



Review:

On dendritic cell-based therapy for cancers

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Received Oct. 12, 2004; revision accepted Oct. 23, 2004

Abstract: Dendritic cells (DCs), the most prevalent antigen-presenting cell in vivo, had been widely characterized in the last three decades. DCs are present in almost all tissues of the body and play cardinal roles in recognition of microbial agents, autoantigens, allergens and alloantigen. DCs process the microbial agents or their antigens and migrate to lymphoid tissues to present the antigenic peptide to lymphocytes. This leads to activation of antigen-specific lymphocytes. Initially, it was assumed that DCs are principally involved in the induction and maintenance of adaptive immune responses, but now it is evident that DCs also have important roles in innate immunity. These features make DCs very good candidates for therapy against various pathological conditions including malignancies. Initially, DC-based therapy was used in animal models of cancers. Data from these studies inspired considerable optimism and DC-based therapies was started in human cancers 8 years ago. In general, DC-based therapy has been found to be safe in patients with cancers, although few controlled trials have been conducted in this regard. Because the fundamentals principles of human cancers and animal models of cancers are different, the therapeutic efficacy of the ongoing regime of DC-based therapy in cancer patients is not satisfactory. In this review, we covered the various aspects that should be considered for developing better regime of DC-based therapy for human cancers.

Key words: Dendritic cells, Cancer immunology, DC-based therapy, Safety, Efficacy, Animal model of cancers, Human cancers
doi: 10.1631/jzus.2005.B0001 **Document code:** A **CLC number:** R979.1

After the discovery of the 'present day' dendritic cells (DCs) by Steinman and Cohn (1973), extensive studies to develop understanding of the origin, phenotypes and functions of different populations of DCs revealed that: (1) DCs are distributed in different forms in most tissues of the body; (2) they are endowed with potent antigen recognition and processing apparatuses; (3) DCs are highly mobile, interact with immunocytes and migrate to tissues of their habitual locality or lymphoid tissues; and (4) they present antigenic peptides to clonally-selected lymphocytes at lymphoid tissues.

It was first assumed that presentation of antigens by DCs will elicit immune responses (Steinman, 1991), however, it is now evident that DCs can also induce immunogenic tolerance (Onji, 2004). DCs produce various proinflammatory, anti-inflammatory and immune regulatory cytokines (Akbar *et al.*, 2004a), which information led to great interest in using DCs as therapeutic agents.

Impaired and exacerbated immune responses accompany different pathological conditions such as malignancy, persistent infection, autoimmunity and allergy. However, there is little information on whether altered immune responses are characteristics of those diseases or whether immune abnormality results from the secondary effects of the pathological processes. Circumstantial evidences point to involvement of DCs in several pathological conditions. So a new trend of immunological researches on and clinical applications of DCs was started 10 years ago.

Initially, DC-based therapies were conducted in animal model of human diseases. Some of these therapies were intended to activate or deactivate DCs in situ by administration of several agents including disease-specific antigens. In other methods, activated or deactivated DCs were administered to upregulate or inhibit immune responses in the host to get desired therapeutic effects. In general, the outcome of these therapies was encouraging in animal models with

cancer, persistent infection and autoimmune diseases (Onji, 2004; Akbar *et al.*, 2004a; Byrne and Hallyday, 2002; Schuler *et al.*, 2003; Steinman and Dhopadkar, 2001).

Initial success of DC-based therapy inspired considerable optimism and DC-based therapy was started against human diseases by the mid-nineties. However, DC-based therapies have not shown considerable therapeutic effects in patients with cancers (Byrne and Hallyday, 2002; Schuler *et al.*, 2003; Steinman and Dhopadkar, 2001). It is true that few controlled trials have been conducted regarding this. The utility of DC-based therapy has not been tested in patients other than those with malignancies mainly because the safety and efficacy of antigen-pulsed DCs have not been assessed in immune-competent individuals.

This is the time to evaluate why DC-based therapy succeeded in animal models with cancers but not in human models with cancers. Based on the present scientific developments, the following logical reasons can be put forward. The first is lack of obvious correlation between animal models of human cancer and patients with cancers. The animal models of cancers are developed by implantation or administration of malignant cells into susceptible animals. Malignant tumors develop within days, weeks or months in these animals. On the other hand, malignancy in human is the final outcome of a long-lasting disease process. For example, liver cancer is developed in animals within 1~3 weeks after implantation of liver cancer cells into the skin of mouse. However, human liver cancers develop usually 20~60 years after hepatitis B virus and hepatitis C virus infection. During this period, most of the patients exhibit exacerbation of remission of diseases and develop features of chronic hepatitis and liver cirrhosis prior to development of liver cancer. The pathological events in carcinogenesis are not clear in many cancers, but usually a long-lasting process proceeds before the development of visible cancers.

The ultimate goal of DC-based therapy against malignancy is not clear. Traditionally, the primary goal of treatment of cancer patients is to increase their survival rate. In order to attain this goal, the following are important: (1) complete eradication or delaying the progression of already-developed cancer by immune-mediated mechanism, (2) prevention of recur-

rence of new cancer nodules, and (3) prevention or delaying of development of cancer in precancerous patients. The need to reexamine DC-based therapy for advanced cancer patients is understandable in the context of ethical limitations and scientific constrains in using new immune therapy on human. The purpose of DC-based therapy in cancer patients is to induce cancer-specific immune responses. Although cancer patients, especially patients with advanced cancers, are usually highly immune compromised. In most cases, these patients cannot induce adequate levels of innate and adaptive immune responses and can survive only for limited period of time and thus did not allow reasonable time for assessing the therapeutic efficacy of DC-based therapy. Moreover, the side effects of DC-based therapy could not be studied properly in these patients due to their immune compromised status and limited survival time. DC-based therapy has not been done in patients with precancerous state of some malignancies to develop insight if they have any role in blocking the pathogenesis of cancers from precancerous state.

In addition to these factors, insight on the nature and properties of tumor antigen-pulsed DCs is extremely important for developing DC-based therapies for cancers. In order to prepare tumor associated antigen (TAA)-pulsed DCs, DCs have been cultured with cancer extracts, cancer antigens, RNA of cancer tissues or fused with cancer cells. However, very few studies have checked whether these culture methods led to the production or not of TAA-pulsed DCs. Moreover, it has not been tested in many instances whether tumor antigen-pulsed DCs will induce antigen-specific immunity or tolerance. In fact, very few studies have checked the quality of the final products (TAA-pulsed DCs) before administering to cancer patients.

Below is an outline for improving DC-based therapy in cancer patients.

1. Patients with cancer in its earlier stages should be tested for use of DC-based therapy. Preferably, they should be immune competent. There should be adequate study on the safety or antigen-pulsed DCs in immune competent cancer patients. We recently evaluated the safety and efficacy of hepatitis B surface antigen (HBsAg)-pulsed DCs in immune competent normal volunteers (Akbar *et al.*, 2004b). Although HBsAg-pulsed DCs prepared in our labora-

tory were safe for human usage, every laboratory should confirm and reproduce their protocols. There is probably no universal protocol for production of antigen-pulsed DCs because the nature of the antigens is extremely diverse.

2. TAA-pulsed DCs should be prepared with caution and should be tested whether TAA-pulsed DCs are immunogenic, not tolerogenic. This must be accomplished in a case by case manner. Availability of cancer antigen, a limiting factor for preparation of TAA-pulsed DCs, can be dealt with by transfecting DCs with cancer-derived mRNAs. Recent studies indicate that culture of DCs with cancer cells or fusion product of DCs and cancer cells are less likely to be immunogenic in nature. Alternatively, the cancer tissues can be damaged by administration of apoptotic or necrotic agents in situ and DCs can be introduced there for capturing TAAs in situ. We reported the feasibility of this approach in an animal model with colon cancer, but this should be tested in human cancers (Kumagi *et al.*, 2003).

Therapy for cancer is a challenging issue in clinics and it will take several years to develop acceptable immune therapy for cancers. There is need to systematically develop therapy for cancer patients. If we do it in haste, we may come back to the starting point. This has happened regarding DC-based therapy against human cancers. Important insight has been

developed regarding the scope and limitation of DC-based therapy in pathological conditions.

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