European Journal of Molecular & Clinical Medicine
ISSN 2515-8260 Volume 9, Issue 4, Summer 2022

# DENDRITIC CELL BASED IMMUNOTHERAPY IN RECURRENT AND METASTATIC ADVANCED SOLID TUMORS SHOWING EXCELLENT RESPONSE: THREE CASE STUDIES

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**ABSTRACT**

Background: Despite conventional treatment approaches for cancers, relapsed and metastatic refractory cancers have overall poor prognosis with poor quality of life. Dendritic Cell (DC) - based immunotherapy is a viable and promising treatment option in such cases. Dendritic Cell Therapy (DCT) induces antitumor T-cell response in-vivo.

Case Series : We describe three of the ten cancer cases of patients who despite being successfully treated by conventional treatment had disease recurrence with multiple metastases and disease progression. In the first case, a 17 year male patient who is a known case of osteosarcoma of right femur who had undergone successful conventional treatment had a recurrence with bilateral lung metastases. The second case is a 64 year female patient who is a known case of Metastatic adenocarcinoma of unknown primary with metastases at diagnosis who despite being treated by conventional treatmenT had disease progression. The third case is a case of 47 year female patient who is a known case of Non-small cell Lung cancer who was treated successfully by conventional treatment had a recurrence with multiple metastases. All the three cases were advised further treatment by Dendritic Cell therapy.

Results: One of three patients has shown complete response and remaining two patients has shown partial response with longer survival and improvement in quality of life.

Conclusion: Dendritic cell based Immunotherapy can activate antitumoral T cell responses in patients with various cancers. This data indicates that treatment with autologous tumor-pulsed

DCs is safe and can activate tumor specific cellular cytotoxicity. Clinical responses can be achieved even in patients with metastatic and advance stage cancer.

**Introduction**

Cancer continues to grow globally and is a leading cause of death , accounting for approximately 1 in 6 human deaths worldwide. In 2020, cancer accounted for approximately 10 million deaths [1] Over the course of past decade though treatment of cancer is on the fast track, many tumors are still incurable. There are three basic approaches in cancer treatment which includes surgery, chemotherapy, and radiation therapy. Due to several limitations, the efficacy of these treatment strategies for cancer has been hampered, so there is a necessity for other therapeutic methods. Thus there is a shift in focus to more specific targeted therapies and immunotherapy. One viable therapeutic approach in cancer immunotherapy is the use of dendritic cells (DCs) to help in orchestrating a repertoire of both innate (natural killer cells) and adaptive (T cells) immune responses against cancer. There is increasing evidence from animal studies and clinical trials which has shown DC-based immunotherapy strategy may be a viable option in cancer treatment and thus it has emerged as a rational new concept in the treatment of malignant tumors. Steinman et al. discovered Dendritic Cells[DCs] in 1973, for which he was awarded the 2011 Noble Prize in Medicine [2]. Since its discovery, DCs have evolved from subset curiosity to the most sought-after treatment option in immunotherapy. DCs are the most potent antigen-presenting cells. Their key role is in programming and regulating tumor-specific immune responses by processing and presenting tumor antigens to naive or effector T lymphocytes [3]. DCs are found in many parts of the body like the epidermal layer of the skin, the gastrointestinal and respiratory systems, and the interstitial regions of several solid organs. These DCs play a role as sentinels and engulf invading foreign microorganisms or pathogens for presentation to immune cells [6]. DC capture proteins, then proteolytically digest them, and the resulting peptides are presented on its cell membranes bound to MHC antigens[4] . This complex of MHC-peptide is the key stimulus to activate T cells. Also, DCs have high levels of the costimulatory molecules, CD80 and CD86. This CD80 and CD86 along with MHC-peptide leads to the full T cell activation [5]. In 1996, the first clinical trial using DC-based immunotherapy was reported, and since then DC-based immunotherapy has been developed and used for the treatment of various cancers [7]. Recently, in clinical trials with several types of cancers being treated by DC-based Immunotherapy has tested with great success and positive outcome [8-10]. Dendritic cell (DC)-based Immunotherapy is an approved approach to harness the potential of a patient's own immune system to eliminate tumor cells in metastatic hormone-refractory Prostate cancer [11]. US Food and Drug Administration on April 29, 2010, has approved Provenge (Sipuleucel-T) which is a Dendritic cell based immunotherapy for asymptomatic or minimally symptomatic metastatic castrate resistant (hormone-refractory) prostate cancer [12]. Extensive experience has been gained and there is evidence for immunological and clinical responses with DC-based vaccination for a subgroups of patients with different malignant tumors like melanoma, prostate cancer, malignant glioma, renal cell carcinoma as well in other cancers.

There are numerous studies which show that DCs loaded with tumor-associated antigens, exhibit protective antitumor responses which can cause therapeutic regression of preexisting tumors or increase time to progression (TTP) without any significant toxicity (13 to 16). Here we present a case series of three of the ten cases of different recurrent and metastatic cancer cases who were treated using DC-based immunotherapy and showed good response to DC-based immunotherapy.

***Case 1 – Recurrent Osteosarcoma with Multiple Bilateral Lung Metastases***

A 17-year-old male was diagnosed with osteogenic sarcoma of his right femur in 2017. This was treated with a combination of surgical resection and perioperative MAP regime of neoadjuvant chemotherapy completed on May 2020. One year later, a solitary nodule of size 8mm in Lung in March 2021 was detected. On observation the nodule had grown to 16mm on pet scan on follow-up. Patient was posted for VATS removal of nodule but he pre-op scan showed multiple lung nodules in bilateral lungs (size 1-2mm) - June 28, 2021. Since patient had Recurrent disease with bilateral multiple lung metastases patient was advised palliative chemotherapy plus Dendritic cell based Immunotherapy. Six cycles of Dendritic Cell based immunotherapy with concomitant palliative chemotherapy was the treatment planned. 3 cycles of palliative chemotherapy and Denritic cell based Immunotherapy were given between July 2021 to September 2021. HRCT Chest scan done showed mild reduction in primary lesion, disappearance of other lung lesions and pseudoprogression in some lung lesions . Patient was planned and treated by surgical metastectomy of the primary lesion. Histopathology showed viable tumor to be less than 1% with large areas of mineralised osteoid and chondroid tissue with necrosis seen. Patient was given another 3 cycles of concomitant Immunotherapy and chemotherapy between november 2021 to January 2022. Follow-up HRCT Chest scan on 28.3.22 showed disappearence of almost all pseudoprogression lesions. Follow-up HRCT Chest scan done on 07.07.2022 shows no evidence of disease. The present interesting case of Recurrent osteosarcoma with multiple bilateral lung metastases who was put on palliative chemotherapy became disease free (complete response to treatment) by addition of Dendritic cell based Immunotherapy.

***Case 2 – Metastatic Adenocarcinoma Of Unkonown Primary with Multiple Metastases***

A 64 year old female patient was diagnosed with Metastatic Adenocarcinoma of Unknown Primary with multiple metastases in 2018. She was treated with palliative chemotherapy and follow-up scan in March 2019 showed disease progression. Pet CT Scan in March 2019 showed multiple metastases to multiple vertebral bodies, pelvic bones, sternum, both scapula, both humerus, both femur, few bilateral ribs, lung metastases, adrenal metastases, etc. Patient was advised for 6 cycles of Dendritic cell based immunotherapy in June 2019. 6 cycles of Dendritic cell based immunotherapy was given at 2-3 weekly interval between June 2019 to October 2019. Follow-up Pet CT Scan was done in January, 2020 which showed significant reduction of disease at almost all metastatic sites. Patient is alive with no physical restriction in activity and leading almost a normal life after almost 36 months (as of June 30, 2022) since start of treatment with Dendritic cell based immunotherapy.

***Case 3 – Non-small Cell Lung Cancer with Multiple Bilateral Lung Metastases and Spinal Metasis***

A 47 year female patient who is non-smoker presented in December 2019 with recurrent lung cancer with bilateral lung metastases and metastasis to D12 vertebra. Patient presented with complaints of hemoptysis, severe dyspnea on exertion, orthopnea with sleep disturbance, weight loss, continuous and persistent coughing, low back pain, anorexia and severe restriction in her physical activity. Patient was advised for 6 cycles of Dendritic cell based immunotherapy in December 2019. 6 cycles of Dendritic cell based immunotherapy was given at 2-3 weekly interval between December 2019 to March 2020. Patient started showing improvement in her signs and symtoms after 3$^{rd}$ cycle and after completion of 6 cycles almost all her complaints disappeared. Patient had gained almost 4kgs of weight by the time of completion of 6 cycles. Follow-up after 6 months after completion of Dendritic cell based immunotherapy, patient had gained another 6 kg weight with dramatic and persistent improvement in her quality of life with no physical disability. Patient is alive with no physical restriction in activity and leading almost a normal life after almost 30 months (as of June 30, 2022) since start of treatment with Dendritic cell based immunotherapy.

## Discussion

Potential efficacy in tumor growth control and patient survival was shown by cancer immunotherapy as the news released that ‘‘Instead of using surgery, chemotherapy, or radiotherapy, researchers from the National Institutes of Health are finding so far limited but inspiring success in a new approach for fighting cancer, using the immune system to attack the tumors the way it would be a cold or flu. -CNN.com (August 2006)’’ [17-19]. Over the past few decades, there has been a shift in conventional therapies for cancer with immunotherapy booming as a promising candidate with survival benefits and better quality of life for cancer patients [20]. In many cancer types, DCT that contains patients’ own DCs pulsed with the patient-specific tumor antigens has shown to be efficient. Indian FDA has approved Dendritic cell therapy for use in refractory cancer cases of multiple indications [21]. DCs priming of native T-cells has been well established and DC immunotherapy as a novel therapeutic approach has achieved encouraging promise for disease control in many cancers [22-26]. DCs activate the specific cytotoxic T cells against tumor by their ability to present tumor antigens to T lymphocytes [27-30]. Based on improvent in patients Overall Survival in phase III trial, US FDA had approved the first DC immunotherapy, Sipuleucel-T for clinical application to treat asymptomatic metastatic castrate-resistant prostate cancer [31]. Additional promising results were reported in Recent phase III trials has also shown promising results using DC Immunotherapy to treat various late stage cancers, including melanoma, follicular lymphoma, CRC, and NSCLC [32]. DCs capture and process tumor-associated antigens and secrete cytokines to initiate an immune response as is established by studies in clinics [33, 34]. Minimal toxicity, evidence for the induction of tumor-specific cellular immunity, and, in many patients,

clinical response have been demonstrated in clinical trials of DC vaccines [35-40]. In the context of DC-mediated co-stimulation, the use of whole cell approaches such as DC/tumor fusion allows for the presentation of multiple antigens, including those yet to be identified . DC Immunotherapy has shown to induce tumor-specific effector and memory T cells [41]. Therefore, this therapy may have potential higher cytotoxic activity and specificity in the effector T cells, which shows both short and long term anti-tumor efficacy. Our case series suggest that DC treatment can significantly enhance patient survival which is in agreement with the clinical benefits observed in other clinical trials, prompting its future clinical investigation [42]. Based on the present results, which demonstrate the induction of immunological and clinical antitumor activity, and the potential for improving these responses, Dendritic cell therapy seems to have significant promise as a treatment modality where no effective treatment previously existed as is seen in present case series and also other case series published [43]. In patients with malignancies, effective antitumor responses depend on the presence and function of immune cells that can recognize and eliminate tumor cells [44-47]. Among the immune cells, DCs are the antigen presenting cells (APCs) that play major role to activate the immune system against cancer cells. Due to dysfunctional endogenous DCs in cancer patients, the application of ex vivo generated DCs emerged in an effort to improve the therapeutic efficacy in cancer patients . To establish the therapeutic efficacy of DC vaccines a large number of clinical trials were carried out In the last decade. Melanoma was the most common cancer treated which established the feasibility and safety of DC immunotherapy among over 200 DC based clinical trials so far [48]. The advantages of the DC immunotherapy include induction of immunogenicity even in advanced malignancies, low toxicity (grade 3 and 4 level toxicities are rare), and less possibilities of immunotherapy induced autoimmunity [49,50].

**Synergistic Effect of DC and Chemotherapy:**

Dendritic cells become tolerogenic because of tumor induced immune suppression caused by T regulatory cells (Treg cells). Chemotherapeutic drugs by blocking activity of Treg cells inhibit Treg induced immune suppression. Chemotherapeutic drugs indicated here can cause direct stimulation of T effector and NK cells that can lead to anti-tumor activity. Cancer cell death occurs because of cytotoxic function of chemo drugs and this enhances immunovisibility of tumor debri favoring phagocytosis by dendritic cells [51]. Hence, this combination of DC activated cytokine induced killer cells (CIKs) along with chemotherapy leads to upregulation of anti-tumor cytokines including IFN-γ, TNF-α, TNF-β and MIG [52, 53]. This combination approach of Dendritic cell based immunotherapy with chemotherapy has yielded excellent response in form of complete response in our Recurrent Osteosarcoma with multiple bilateral lung metastasis case and is in agreement with the discussion above.

**Conclusion**

We conclude that dendritic cell therapy is a safe and well tolerated immunotherapeutic method and it can elicit very effective immune response even in patients with advanced-stage cancer patients as seen in the present case series.

Many studies though not designed primarily to measure survival , an increasing number indicate that dendritic cell therapy could confer a survival benefit. These preliminary but encouraging survival data provide a strong evidence to begin a new series of clinical trials using overall survival as the primary endpoint. The combination of this immunotherapy with other anticancer therapies could result in more improved outcomes. These developments might hold the key to the full therapeutic potential of dendritic cells for cancer immunotherapy.

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