

Efficacy of Dendritic Cell-Based Cancer Immunotherapy

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Abstract

Dendritic cells (DCs) have antigen-specific bioactivity against tumor-associated antigens. The acquisition of tumor immunity with DC vaccination could be determined using both tetramer analysis and interferon γ -producing clones in enzyme-linked immunosorbent spot assays. A combination of DC vaccination with low-dose metronomic therapy and chemoradiotherapy would contribute to an enhanced acquired immunity for cancer therapy. The efficacy of DC vaccination may provide a survival benefit in some patients with cancer by achieving a prolonged quality-adjusted life year.

Keywords: Dendritic cells; Cancer vaccination; Wilms' tumor 1; Metronomic therapy; Quality-adjusted life year

Abbreviations: DCs: Dendritic cells; CTLs: Cytotoxic T Cells; WT1: Wilms' Tumor 1; HLA: Human Leukocyte Antigen; WT1-CTLs: WT1 Antigen-Specific Cytotoxic T Cells; ELISPOT: Enzyme-Linked Immunosorbent Spot

Dendritic Cell-based Cancer Immunotherapy

Dendritic cells (DCs) may have antigen-specific bioactivity against tumor-associated antigens. Factors affecting the induction of tumor antigen-specific cytotoxic T cells (CTLs) with DC vaccination remain to be completely elucidated. DC vaccination therapies as an adjuvant to chemo- and/or radiotherapy and the duration for adapting these therapies have been investigated.

Wilms' tumor 1 (WT1) antigen has been reported to be strongly immunogenic [1]; moreover, human leukocyte antigen (HLA)-A*24:02-restricted modified WT1 peptide may have considerable efficacy in promoting cancer immunity [2]. DC vaccines primed with WT1-class I/II peptides were safe during chemotherapy for pancreatic cancer [3].

Immunological monitoring of DC vaccination is an important validation tool in clinical studies and trials for proving the concept. WT1 antigen-specific cytotoxic T cells (WT1-CTLs) were determined using both WT1-peptide/HLA-A*24:02 tetramer analysis and interferon γ -producing clones in enzyme-linked immunosorbent spot (ELISPOT) assays during the course of DC vaccination; these analyses are required to be reproducible and validated methods with simple, easily reproducible protocols as shown in Figure 1. The presence of WT1-CTLs in ELISPOT assays was defined according to the following criteria: (1) at least 15 WT1-specific spots per 1×10^6 peripheral blood mononuclear cells and (2) at least a 1.5-fold increase in the presence of WT1-specific spots compared with peptide spots in the negative control. In contrast, WT1 tetramer-positive CTLs were defined according to the following criteria: (1) comprising at least 0.02% of CD3⁺CD8⁺ subset of 50,000–100,000 lymphocytes and (2) forming a clustered and not diffused population [4]. A positive relationship was determined between the ELISPOT assays and tetramer analysis, and WT1-specific immune responses were detected in 89.1% of patients with cancer during post-vaccination analysis [4].

Following one course of DC vaccination primed with HLA-A*24:02-restricted-modified WT1 peptide, the tetramer analysis and ELISPOT assays revealed that WT1-CTLs persisted over 1–2 years without any

additional DC vaccines [5,6]. Furthermore, the amount of WT1-CTLs markedly increased after a second course of DC vaccination primed with WT1-class I/II peptides, suggesting a boosting reaction and an efficacy of additional reaction with the WT1-class II helper peptide.

Perspectives

Additional DC vaccinations with chemotherapy and chemoradiotherapy were safe and tolerable, suggesting an enhanced acquired immunity [5]. A low-dose metronomic chemotherapy with cyclophosphamide and/or methotrexate would be a selective combination therapy targeting vascular endothelium [7]. Low-dose metronomic therapy generates tumor adjuvanticity by selective control of regulatory T cells, increase in natural killer cell activity, and activation of DCs [8–11]. A combination of DC-based adjuvant vaccination and metronomic therapy may contribute to an increase in the efficacy of acquired immunity [6]. Combination therapy with immune checkpoint

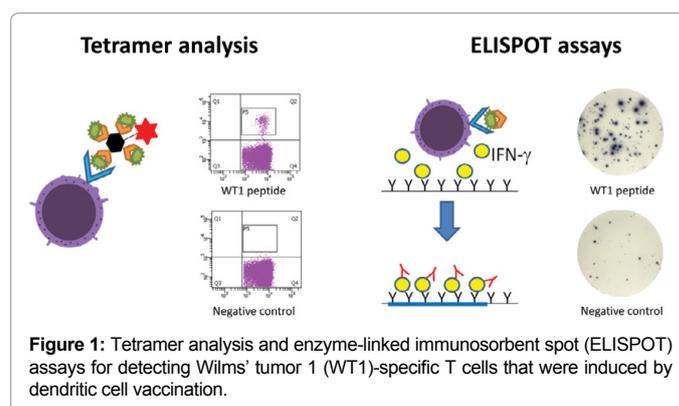


Figure 1: Tetramer analysis and enzyme-linked immunosorbent spot (ELISPOT) assays for detecting Wilms' tumor 1 (WT1)-specific T cells that were induced by dendritic cell vaccination.

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Received: January 16, 2016; **Accepted:** January 25, 2016; **Published:** January 28, 2016

Citation: Shimodaira S, Higuchi Y, Yanagisawa R, Okamoto M, Koido S (2016) Efficacy of Dendritic Cell-Based Cancer Immunotherapy. *Biochem Anal Biochem* 5: 240. doi:10.4172/2161-1009.1000240

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inhibitors, such as blockade of programmed death 1 and programmed death ligand 1 [12], has the potential to further improve the efficacy of DC vaccination therapies in patients with cancer.

The efficacy of DC vaccination as an adjuvant therapy in some patients with cancer may provide a survival benefit by achieving disease stability and relapse-free survival. In addition to standard cancer therapies, DC vaccination is essentially expected to achieve prolonged quality-adjusted life year, which is a generic measure of both quality and quantity of life under a medical intervention and a measure of the economic value for each individual [13].

Acknowledgment

This study was supported by the grants-in-aid for scientific research from the Japan Society for the Promotion of Science.

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