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Future Prospective of Cancer Vaccination Technology in Japan

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Abstract

Dendritic cell (DC)-based immunotherapy has been developed against various types of cancers. To develop and promote regenerative medicine and cell therapy in Japan, the Act on the Safety of Regenerative Medicine and the Revised Pharmaceutical Affairs Law have been enforced since November 25, 2014. Therapeutic vaccination with active DCs was evaluated under the legal framework. Cancer vaccination therapies with autologous monocyte-derived mature DCs are principally attributed to the presence of tumor-associated antigens. Clinical studies and trials should be conducted in accordance with legislation for approval of either DC-based cancer therapy or DC vaccine products. The following issues with regards to DC-based vaccination and vaccine products for clinical use may be raised: 1) Manufacturing of DCs according to the standard grade of Good Gene, Cellular, and Tissue-based Products (GCTP) Manufacturing Practice; 2) Peptides that target cancer-associated antigens for any cancer patient; 3) Quality of immunological analyses as proof of concept; and 4) Optimization of DC vaccines as add-ons to chemotherapeutic drugs and/or radiotherapy to predict potential biomarkers of response. Phase II clinical trials that are covered by Advanced Medical Care System would be conducted on DC vaccine pulsed with Wilms' tumor 1-specific MHC class I/II-restricted epitopes for pancreatic cancer. The designed clinical trial adopted with new technology could reveal the efficacy of DC vaccine in combination with optimized therapies. This would be relevant to the development of personalized therapy in cancer patients.

Keywords: Dendritic cell; Vaccine; Good gene; Cellular and tissue-based products; Cancer immunotherapy

Abbreviations: DC: Dendritic Cell; PAP: Prostatic Acid Phosphatase; GM–CSF: Granulocyte–Macrophage Colony-Stimulating Factor; Ips Cells: Induced Pluripotent Stem Cells; MHLW: Ministry Of Health, Labour And Welfare; ES Cells: Embryonic Stem Cells; PMDA: Pharmaceuticals and Medical Devices Agency; GCTP: Good Gene, Cellular and Tissue-Based Products Manufacturing Products; CPC: Cell Processing Center; IFN: Interferon; WT1: Wilms' Tumor 1; OS: Overall Survival; PFS: Progression-Free Survival; S-1: Tegafur–Gimeracil–Oteracil Combination

Introduction

Various regulatory frameworks exist for clinical trials and studies on stem cells and somatic cells. Guidelines for the industry containing nonbinding recommendations were released not to establish legally enforceable responsibilities, but for Clinical Considerations for Therapeutic Cancer Vaccines [1] and Preclinical Assessment of Investigational Cellular and Gene Therapy Products [2]. The US Food and Drug Administration (FDA) approved sipuleucel-T (Provenge®), an autologous dendritic cell (DC)-based immunotherapy for men with metastatic hormone-refractory prostate cancer, as a new treatment option for patients with this type of cancer. Sipuleucel-T is manufactured by exposing patient's blood cells to a recombinant fusion protein composed of prostatic acid phosphatase (PAP) and granulocyte–macrophage colony-stimulating factor (GM–CSF) to enhance their activity against cancer cells. The patient's own DC product is administered intravenously in a 3-dose schedule, with about 2-week intervals. This regimen was demonstrated to yield a survival benefit of about 4.1 months in patients with hormone-resistant prostate cancer [3].

"The Act on the Safety of Regenerative Medicine" in Japan was enforced since November 25, 2014; it covers all kinds of medical technologies on processing cells, not only for regenerative medicine using induced pluripotent stem cells (iPS cells) or somatic stem cells but also for cell-based cancer immunotherapy [4]. The scope of the Act excludes medical treatment such as blood transfusion, stem cell transplantation for hematological malignancies, and reproductive treatment, which are widely employed in daily practice. The Act categorizes medical technologies into 3 classes depending on the potential risk on human life and the effect on health. Protocols of proposed clinical trials or therapeutic plans using any class that are approved by a certified committee must be submitted to the Ministry of Health, Labour and Welfare (MHLW). Class III technologies use somatic cells with accumulated clinical experiences and are regarded as low risk technologies. Class II technologies that use somatic stem cells that require certification by a special committee, composed of highly competent reviewers as third party, are categorized as intermediate risk technologies. Class I technologies (high risk) include gene modified T-cell, allogeneic cell, and regenerative therapies with Embryonic stem cells (ES cells) or iPS cells; this class requires additional 90 days of restriction by the MHLW [4].

On the other hand, the Revised Pharmaceutical Affairs Law, a new legal framework that provides timely provision of safe and effective therapeutic products or devices, was enforced simultaneously on November 25, 2014. Clinical trials with confirmed or predicted efficacy and safety are followed by conditional, time-limited marketing authorization by the Pharmaceuticals and Medical Devices Agency (PMDA) of Japan [4].

Manufacturing of DCs

Manufacturing of DCs according to Good Gene, Cellular, and Tissue-based Products (GCTP) Manufacturing Practice is the common standard grade between the two legislations used at cell processing

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centers in any institute. Preparation of conventional DCs with peripheral mononuclear cells was obtained by leukapheresis in a CO_2 incubator equipped with a cell processing isolator (H_2O_2-sterilizing system, Panasonic Corporation, Osaka, Japan) in the cell processing center, as described [5].

The technology of DC vaccination therapy defined as Class III (low risk) should be reviewed and approved by a certified committee for regenerative medicine. Next, the medical plan should be submitted to the MHLW in Japan for provision. The institute providing DC vaccination for clinical trials is required to keep track of the treatment records, the bulletin to the MHLW, and the compensation duty for possible health hazards.

It is possible to manufacture DC vaccine for clinical use at the Cell Processing Center (CPC) of a medical institution [5]. However, it is not usually easy to maintain the CPC in a hospital owing to high expenses. The frozen DC vaccine using liquid nitrogen conveyance container (dry shipper) is enabled on a certified premise following the Act on the Safety and Regenerative Medicine [4]. Furthermore, a DC vaccine factory with authorization from two legislative bodies of a medical institution will be necessary in the future, either for approval of cell technologies or for provision of cell-based products.

Quality Control of DCs

Different from the conventional adherent system for GM–CSF and IL-4, there are several cytokine mixtures containing interferon (IFN) to generate DCs. It is difficult to keep the uniformity and stability of bioactive DC vaccines because as compared with chemical drugs, the activity of apheresed monocytes as biomaterials vary among patients [5]. It is necessary to determine the criteria for validation of the safety and efficacy of DC vaccination; however, the quality of DC products is not constant in individualized therapy. Therefore, quality control (verification) of manufactured DCs under GCTP manufacturing conditions is proposed in Figure 1 based on the Act on the Safety of Regenerative Medicine and harmonized with the criterion shown in the guidelines [6]. The released criteria for DC vaccine administration to patients include purity mature DC phenotype ≥ 70%, viability ≥ 70%, negative culture for bacteria and fungi after 14 days, endotoxin testing < 0.25 EU/mL, and negative result for mycoplasma.

Advanced Medical Care system

"Advanced Medical Care" is accepted in Japan to evaluate a medical technology at one's own expense, together with the National Health Insurance, at institutes and hospitals approved by the MHLW. The technological intervention includes regenerative medicine and immunotherapy, the safety and efficacy of which have not been established by previous clinical studies. When clinical trials on DC vaccination reveal its safety and efficacy, the technology would potentially be covered by insurance as public knowledge-based application. As Advanced Medical Care is temporary, other options are to seek pharmaceutical approval as biomedical products or medical devices from the PMDA, following the Revised Pharmaceutical Affairs Law.

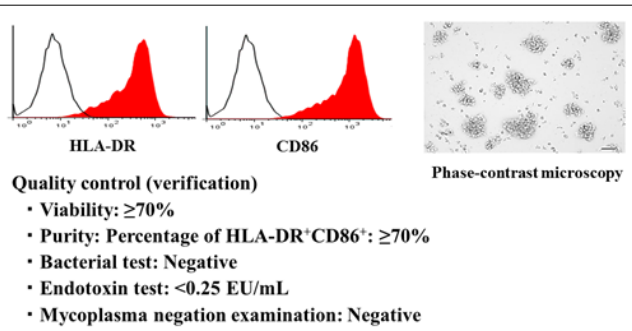

Figure 1: Quality control (verification) of manufactured dendritic cells under GCTP condition according to the Act on the Safety of Regenerative Medicine. Phase-contrast microscopy indicates over 70% $CD86^+HLA\text{-}DR^+$ DCs manufactured using GM–CSF and IFNα.

Based on retrospective clinical studies and Phase I clinical trials [7-10], Phase II clinical trials for pancreatic cancer targeting Wilms' tumor 1 (WT1) would be conducted with the approval from the MHLW as Advanced Medical Care. To clarify the efficacy of DC vaccination therapy, the primary endpoints are overall survival (OS) and progression-free survival (PFS), whereas secondary endpoints are adverse reactions and WT1-specific immune responses. Combination immunotherapy is necessary as an add-on to chemotherapeutic drugs such as gemcitabine and tegafur–gimeracil–oteracil combination (S-1), with off-target effects.

The Future Prospects

Oil adjuvant for peptide vaccines acts to locally accelerate activation of lymphocytes [11]; however, DCs has a potential antigen-specific bioactivity as an adjuvant. DC vaccination therapy, applied with compatible WT1 and helper peptides, has the potential efficacy as the next-generation of cancer vaccines [9,12,13]. Immunological monitoring of DC vaccination is an important validation tool in clinical studies and trials. Tetramer analysis and enzyme-linked immunosorbent spot assay require reproducibility and validation [14]. Allogeneic DC vaccination targeting WT1, categorized as Class I (high risk) technology in the Act on the Safety of Regenerative Medicine, may be a potential strategy for patients with relapsed leukemia after hematopoietic stem cell transplantation [14]. The designed clinical trial could reveal the efficacy of DC vaccine, together with rapidly progressive immune checkpoint inhibitors, for the treatment of cancers in the near future. Predictive biomarkers are relevant for the development of personalized therapy for cancer patients.

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Disclosure of Interest

All authors declare no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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