Tumor Antigens after Treatment with Sipuleucel-T and Its Association with Improved Clinical Outcome. *Clinical Cancer Research,* *21*(16), 3619-3630. doi:10.1158/1078-0432.ccr-14-2334
2. Higano, Celestia S, et al. “Real‐World Outcomes of Sipuleucel‐T Treatment in PROCEED, a Prospective Registry of Men with Metastatic Castration‐Resistant Prostate Cancer.” *Cancer*, vol. 125, no. 23, 2019, pp. 4172–4180., doi:10.1002/cncr.32445.
3. Immunotherapy for cancer. (2019, September 24). Retrieved April 30, 2021, from <https://www.cancer.gov/about-cancer/treatment/types/immunotherapy#how-does-immunotherapy-work-against-cancer>
4. Kantoff, P. W., M.D., Higano, C. S., M.D., Shore, N. D., M.D., Berger, E. R., M.D., Small, E. J., M.D., Penson, D. F., M.D., . . . Schellhammer, P. F., M.D. (2010). Sipuleucel-T Immunotherapy for Castration-Resistant Prostate Cancer. *New England Journal of Medicine,* *363*(5), 411-422. doi:10.1056/NEJMoa1001294
5. Small, E. J., Lance, R. S., Gardner, T. A., Karsh, L. I., Fong, L., McCoy, C., . . . Shore, N. D. (2015). A Randomized Phase II Trial of Sipuleucel-T with Concurrent versus Sequential Abiraterone Acetate plus Prednisone in Metastatic Castration-Resistant Prostate Cancer. *Clinical Cancer Research,* *21*(17), 3862-3869. doi:10.1158/1078-0432.ccr-15-0079