THE APAC TIMES
Emerging Innovations In Cancer Immunotherapy
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The Men in Blue

Listed among top ten leading cancers in India, Prostate cancer nearly affects 15% of total men population with majority of cases diagnosed at ~ 65 years. Men with family history of prostate cancer have five times greater risk of developing the disease. India being a socio-cultural and ethnically diverse country lacks a standardized range of serum PSA. Despite the ***PSA era,*** a large number of prostate cancer patients in India have locally advanced /metastatic disease at presentation. Although treatments are available for organ filled carcinoma of prostate, advanced prostate cancer remains a disease with few options beyond palliation. The use of bisphosphonates in metastatic prostate cancer has been debated since the last decade. Although some success is achieved with taxane-based chemotherapy, cancer-specific immunotherapy is yet another emerging treatment in the management of Hormone Refractory Prostate Cancer.

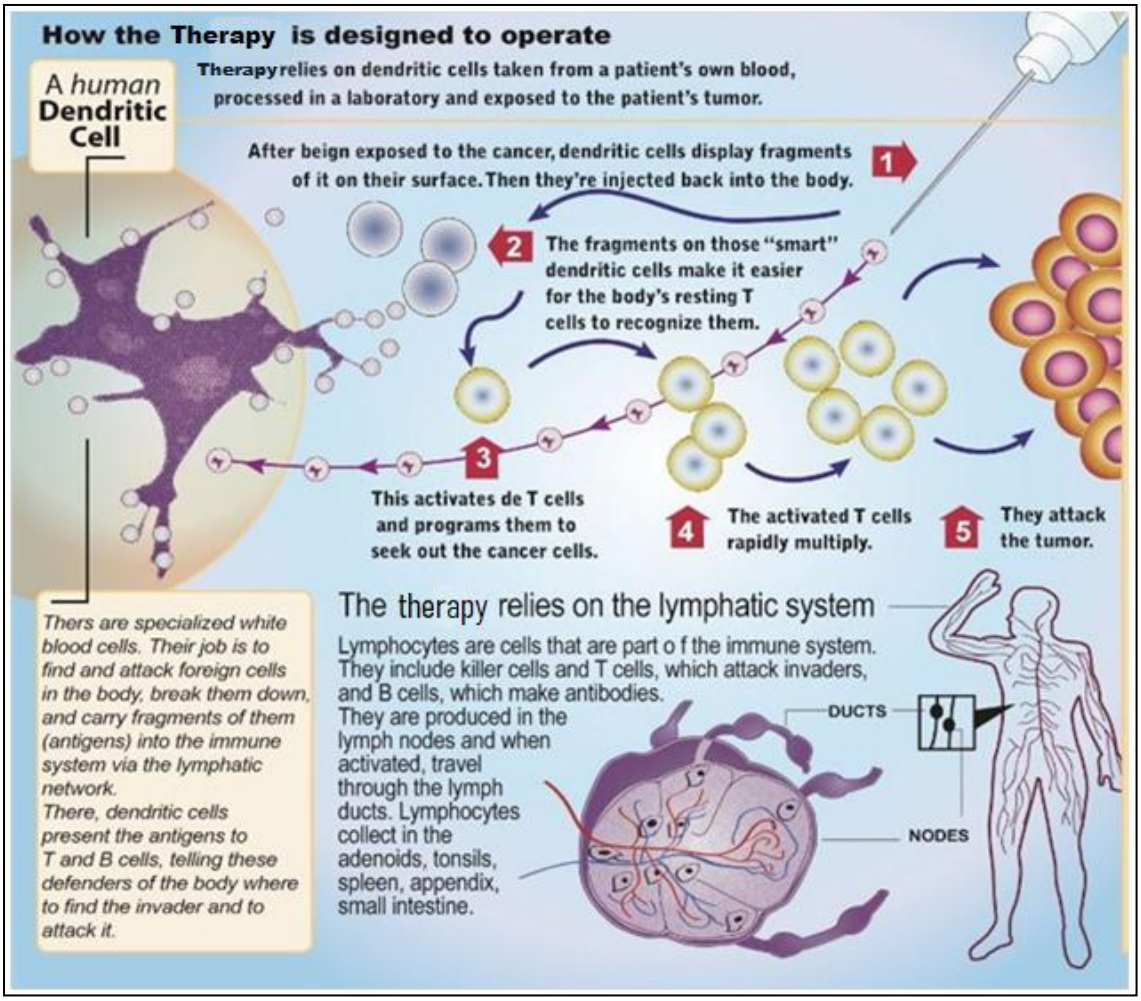


Figure 1: Overview of Personalized Immuno-therapy with Dendritic Cells

Nowadays, scientists are of the opinion for enhancing the natural immune system of the body so as to fight against malignant cells. Many types of immunotherapy for treatment of metastatic prostate cancer has been

in use such as vaccine-therapy, Dendritic Cell Therapy (DCT), Chimeric Antigen Receptor therapy (CAR) and check point inhibitors.

Out of all the above mentioned, dendritic cell therapy (DCT) has shown promising results in treatment of metastatic/ advanced prostate cancer. Being autologous in nature, DCT is safe without side- effects and has been very effective.

Era Where Cure Lies Within the Patient: Dendritic Cell Therapy

Additional treatment strategies are required to avoid progression from localized to advanced disease and to further improve survival outcomes. Several studies generally aim to induce T-cell responses against ***tumor specific antigens*** (TSA) to both reduce tumor mass and potentially avoid relapse.

One promising technique is to use autologous Dendritic Cells (DCs), the most potent antigen presenting cells ***(Figure 1)***. DCs display a unique capacity to ***induce, sustain***, and ***regulate*** T-cell responses. Studies have shown that DC can be loaded ***ex-vivo*** with a given antigen and subsequently injected back into the patient to stimulate the desired effect.

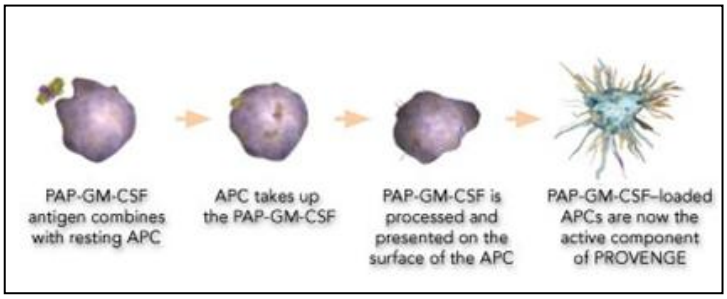


Figure 2: Preparation Of Sipuleucel-T

Till now, around 20 clinical trials have been conducted globally to investigate the benefits of DC-based therapy on patients with recurrent prostate cancer. Several strategies have thus far been employed using DCs for cancer therapy, including whole tumor tissue lysate, peptides, mRNA, and DNA-based approaches.

Sipuleucel-T: Product That Transformed the Term Immunotherapy

In 2010, Sipuleucel-T was approved by US-FDA for the treatment of asymptomatic or minimal symptomatic metastatic castration-resistant prostate cancer. This personalized therapy is manufactured from autologous mononuclear cells obtained via Leukapheresis that are further pulsed with **PA2024**, a fusion protein of the tumor antigen Prostatic Acid Phosphatase (**PAP**) which is expressed on more than 95% of prostate cancer cells and Granulocyte-Macrophage Colony-Stimulating Factor (**GM-CSF**). A phase III clinical trial (n = 512) was conducted where authors reported that treatment with Sipuleucel-T resulted in a statistically significant longer overall survival time of 4.5 months when compared with the placebo group (25.9 months in the treatment arm vs. 21.4 months on placebo; p = .01)***(Figure 3)*** The therapy involves the use of artificially synthesized antigenic peptides to induce **PAP/PA2024**-specific immune response. Regardless of being the first one, Sipuleucel-T therapy has encountered few limitations.

Figure 3: Detailed summary of overall survival and rate of disease progression in trials conducted with Sipuleucel-T.

Parameter	D9901		D9902A		Integrated Analysis D9901 and D9902A		IMPACT Study D9902B	
	Sipuleucel-T (N = 82)	*Placebo (N = 45)*	*Sipuleucel-T (N = 65)*	*Placebo (N = 33)*	*Sipuleucel-T (N = 147)*	*Placebo (N = 78)*	*Sipuleucel-T (N = 341)*	*Placebo (N = 171)*
Median survival (CI), months	25.9	21	19	15.7	23.2	18.9	25.8	21.7
Hazard ratio* (CI)[b]	1.71 (1.13–2.58)		1.27 (0.78–2.07)		1.50 (1.10–2.05)		0.775[a] (0.614–0.979)	
Overall survival, *P* value[c]	*P* = 0.010		*P* = 0.331		*P* = 0.011		*P* = 0.032[a]	
Median time to disease progression (CI), weeks	11	9.1	10.9	9.9	11.1	9	14.6	14.4
Hazard ratio* (CI)	1.45 (0.99–2.11)		1.09 (0.69–1.70)		1.26 (0.95–1.68)		0.92 (0.75–1.12)	
Overall TTP, *P* value	*P* = 0.052		*P* = 0.719		*P* = 0.111		*P* = 0.40	

CI = confidence interval; IMPACT = IMmunotherapy for Prostate AdenoCarcinoma Treatment; ln = natural logarithm; TTP = time to disease progression.

*The hazard ratio expresses the risk in patients treated with placebo divided by the risk for patients treated with sipuleucel-T. Therefore, a hazard ratio greater than 1 indicates a greater risk for patients treated with placebo relative to sipuleucel-T.

[a]The hazard ratio and *P* value are based on the Cox model, adjusted for prostate-specific antigen (ln) and lactic dehydrogenase (ln) and stratified by bisphosphonate use, number of bone metastases, and primary Gleason grade.

[b]The hazard ratio is based on the unadjusted Cox model (not prespecified).

[c]The *P* value is based on a log-rank test (not pre-specified).

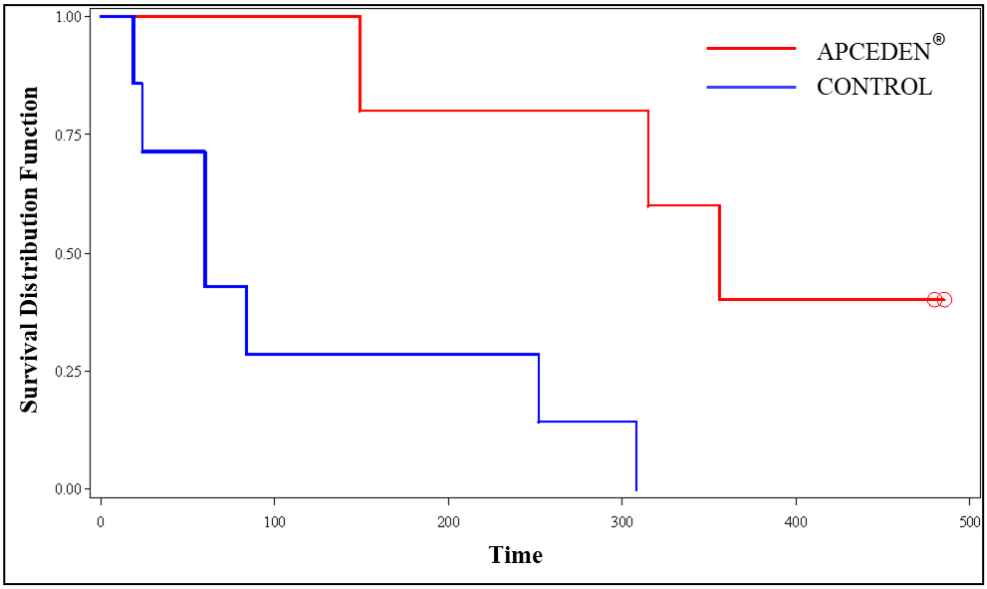
Data from Small EJ, et al. *J Clin Oncol* 2006;24:3089–3094;[13] Higano CS, et al. *Cancer* 2009;115:3670–3679;[14] Provenge prescribing information;[15] and Kantoff PW, et al. *N Engl J Med* 2010;363:411–422.[18]

Besides high production costs (USD 125,000$), patients experience discomfort as they have to undergo apheresis each time for a new dose preparation. Moreover, the therapy comprises of total number of 3 doses each containing mixed population of immune cells (less than 20% of mature dendritic cells). Despite this, it is the first DC-based therapy approved by the US-FDA that has been brought into the market by a private company (APC8015, Provenge®; Dendreon, Seattle, WA). Recently, a Chinese conglomerate (Sanpower) acquired Dendreon (producer of Sipuleucel-T) for over $800 million with the intention to extend the market to Asia.

APCEDEN® Upgraded To Match Sipuleucel-T Vision

The shortfalls encountered during preparation of Sipuleucel-T were taken into consideration while designing and manufacturing **APCEDEN®**(product of APAC Biotech) for cancer patients. In 2011, APAC Biotech conducted its first Phase II clinical trials with top leading hospitals of India to investigate the efficiency and efficacy of autologous whole tumor tissue lysate DC therapy on patients with recurrent prostate cancer (n=5). These patients reported a progression free survival of 306 days and median survival benefit of 356 days compared to the control group ***(Figure 4)***. Among 5 patients enrolled, due to geographical and financial constraints, 1 patient was actively followed post-trial completion & was able to maintain a stable disease progression until 2017 with a single round of therapy. Based on the trial

Figure 4: Kaplan Meier plot depicts an increased survival distribution (p=0.0252) among treated group. 5 patients enrolled for prostate cancer were able to demonstrate an increased overall survival of 356 days compared to their control arm of 7 patients devoid of DC therapy.



outcome, APCEDEN® (product of APAC Biotech) became the first Indian autologous personalised DC therapy to get Indian FDA approval for 4 indications of cancer (**Prostate**, **Ovarian**, **Colorectal** and **Lung**). Compared to Sipuleucel-T, APCEDEN® is more efficient, advanced and effective in treating recurrent prostate cancer patients in several ways.

The preparation of APCEDEN® involves isolation of monocytes form patient's blood followed by incubation with whole tumor tissue lysate isolated from the same patient to induce DC maturation.

Unlike Sipuleucel-T, the patient has to undergo Leukapheresis only once for monocyte isolation thus saving cost, time and offering more comfort to patient. Once matured, doses are thoroughly analysed for quality checks and cell number via flow cytometry. The final product comprises of 6 doses administered bi-weekly each containing ~5-7 million mature DC's that recognize most of the epitopes expressed on tumor tissue ***(Figure 5).*** The use of whole-tumor tissue allows DC to present multiple tumor associated antigen thus allowing generation of long-lasting effective memory response against tumor cells only. Moreover, APCEDEN® is available at all the leading hospital across India. When compared, the production cost of six-doses of Indian FDA approved personalized autologous DC therapy APCEDEN® is 1/10th of the Sipuleucel-T therapy.

APAC Biotech has been successful in delivering this therapy to patients for the similar indications. Among several successful prostate cancer cases, we have managed to highlight one of the study. In 2016, a 64-year-old Indian male was diagnosed with an advanced stage prostate cancer. The patient was bed ridden and had high PSA levels and was kept on hormonal therapy post radiation therapy. Following APCEDEN® dose completion, patient was actively followed up every six months. His recent scan in 2018

depicts complete remission of the tumor lesion. The patient is currently alive and is living a healthy life without the support of hormonal or chemotherapy (***Figure 5***).

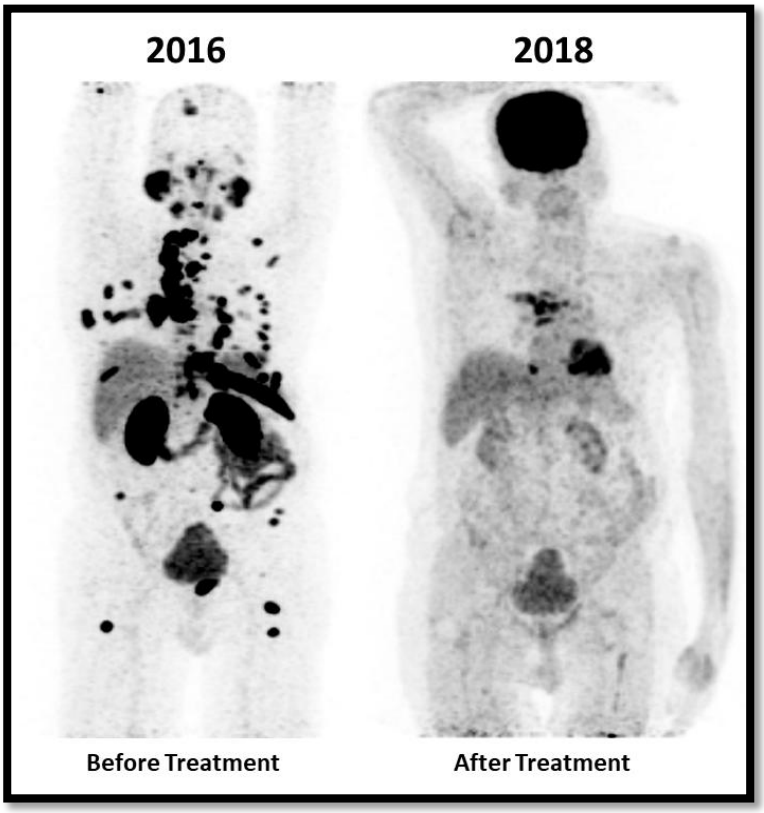


Figure 5: A comparison of PET-CT scan of a Prostate Cancer patient treated with APCEDEN® DC-based Immunotherapy

The Way Forward

DC therapy has proven to be feasible and safe in multiple clinical trials involving a diverse array of population. Emerging clinical data highlighting long-term safety and early evidence of clinical benefit raises hopes that DC therapy is capable of fighting against prostate cancer. DC therapy earlier in the course of disease is acceptable because of its low toxicity profile and is more beneficial as it more frequently induces tumor-specific immune responses. However, further progress in the field is needed to improve clinical outcomes and to exploit the full potential of DC-based immunotherapy. This may involve the use of combination regimens designed to overcome immunosuppression or alter tumor phenotype, thus making it more susceptible to immune-mediated killing. DC-therapy and antibodies administered in combination with radiation, chemotherapy may generate substantial synergistic effects. For cancer patients in otherwise excellent health, DC therapy may become a promising therapeutic option that avoids toxicities associated with chemotherapy or radiation.