

Clinical development in dendritic cell based immunotherapy

Abstract

Immunotherapy using dendritic cells has emerged as a potent option for the treatment of the solid tumours. Over the past few decades, multiple clinical trials have been carried with the aim of increasing the efficacy of this therapy. Many protocols have been developed to generate large scale production of dendritic cell which have been used in clinical trials. Dendritic cell therapy has demonstrated high overall response rates, resulting in tumor regression and prolonged survival. Various factors, viz., number of dendritic cell administration, antigen source, mode of administration, combination strategy are still under clinical development. This review summarizes the results of clinical trials for multiple solid malignancies. As a sole review for oncologist, it can help improve understanding of the subject matter, with the aim of increasing the participation of patients at earlier stages of malignancies to participate in clinical trials or treatment plans using dendritic cell immunotherapy.

Keywords: dendritic cell therapy, clinical trials, cancer vaccines, solid tumours, immunotherapy

Volume 1 Issue 2 - 2016

Chandan R Bora, Luis Martinez

NOVO Cellular Medicine Institute, Southern Medical Clinic Campus, Trinidad & Tobago

Correspondence: Luis Martinez, Director-Cancer Research Therapeutics, NOVO Cellular Medicine Institute, Southern Medical Clinic Campus, 26-34 Quenca Street, San Fernando, Trinidad & Tobago, Tel +18683482702, Email chabora@gmail.com

Received: January 27, 2016 | **Published:** April 26, 2016

Abbreviations: CT, computed tomography; ANA, anti nuclear antibody; RECIST, response evaluation criteria in solid tumours; OR, objective response; PD, disease progression; SD, stable disease; PR, partial response

Introduction

Dendritic cell have been recognized as most potent antigen presenting cells that capable of activating T cells against tumor antigen. Dendritic cells were first discovered by Steinman RM & Cohn ZA et al.¹ He was awarded Nobel Prize in medicine in 2011 for discover of these novel cells. Expression of costimulatory molecule and ability to generate strong immune response differentiate it from B cell and macrophages.^{2,3} Human dendritic cells mainly classified into two main categories viz plasmacytoid (pDCs) and myeloid (mDCs). pDCs mainly found in blood, bone marrow, thymus spleen etc however mDCs mainly found in peripheral blood.⁴

Due to unique characteristics of the dendritic cell, Immunotherapy using dendritic cell therapy has emerged as one of the potent treatment options for solid tumors. Most of the clinical trials are carried out with autologous dendritic cell therapy with antigen loaded enhancing antitumor immune response. Recently there have been a number of groups conducting trials based on improving efficacy of the dendritic cells by different maturation stimuli, choice of the antigen, route of the delivery etc. Combination approach especially with Chemotherapy or other immunotherapies like Tumor lymphocytes therapy also have promising results. Injected DC will migrate to lymphoid organ to activate tumor specific CD4+ and CD8+ T cells.⁴ There are number of ways to analyse clinical response like Lymphocyte proliferation assay, ELISPOT assay, cytokine release assay, cytotoxicity assay, CD4/CD8 counts, computed tomography(CT), scans, Radiological assay, Biochemical assay viz in prostate cancer increase or decrease in PSA level, elevated of serum ANA (antinuclear antibody). Response Evaluation Criteria in Solid Tumors (RECIST) were used widely for evaluation of clinical responses like Objective response (OR), Disease

progression (PD), Stable disease (SD), Partial response (PR), Mixed Response etc.⁵

Constantino J et al.⁶ reviewed last 20 years of clinical trials on dendritic cell based vaccines However to examine exact antitumor response it is very important to administer the therapy in early stage of the cancer. In later stage of the cancer it is very difficult to predict antitumor response due to multiple malignancies and lower survival rate. Therefore we provide an updated review for Oncologists, showing the results of the trials, so that they may gain additional knowledge and confidence in enrolling patients for clinical trials and treatment program, especially at earlier stage of the cancers.

Generation of clinical grade of dendritic cells from peripheral blood

Two general protocols have been used in different clinical trials 1. The conversion of mature dendritic cells from immature DC precursors from peripheral blood 2. *In vitro* conversion of DC from CD34- or monocyte.⁷ Most cost effective method for isolation of monocyte (CD14+) is isolation of buffy coat from whole blood or leukopheresis by Ficoll Hypaque density gradient centrifugation.^{8,9} Further CD14+ cells were enriched by plastic adherence or immunomagnetic beads. Immature DCs will be differentiate from CD14+ cells by keeping several days in presence of Granulate macrophage colony stimulating factor (GM-CSF) and Interleukin-4 (IL-4).¹⁰ Mature and Immature DC have significant importance in dendritic cell based immunotherapy. Immature DCs will differentiate into mature DC by adding maturation stimuli like Poly I: C, TNF-alpha, FLT3 ligand, LPS, or CD40L.¹¹ Immature and mature DC has significant impact on ineffective antitumor response.^{12,13} DCs are characterized by presence of CD80 and CD86, CD40, CD70, or inducible T-cell co stimulator ligand (ICOS-L) molecules. Flow cytometry is widely used to count the number viable DC generated from peripheral blood. However single surface marker is not sufficient to count number of viable DCs. Therefore combination marker study has been viz Presence of

CD80, CD83, CD86, CMRF44 and absence of marker like CD14, CD19, CD56 etc.¹⁴ Dauer M et al.¹⁵ described a novel strategy for the development of mature DCs from monocytes within only 48 h. The study demonstrated fast generation of DCs that reduces the time, work load, and cost associated with *in vitro* culture of DC precursors. Kvistborg P et al.¹⁶ studies two protocols (2 days and 5 days) to shorten the standard 8 days protocol. They found short day protocol will have less laborious, cost effective and physiologically correct. Provenge (Sipuleucel-T) got the US-FDA approval for the treatment of hormone refractory prostate cancer. Their methodology is directly isolating DC from peripheral blood. Further DC product was enriched with growth factors and recombinant proteins. The complete process is about 48h after leukopheresis.¹⁷ DC vaccines should check for any bacterial contamination, Mycoplasma contamination, endotoxin level and hypersensitivity reactions prior to administering to patients.

Antigen priming

Antigen exposure is the most important factors in dendritic cell therapy. Most of the trials disappointing results due to lack of identifying tumor specific target antigen which is unique to the tumors or, over expressed on the tumors as compared to normal cells.¹⁸ Different types of clinical trials were conducted using different type of antigen (Table 1).¹⁹⁻⁷⁸ Being as an autologous therapy, whole tumor lysate is the best way to expose the antigen. Because dendritic cells will be exposed to those proteins, which are over expressed on the tumour cells.⁵⁶ However sometimes it not possible to get biopsy samples from patients in that case Paraffin block can be used.⁶⁵ Allogenic whole tumour cell line is also used in few clinical trials.^{26,38,41,68} Over expressed proteins/peptides can also used as antigen in DC vaccination therapy like in prostate cancer few proteins are over expressed like Prostate-specific antigen (PSA), Prostate-specific membrane antigen (PSMA), Prostatic acid phosphatase (PAP), Prostate stem cell antigen (PSCA), Prostein, Transient receptor potential-p8 (Trp-p8), Human telomerase reverse transcriptase (hTERT), Survivin⁷⁹ in breast cancer HER-2/neu,³⁵ in pancreatic cancer The Wilms' tumor gene 1 (WT1)^{50,51} etc. Several strategies is being used to increase clinical outcomes of the peptides based vaccines like testing of Toll-Like Receptors (TLRs) agonists, agonists for Pattern Recognition Receptors (PRRs), improve immuneogenicity of the peptides etc.¹⁸

Mode of administration

The Mode of DC administration and number of DC doses are still under clinical development. Once DC are administrate they will migrate to lymphoid organ to activate T cells. The route for DC administrated varies for different malignancies viz. Intravenous,^{23,75} intradermal,^{39,45} subcutaneous,⁵⁷ intranodal,³⁵ intratumoral.⁷⁹ In case of Intravenous administration, DC will temporary uptake by lung and then it will transferred to liver, spleen and bone marrow however in case of intradermal and subcutaneous administration DCs will migrate to lymph node.^{4,80} Several strategies are being used like multiple routes of administration of DCs.³⁷

Clinical development

Clinical development in dendritic cell therapy in different malignancies in clinical trials including the number of patients, number of DC infused, antigen source, and mode of infusion with reference have been presented in (Table 1).

Prostate cancer: Small EJ et al.¹⁷ treated 127 Sipuleucel-T against prostate cancer. They showed overall advantage to asymptomatic

Hormone refractory prostate cancer patients. The group of Higano CS et al.²¹ treated 225 patients with Sipuleucel-T against prostate cancer. Their group showed 33% reduction in risk of death. Further study on Sipuleucel-T Sheikh NA et al.²³ treated 737 patients showed antigen specific mechanisms by which Sipuleucel-T prolongs overall survival. The data of these clinical trials with Sipuleucel-T consisting of PA2024 fusion protein-loaded APCs allowed it to receive approval by the US-FDA for the treatment of prostate cancer.

Renal cell carcinoma: Azuma T et al.²⁹ showed that by the treating of dendritic cell therapy in RCC patients, there was induced T cell immunological response without toxicity. In the trial; 4 DC vaccinations gave over the period of two months. Effective antitumor response indicates DC is potential effective therapy. Wei YL et al.²⁸ treated 10 renal cell carcinoma patients with dendritic cell therapy. They used IL-2 as an adjuvant along with DC therapy. The group found 40 % patients showed clinical outcomes, 3 of which showed disease stabilization and one show partial response with reduction in tumor size.

Ovary cancer: The group of Kobayashi et al.⁵⁶ used different recombinant proteins like Synthetic peptides WT1, MUC1 and CA125. Result of this showed 71% enrolled patients for Ovary cancer developed immunological response. The study proved safety, immunological responses, and clinical effects of DC vaccines targeting synthesized peptides in ROC patients.

Pancreatic cancer: Koido S et al.⁵¹ Used WT1 peptides in dendritic cell therapy in 11 pancreatic cancer patients. The Study showed significant increase in overall survival (OS) and progression free survival (PFS). A Similar type of study was carried out by Mayanagi S et al.⁵⁰ in 10 pancreatic cancer patients. The study proved dendritic cell therapy is Feasible and effective for inducing antitumor T cell response. Zhu H et al.⁶⁵ treated 100 colorectal patients with dendritic cell therapy along with CIK treatment. Their study showed 62% patients developed positive cell mediated cytotoxicity response and effective and safe treatment observed by quality of life and Overall Survival of patients.

Breast cancer: In 2007 different group of Scientist^{33,36,66} used recombinant proteins/peptides for DC vaccination in breast cancer solid tumors. They found therapy is feasible, safe and tolerated. Their study showed significant antitumor immune response. Svane IM et al.³³ mentioned that all enrolled patients in the clinical trials had metastatic breast cancer with a high tumor burden. Therefore p53 specific activation of immune system into significant tumor regression might not possible.

Lung cancer: In 2004 Hirschowitz EA³⁸ used adenocarcinoma 1610 cell line as an antigen source in 16 lung cancer patients. They found increased interferon gamma production by CD-8 cells. The study proved that DC therapy can be used as multimodality therapy for all stages of NSCLC patients. Chang GC et al.⁴⁰ studied DC therapy in 8 lung cancer patients. The study showed No grade II/II toxicity, Increased in T cell response against tumor antigen and 5 patients showed PD, 1 tumor response and 2 SD. Their group injected DC Intranodal for high expression of CCR7. High expression of CCR7 indicated that DC has been migrated to lymph node.

Melanoma: DC therapies have promising outcomes in Melanoma cancer. Rosenblatt J et al.⁴³ studied DC therapy in 17 Melanoma patients. The group found study is feasible and well tolerated. Antitumor response and disease stabilization found in majority of the

patients. Timmerman JM et al.⁶⁰ Studied DC therapy in 35 lymphoma patients. The study showed induced T cell and humoral anti ID immune responses and tumor regression. Maier T et al.⁶¹ studied DC therapy in 10 lymphoma patients. They found 50% patients showed objective response.

Hepatocellular carcinoma: Palmer DH et al.⁶⁸ studied DC therapy in 39 Hepatocellular carcinoma patients. Their study showed antitumor immune response by significant decline in serum AFP and release of IFN-gamma. Study of Tada F et al.⁶⁷ proved DC therapy in Hepatocellular Carcinoma is well tolerated and induced antitumor immune response however author suggested patients should consider for clinical trials in less advance stage of cancer for better clinical response.

Brain cancer: Cho DY et al.⁵² studied DC therapy in Glioblastoma Multiforme in 18 patients. The study found survival rate of patients for 3 years 88.9%, 44.4% and 16.7% respectively while study of Yamanaka R et al.⁵³ showed average rate of survival 480 days in Glioma cancer. 13 Astrocytoma patients treated with DC therapy and found therapy is Safe, induces tumor response and favourable tumor response with adjuvant chemotherapy.⁵⁴

Gall bladder: Safety of the DC vaccination also has been proved by Khan & Sharmin et al.⁷² in gall bladder cancer. The patient was treated with 10 doses of DC vaccination over the period of 14 months. Positive clinical response was obtained which reflects therapeutic approach of DC Vaccination for gall bladder cancer.

Multiple malignancies: The DC therapy was studied in multiple malignancies in all over the world.^{73,74,76,62,69,78} Their study showed therapy is well tolerated without side effect. There is increase in Cd4 and CD8 T cells expressing IFN-gamma release and induced tumor specific cellular cytotoxicity. Datta J et al.⁸¹ reviewed optimizing DC based multimodality strategy for cancer immunotherapy. Due to multiple studies proving the safety of DC vaccination investigators may skip additional safety studies.

Emerging trends in dendritic cell therapy

Suehiro et al.⁵⁸ used novel Tax peptide-pulsed dendritic cells for adult T cell leukaemia/lymphoma in a pilot study. Their study found DC Vaccine is safe with promising clinical outcomes. Kumar J et al.⁸² isolated CD11c+ DCs from umbilical cord blood samples and Peripheral blood samples. Their study proved that DC derived from umbilical cord blood samples are equally potent as compared to DC derived from Peripheral blood samples. This data append novel allogeneic anti-tumor vaccines in cancer immunotherapy, Adoptive T cell therapy based on tumor infiltrating lymphocytes (TILs) is the most effective treatment in few malignancies. Bora et al.⁸³ critically reviewed different aspect of Tumor Infiltrating Lymphocytes (TILs) Therapy and its possible combination with dendritic cell therapy. Osorio F et al.⁸⁴ reviewed function of DCs in induction of lymphocyte tolerance and discussed on the mechanisms to induce tolerogenic DCs. Wares JR et al.⁸⁵ developed model that contain combination of Oncolytic Viruses and dendritic cells. The model contains varying doses of Oncolytic Viruses and DC injections to test combination approach. The model was successful in increase efficacy to eliminate tumors.

Role of CD4 and CD8 T cell population in DC based vaccination therapy

Activation of T cell is depending upon the interaction of DC with

T cell. For making stable long lasting contact with the T cell proper maturation of DC is important.⁴ Cytokines and chemokines in DC environment plays important role in generation of immune response to acquired antigens. Activated T cells may produce cytokines that support the development of an adaptive immune response.⁸⁶ Hasumi K et al.⁸⁶ treated 26 patients with advanced malignancies treated with Combined Dendritic Cell-Activated T Cell Based Immunotherapy and Intensity-Modulated Radiotherapy. The study showed successfully eliminates metastatic and recurrent tumors on initial treatment in 21 of 26 patients. CD4 and CD8 T cell surface molecules that play a role in T cell identification and activation by binding to their relevant major histocompatibility complex (MHC class I and II) ligands on a dendritic cells. Antigen that bound to MHC class I molecule recognized by CD8+ T cells and antigen that bound to MHC class II molecule recognized by CD4+ T cells that result in decrease in tumor burden.⁴ After interaction of DC with CD4+ T cells antigen specific T cells with different function like T helper 1 (TH1) cells, TH2 cells, TH17 cells or T follicular helper (TFH) which help B cells to differentiate into antibody-secreting cells and regulatory T (TReg) cells that down regulate the functions of other lymphocytes. CD8+ T cells after interaction with CD8+ T cells give rise to effector cytotoxic T lymphocytes (CTLs).⁸⁷ In study of cytotoxicity assays; 10-100 times more CD8+ effectors than target cells are necessary to reach 50-60% of tumor cells lysis.⁷ Antigen stimulated CD8+ T cells have been produce huge amount of chemokines and cytokines such as RANTES, MIP-1-2, IFN-gamma and TNF-alpha.⁸⁸ Few study reported that antigen presentation by IFN gamma DCs resulted in higher number of IFN gamma producing cells as compared to conventional immature DCs. Currently most of clinical trials are going using cytokines such as GM-CSF, IFN-alpha, IL-2 and IL-12.⁸⁹ Immunotherapy using adoptive T cells has emerged as one of the potent treatment options for metastatic tumors. The Tumor Infiltrating Lymphocytes therapy has demonstrated high overall response rates, resulting in tumor regression and prolonged survival in comparison to IL-2 and ipilimumab treatments. Expansion of TILs under ex-vivo conditions using patients' own tumor tissue is a prerequisite for effective adoptive transfer immunotherapy. The existence of lymphocytes in tumors is often associated with better clinical outcomes and reflects tumor-host interaction. Clinical studies have demonstrated higher percentage of activated T regulatory (Treg) cells and activated CD8+ T cells in peripheral blood during the TILs treatment; compared to the untreated control subjects.⁹⁰ Fukunaga et al.⁹¹ demonstrated that CD8+ TILs together with CD4+ TILs and dendritic cells improved the prognosis of patients with pancreatic adenocarcinoma.⁹¹ The results showed that overall survival rate was significantly higher in CD4+/8+ patients (13 cases) compared to those in other groups CD4+/8-, CD4-/8+; CD4-/8- (67 cases). Aquilar-Cazares et al.⁹² studied the density of Intratumoral DCs and their impact on the density of TILs in 82 patients with non-small cell lung carcinoma (NSCLC).⁹³ A 2.5-fold boost in TILs cell count was found in specimens with high infiltrating DCs densities compared to those with low DCs densities. The study showed that quality of life and survival of NSCLC patients improved with the combined treatment of tumor-DCs-TILs.⁹³

Conclusion

The results of the clinical trials provide evidence for the potential applications of dendritic cells as a cellular adjuvant for the development of therapeutic vaccines for solid tumors. Cellular cancer therapies like dendritic cell therapy are becoming more popular choices for cancer treatment due to the generation of clinically effective antitumor

response and relatively low side effects. Based on the clinical trials data, dendritic cell therapy has shown good effectiveness in treating prostate, melanoma, Renal cell carcinoma, breast, lymphoma, colorectal, ovary and other multiple groups of solid malignancies. There have also been some clinical trials that failed to produce good results with dendritic cell therapy. The negative outcomes may be attributed to the advanced tumor stages of the patients. Despite considerable progress over the last decade, it is very difficult to draw a comprehensive conclusion on immunotherapeutic strategies in treating cancers. Treatment with dendritic cell therapy in patients with early stage cancer may provide us more insights in this field. Cancer immunotherapy needs further in-depth investigations on combination approaches that can improve long term efficacies and reduce the cost to a more affordable level.

Acknowledgements

None.

Conflict of interest

The author declares no conflict of interest.

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