Available online at www.abhipublications.org
Review Article
International Journal of Pharmacy and Engineering (IJPE)
ISSN 2320-849X

REVIEW ON IMMUNO THERAPEUTIC RESPONSES IN TREATMENT OF PROSTATE CANCER

Subhodip Das*, Pranjal Das.

BCDA College of Pharmacy and Technology, 78 Jessore Road, Kolkata-700127, India.

ABSTRACT

Prostate cancer is most significant and common non-cutaneous malignant in men. Various treatments is applied in adverse prostate cancer which give a limited therapeutic efficacy and several adverse effects in patient. Immunotherapy is a promising treatment for advance castrate resistant prostate cancer(CRPC)and several research is occur in this area over last several years. Provenge is dendritic cell based vaccine , only FDA approved immunotherapy treatment for mCRPC which gives a moderate responses in prostate cancer patients, it power up the patient's own immunity system to identify & target metastatic prostate cancer cell and enhanced overall survival (OS). Other immunotherapy like CAR-T therapy, checkpoint inhibitors (ipilimumb,pemobrocizumb, nivolumab) ,POROSTVAC vaccine therapy are in advance stage in clinical development. Several are gives a better therapeutics immune responses under clinical trials. Combinations stratagies is also make for treated advance prostate cancer such as immunotherpy combined with chemotherapy , radiation therapy, androgen deprivation, which show differents results. In this review discuss immune therapeutic responses in treatment of advance level prostate cancer also provide clinical data& information about current immune therapeutic target in prostate cancer , which helps researcher's to find better immuno responsive therapies in treatment of prostate cancer.

KEYWORD: sipuleucel-T(provenge), ipilimumab , CAR-T cell therapy, combined immunotherapy.

Received: 22nd May, 2018, Revised: 29th May , 2018, Accepted:1ST June , 2018,

Corresponding Author: * Subhodip Das, BCDA College of Pharmacy and Technology, 78, jessore Road, Hridaypur, Barasat, Kolkata-700127, West Bengal, India.
Email- dassubhodip56@gmail.com / subhodipdas3714@gmail.com

1 INTRODUCTION

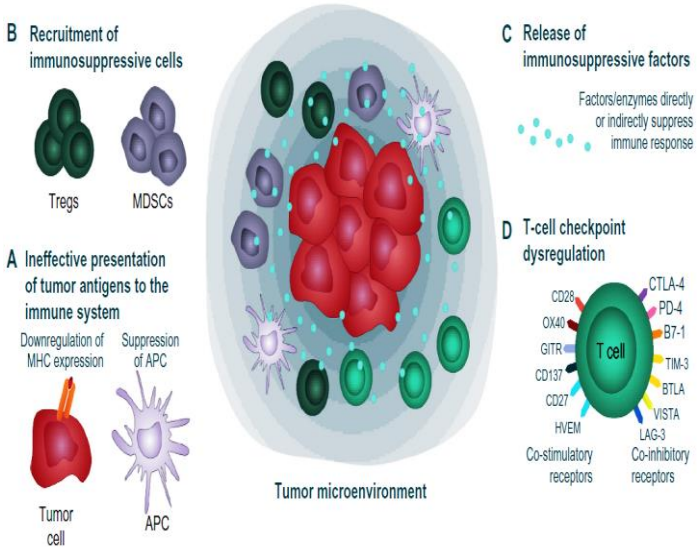
Prostate cancer is the second causes of death from cancer in men worldwide .Each year approx. 2000000 new cases reported in USA.Various technique implicated for treatment include surgery , hormone therapy , radiation therapy and also chemotherapy,these types of therapies only gives temporary relief & minimal long term impact on late stage of metastatic prostate cancer.To find a new way alternative treatment like immunotherapy, combination of immunotherapy with chemotherapy for the treatment of advance level metastatic castrate resistance prostate cancer (mCRPC).William B.Coley first introduced immunotherapy for treatment of cancer in 1890s.,he injected cancer patients with bacteria to activate an immune responses.IN 2010 FDA was approved immunotherapy for treatment of mCRPC.Several immune therapeutic approach were examined in pre-clinical and clinical trails of prostate cancer patients including sipuleucel-T therapy, checkpoint inhibitors, therapeutic vaccine, oncolytic virus therapies, adoptive cell therapies ,modulating &using pateints own immune system to targeted the cancer cells.Several research and evidence show that for cancer tumour to develop and metastasize it to escape anti tumour responses,especially cd8+ cytolytic T cell medieated elimination.prostate cancer specific antigen(PSA) is a best known prostate cancer biomarker ,introduced in 1986, currently targeted antigen for treatment of postrate cancer such as CLT4,PD-1,PAP another well known TAA .The expression of cancer or testis antigen ,AKAP-4, was tested in postate cancer patients to evaluate the possibility of exploting it as a target

for immunotherapy, Currently antibody based technique have focusing on enhancing antitumor immune responses by targeting immune cells, irrespective of tumors antigen. [1,2,5]

1.1 TUMOR ESCAPE MECHANISM: IMMUNOSUPPRESION

Tumours can suppress immunity two way systemically and in the microenviroment of tumour. Complex interactions between immunosuppressive cells such as macrophages, myeloid suppressor cells, regulatory-CELL and cancer cells cooperate to suppress antitumour immune responses and promote tumors

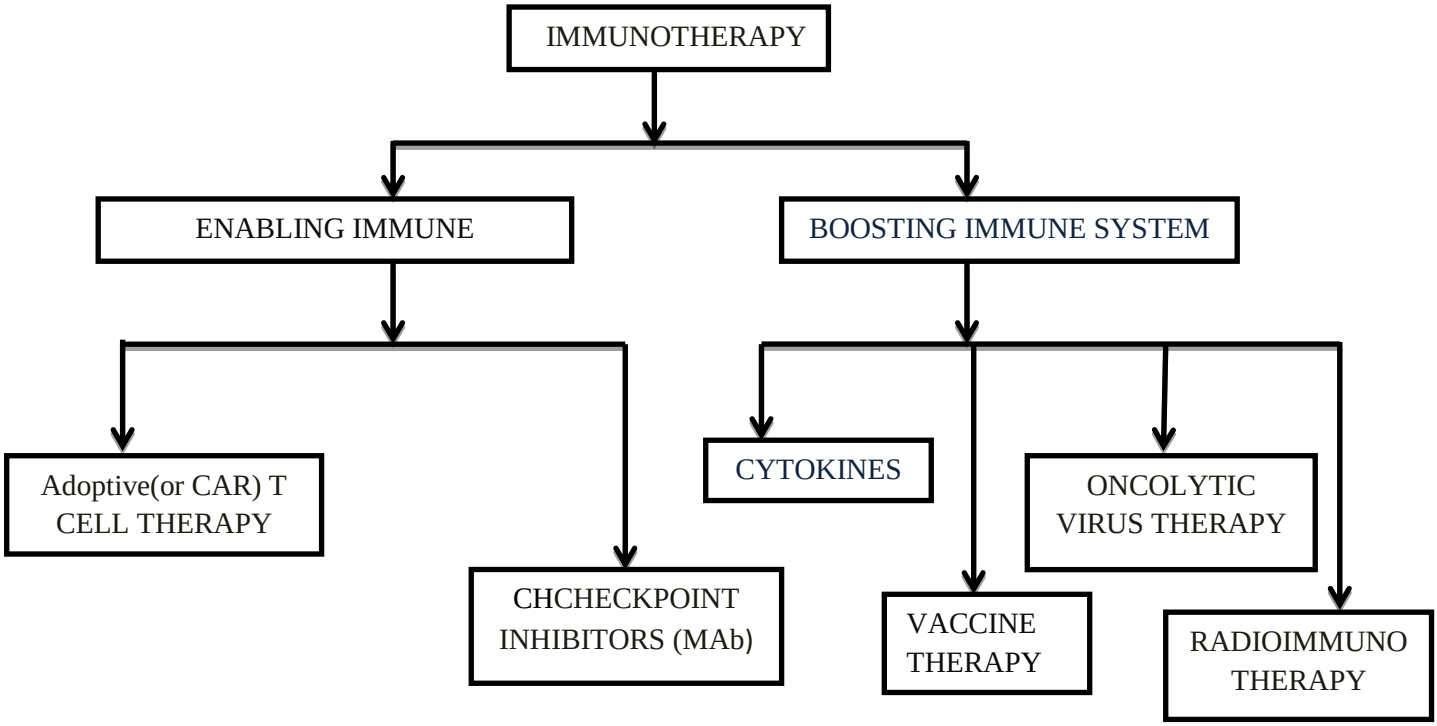
progression. Immunotherapeutic approach block the immunosuppressive pathway as a results slow the tumour growth & metastasis and increased immunogenicity in cancer tumors.[3]



FigNo.1: Immunosuppression in the microenvironment tumors

1.2 TYPES OF CANCER IMMUNOTHERAPIES [1,5]

Most immunotherapies available today are biological therapies made by living organisms.Many kinds of immune therapy treatment in development. They fall into two main categories**:-**

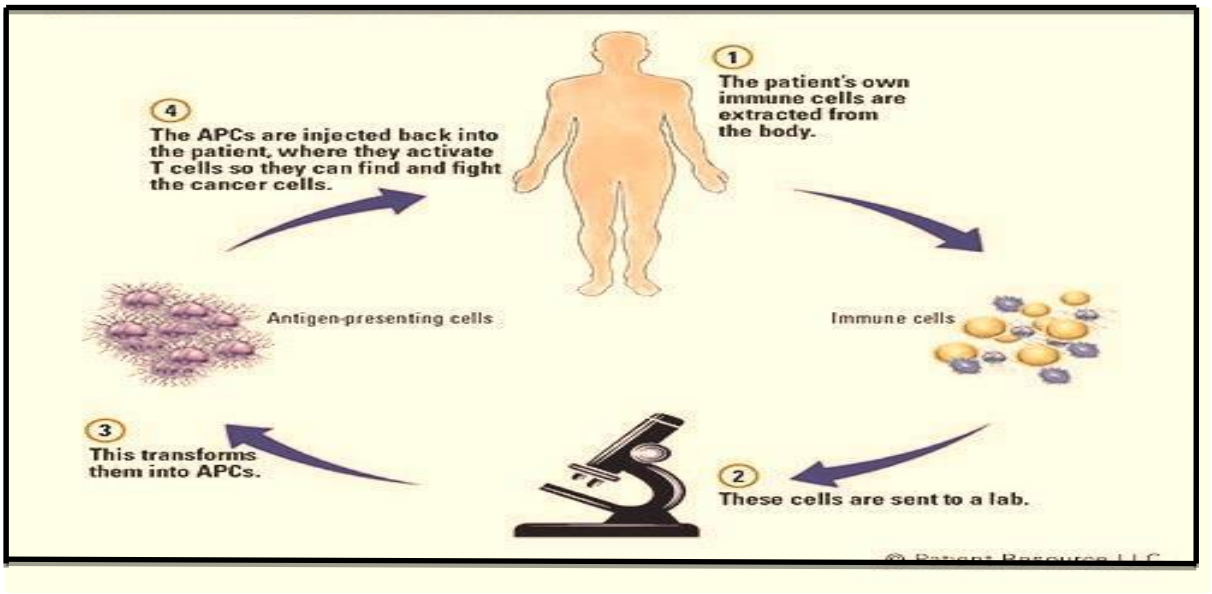


2.0 IMMUNOTHERAPY FOR PROSTATE CANCER TREATMENT

2.1 SIPULEUCEL-T THERAPY: Sipuleucel-T (provenge) is a dendritic cell(DC) based vaccine. It is the first FDA approved therapeutic cancer vaccine (Hammerstrom et al, 2011)[5].It is an autologous personalized vaccine that is prepared from the patient's own peripheral blood mononuclear cells .This immunotherapy use for the treatment of patients with asymptomatic or minimal symptomatic castrate resistance prostate cancer.

PREPARATION: Provenge preparation starts with their extraction by a leukapheresis procedure. After the extraction process these cells are incubated in vitro with a recombinant fusion protein (PAP-GM-CSF) consisting of the antigen prostatic acid phosphate(PAP),which present in 95% of prostate cancer cells& GM-CSF that helps mononeuclear cells to mature to dendritic cells which are professional antigen – presenting cells(APC).These activated cells are thereafter rein fused into the patient. A complete sipueucel-T treatment includes three courses at two week intervals**.** [1,4,5]

MECHANISM: The proposed mechanism of cells sipuleucel-T therapy is that these PA2024 –plused APC cells then present PAP-derived epitopes to the patient's immune system , which active PAP specific cytolytic T-cell immunoresponses that can recognize and lyse prostate tumour cells**. [**1**]**



FigNo.2: Dendritic cell vaccine

SIDE EFFECT: Provenge therapy is well tolerated most common adverse effect include fever, chillis, pyrexia ,fatigue and headache .Most of these symptom occurs with in 1-2 days following infusion.

INCREASING EFFICACY: Patients treated with sipuleucel –T had an increased mean overall survival by 4.1 month compared to the placebo treated group. also improvement in overall survival, time to clinical(HR:0.92;95%Cl,0.77-1.17,P=0.40) and objective disease progression (HR:0.05;95%Cl,o.77-1.77;P=0.63) was similar between the treatment and placebo group(kantoff et al). another phase III trials by small et al also did not show any difference in time progression but did show an overall survival benefit of 4.5 month.Also Various other clinical study performed to evaluate possible immuno therapy for prostate cancer (see table no.1).

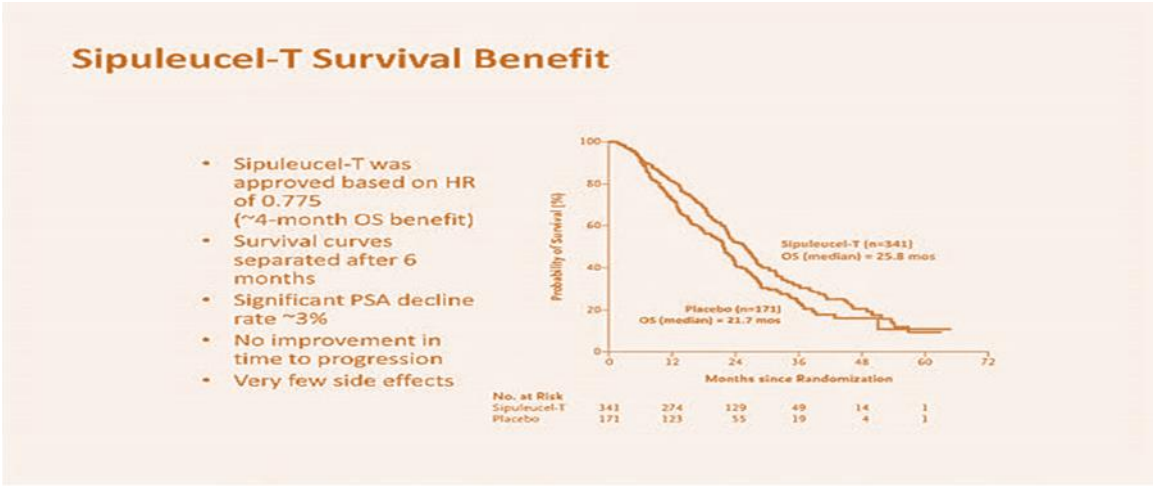


Fig No.3: sipuleucel-T immunotherapy for CRPC(adopted by kantoff pw,et al,N ENG MED ,2010)

Vaccine Therapy	Phase & status	Results
(PROSTVAC)	Phase II trial for mCRPC(complete study)	Improved OS in 125 patients.
(POSTVAC)	Phase III trials for mCRPC(complete study)	Failed to meet primary end point of improved OS.
(CV9104)	Phase I/II trial for mCRPC(complete study)	Failed to meet primary endpoint of improve OS.

TABLE NO.1: clinical trials of vaccine therapy

2.2 CHECK POINT INHIBITORS : In metastatic melanoma treatment checkpoint inhibitors (ipilimumab) improved progression free and overall survival in patien . Currently approved this classes of drug such as nivolumab, pembrolizumb for renal cancer ,melanoma and non- small lung cancer treatment. Checkpoint inhibitors describe as a CTLA-4 Inhibitors AND PD-1Inhibitors .Ipilimumab (anti-CTLA-4Inhibitors) first FDA approved immuno checkpoint inhibitors.CTLA-4 expressed on activated T-cells.B-7(CD80) is expressed on APCs and binds to its cognate receptor CD280 on Tcells.This interaction provides an important costimulatory signal for Tcell activation .Also CLTA-4bind to B7 but instead provides an inhibitory signal. Ipilimumab bind to CTLA-4 and block the interaction between CTLA-4 & B-7 there by abolishing this negative regulation and promoting a persistent Tcell activation. Several clinical trials and investigation occurs to check the efficacy and therapeutic responses in prostate cancer after good response in other cancer. but some immunoreleated adverse effects produce including diarrhea(54% patients), colitis (22%patients), rash(32% patients)and purities(20%).SMALL and COLLEAGUES conducted first trials to evaluate PSA modulation and safety with ipilimumab in mCRPC.In this trials only 14 patients is recived 3mg/kg dose of ipilimumab.Only two of these patients had a PSA response,define as a PSA decline of >50% or equal ,Also phaseII and phaseI/II study done with different type of CRPC patients.The median overall survival was 17.4 month.two type of phaseIII study conducted to determine the survival with ipilimumab in mCRPC.The first was randomized and double blind study that evaluate ipilimumab versus placebo after radiotherapy in mCRPC.in this trials 779 patients recived 10mg/kg ipilimumab or placebo every 3 week for upto 4 dose. The primary objective was os.The study was not meet the primary objective.The midean os was 11.2 month in ipilimumab arm compared to 10 month in placebo arm. Incase of checkpoint inhibitors some clinical study performed for mCRPC. (see table no.2) [1,6].

TABLE NO.2: clinical trials of checkpoint inhibitors

Checkpoint inhibitors	Phase & Status	Result
Ipilimumab(anti-CTLA-4)	Phase III study for mCRPC docetaxel refractory (complete study)	Failed to meet primary end point of improve OS
Ipilimumab	phaseIII study for mCRPC with chemotherapy-naïve (complete study)	Failed to meet primary end point of improve OS

2.3 CAR-T CELL THERAPY : In CAR-T therapy for prostate cancer treatment PSMA AND PSCM tumour associated antigen are used due to their relatively restricted expression to the tumour and tumour associated vasculature. Tcells are removed from a person with cancer, taken to a lab, and modified. Once a retruned to the person, these modified T cells can find and destroyed cancer cells .It is one type of adoptive therapy currently it is approved to treated certain leukemias and lymphomas.This type of therapy is currently under clinical devolopment for prostate cancer treatment but some study was done . CAR-T therapy generally well tolerated according to inferred data from hematologic malignancy trials.In another report using PSMA directed 3rd generation CAR-T cells showed significantly improved overall survival compared to 2nd generation PSMA directed CAR –T cells (zhong et al).[1]

2.4 COMBINATION IMMUNOTHERAPY: Combination immunotherapy effective for prostate cancer treatment .Resarcher will test a combination treatment of the immunotherapy drugs PORSTVAC , CV301 , ipilimumab to try and induce an anti tumour effect. once safe dosage is identified in an initial group with metastasis prostate cancer. Current study done on MDSCs, which are immune cells originating from bone marrow stem cells that posses strong immunosuppressive abilities and are known to play a role in tumour's formation and metastasis researcher targeted drugs for MDSCs combined with ICB which help Tcells to fight against mCRPC tumours in vivo.Targeted drugs such as cabozantinib(tyrosine kinase inhibitors), PI-3065,BEZ235(PI3K/mTOR) dual inhibitor) block the immune suppressive activity of MDSCs by inhibiting PI3K

signaling pathway& MDSCs recureting cytokines, and reducing expression of immunosuppressive genes. ICB enhance Tcell profilation thereby activating strong immune response against mCRPC tumour cells[6,8].This combined immunotherapy technique may be applied for treating the human mCRPC patients. This combination have synergistic efficacy on mCRPC in chimeric mouse model.

3.0 CONCLUSION

Immunotherapy provide a moderest immune response against prostate cancer . Provenge DC- vaccine therapy only approved by FDA for mCRPC treatment .Also currently various clinical trials performed to find a safest and effective immune response for prostate cancer treatment. Immunologist find a immunosuppressive molecule and antigen for preventing the metastasis and prostate cancer growth .It is more important to understand the effect of immunotherapeutic agent on tumour immune supression and how its activated T-cell to inhibit the prostate cancer cells. Recent study performed on combination immunetherapies .various clinical trials recurting example nivolumab with ipilimumab,more research need in future for combination immunotherapy,which is help in future for advance level prostate cancer treatment and provide effective immuneresponse against the cancer tumours cells and metastasis.

4.0 REFERENCES

1. Oladapo Yeku, MD, PhD1 and Susan. F. Slovin, MD, PhD1, Immune therapy for prostate Cancer J.2016;22(5):334-341.,
2. . Gregory T. Wurz, Chiao-Jung Kao and Michael W. De Gregorio, Novel cancer antigens for personalized immunotherapies: latest evidence and clinical potential , Ther Adv Med Oncol
   2016, Vol. 8(1) 4–31
3. Anna Meiliana1,2,□ , Nurrani Mustika Dewi1,2, Andi Wijaya1,2 , Cancer Immunotherapy: A Review, Cancer Immunotherapy (Meiliana A, et al.) Indones Biomed J. 2016; 8(1): 1-20

4. Brian M Olson, Douglas G McNeel, Sipuleucel-T: immunotherapy for advanced prostate cancer, Open Access Journal of Urology 2011:3 49–60.
5. . Minda Asfaw Geresu1 Gezahegne Mamo Kassa2 Temesgen Bedassa3, A Review on Immunotherapy against Cancer, Journal of Health, Medicine and Nursing, Vol.25, 2016 :15-25.
6. Lisa M Cordes1,2, James L Gulley2, Ravi A Madan2, Perspectives on the clinical development of immunotherapy in prostate cancer, Asian Journal of Andrology (2018) 20, 253–259
7. Bently P Doonan and Azizul haque, Prostate cancer immunotherapy:Exploiting the HLA classII pathway in vaccine design,J Clin Cell Immunol.2015 August ; 6(4):1-16.
8. Sufyan suleman, gong –hong wei ;Combined immunotherapy for advanced Prostate cancer:Empowering the T cell army, Asian Journal of urology (2017) 4,199-200.

Received: 22nd May, 2018, Revised: 29th May , 2018, Accepted:1ST June , 2018,

Corresponding Author: * Subhodip Das, BCDA College of Pharmacy and Technology, 78, jessore Road, Hridaypur, Barasat, Kolkata-700127, West Bengal, India.
Email- dassubhodip56@gmail.com / subhodipdas3714@gmail.com