



Cancer Immune Therapy in Clinic: 2016

Shinichiro Akiyama^{1,2*} and Toshio Inui¹

¹Saisei Mirai Clinic, Japan

²Department of Medical Oncology, McGill University, Canada

Editorial

According to the GLOBOCAN 2012 estimates, about 14.1 million cancer cases and 8.2 million cancer deaths are estimated to have occurred in 2012; of these, 57% of the cases and 65% of the deaths occurred in the economically developing world [1]. Knowledge of heterogeneity and cancer stem cell facilitates that cancer is not cured by chemotherapeutic agent alone. Immune surveillance is recent notion that nascent premalignant cells are destroyed by the immune system before tumor formation can occur. Disruptive technologies have continued to advance immune therapy at previously inconceivable rates. As global views of cancer behavior against immune system have emerged, the magnitude of its complexity has become apparently manifest. Although there has been a dramatic progress in chemotherapy for cancer, cancer research of immune system have experienced considerable advancements over the last three decades. The concept of cancer immune therapies follows logically from the investigation of immune intolerance or suppression against cancer. A review of clinical trial results to date, primarily in patients with advanced cancers refractory to conventional treatments, indicates that these therapies can be applicable to solid cancer to elucidates regression or stabilization of cancer tissues. Immune therapy against cancer is not new paradigm with enormous potential. Immunotherapy was introduced in the treatment of lymphoma as FDA approval of rituximab antibodies in 1997 [2]. Not only does tumor-infiltrating T lymphocyte [3,4] but also lower lymphocyte count [5], impaired natural killer (NK) cell activity [6] has been reported. Recent progress manifests that regulatory T cells (Treg) is closely associated with tumor progression by producing TGF- β , interleukin (IL)-10 as well as cytotoxic T lymphocyte-associated protein 4 (CTLA-4) [7,8]. Tumor cells can reduce T-cell-mediated recognition by changing Human Leucocyte Antigen (HLA) class I expression which present processed tumor antigen to T cell [9]. Although this T cell mediated response vary depends on HLA number and complete loss of HLA means unable to recognize cancer cell by T lymphocytes, this phenomena activates strong NK cell activation. To measure the benefit of immune therapy, investigators of immune check point blockade proposed the immune-related response criteria (irRC). Considering of immune therapy acts slowly and sometimes results in mixed response, irRC reflects convenient clinical outcome. There is little or no controversy about FOXP3+CD4+Treg plays an important role in anti-tumor immune system. Tumor infiltrated CD4+Tregs induce anorexic state on CD8+T cells. That is, Treg secrete TGF- β and IL-10 to interfere with T cell priming. Increased infiltrated T_{regs} are associated with poor outcome of breast cancer, non-small-cell lung cancer, and hepatocellular carcinoma [10-12].

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*Correspondence:

Shinichiro Akiyama, Saisei Mirai
Clinic Group, 5-10-26 ORE Hiroo 7F,
Minamiazabu, Minato, Tokyo 106-0047
Japan,

E-mail: akiyamafirst@icloud.com

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T Cell Based Immunotherapy

Peptide vaccine

Although few cancer antigens have been identified until now, several clinical investigations were performed by using WT1, MUC1, CEA, BRAF, MAGE A3 and BCR-ABL peptide in solid [13,14] and hematological [15] cancer. Most of the clinical trials done were concluded “disappointing” whereas another respect of immune therapy is immunological response. That is, it is usually difficult to elicit significant number of Cytotoxic T Lymphocyte (CTL), clinical outcome as long term stable disease is not uncommon in this modality.

Dendritic cell based vaccine (DC)

Not only autologous DC but also artificial antigen have been investigated in preclinical and clinical settings [16-19]. Of all the solid cancer investigated, response rate of almost 20% is meaningful therapeutic approach [18].

CART

The genetic modification of autologous T cells with Chimeric Antigen Receptors (CARs)

represents a breakthrough for gene engineering as a cancer therapy for both solid and hematologic malignancies [20,21]. Although one of the critically successful way is to identify suitable cancer antigens. That is, limited number of cancer antigen presents on the surface of cancer whereas most of them are presented on normal tissue. Furthermore, changing microenvironment of immunosuppressive cancer may elucidate success of CART.

Immune checkpoint blockade

Antitumor immunity is regulated by multiple immune suppression mechanism. Cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) was the first immune checkpoint receptor. Programmed cell death protein 1 (PD-1/PD-L1) and its ligand is another pathway. CTLA-4 acts to regulate immune response early in T-cell activation, PD-1 acts primarily to inhibit effector T-cell activity in the effector phase within tissue and tumors [22]. Of PD-1/PD-L1 antibody, success in phase I studies of nivolumab, pembrolizumab and atezolizumab may result in enthusiastic paradigm shift for cancer therapy [23-25].

NK/NKT Cell Based Immunotherapy

It has been two decades since NK had discovered by Kiessling et al. [26]. Now that human NK cells are defined to lymphocytes that express CD3-CD56+, whereas NKT cells are defined CD3+CD56+ lymphocytes. NK/NKT cell acts as an intermediary between innate and adaptive immune response. Both cells can produce IFN- γ , TNF- α and GM-CSF. Furthermore, when both cells encounter cancer cells, they can release perforin to disrupt endosomal trafficking and granzyme B to induce apoptosis. But in general, it takes several days to restore perforin and granzyme B after the first attack by NK/NKT cells. Also immunosuppressive factors produced by cancer cells are limiting factor of these innate immunity [27]. Though interleukin-2 (IL-2) activates NK cells and increases NK cell numbers, clinical efficiency against malignancy is limited because of its negative aspect of immune suppression and adverse events. As β and γ chains of IL-2 and IL-15 receptors are shared, it has been acknowledged that the signaling pathway of IL-2 and IL-15 have same component. IL-15 have an advantage of not stimulating T_{reg} like IL-2 and inhibiting IL-2 mediated AICD. Kevin et al. revealed that recombinant human IL-15 (rhIL-15) stimulates NK cell and proliferation in clinical setting [28]. Although successful trial of expanded autologous NK cells are reported [29], recent advances in NK cells may focus on genetic engineering approaches [30]. NKT cells play an intermediary role bridging innate and acquired immunity. Activation of NKT cells have an advantage of maturation of dendritic cell because most advanced cancer patients are immunosuppressive status due to tumor produced TGF- β . Taniguchi reported that NKT cell therapy result in promising outcome [31].

Macrophage Based Immunotherapy

As an essential component of innate immunity, it is little or no controversy about role of cancer immunity of macrophage. Gc protein, α 2protein, can be converted into GcMAF (Gc macrophage activating factor) *in vivo* and *in vitro*. GcMAF is the most strongest natural product to stimulate macrophage. Inui et al. [32] reported the efficiency of GcMAF against cancer. Of note, GcMAF stimulates macrophage without producing cytokine production. Due to the progress of methodology of GcMAF, response rate against solid cancer is about 30% (Data not shown).

Coley's Vaccine

In 1893, a New York surgeon, William Coley noticed tumor

regression who suffered from erysipelas. Inspired by this finding, W. Coley started injecting live *Streptococcus pyogenes* to his cancer patients. This is the first description of cancer immune therapy. As it was the age of emerging chemotherapy as well as radiation therapy, Coley's vaccine came to an end after two decades.

Cytokines

IL-2, IFN- α 2a, IFN- α 2b are cytokines approved by the US FDA and/or EMA for limited solid cancer. Their main purpose is to stimulate immune system. These cytokines stimulate whole immune system, that is non-specific manner, then usually cause adverse events. They are generally accompanied with little benefits [33].

Monoclonal Antibody

Immunomodulatory monoclonal antibodies are designed to elicit anti-cancer response. This tumor-targeting mAbs aim at i) targeting cancer cell surface receptor referring as cell signaling, ii) blocking the Tumor Associated Antigen (TAA). But because most cancer patients have mutated protein on its surface to which immune system is not tolerated. The enthusiasm expected from imatinib mesylate, a kind of selective ABL tyrosine kinase inhibitor, seemed to provide powerful clinical validation of oncogene addiction principle [34]. In other word, conserved genomic view of cancer is closely associated with clinical outcome.

PRR Agonists

Pattern Recognition Receptors (PRRs) are evolutionally preserved proteins. Combining both toll-like receptors (TLRs) and nucleotide-binding oligomerization domain containing (NOD)-like receptors (NLRs) induces significant CD4+ and CD8+ T cell response to hold long term immunity against tumor. TLR2/TLR4 agonist, TLR7 agonist, NOD2 agonist are approved drug. Of them, TLR2/TLR4 agonist, Cervarix, is the most prevailing PRRs and acts as vaccine for HPV-16 and -18 infection.

Concluding Remarks

Cancer immunotherapy have a miscellaneous history, affluent basic research until now and a promising future. In this report, current cancer immune therapies are classified by using main target of immune reaction. The application of cancer immunotherapy for certain types and stage is particularly compelling because the potential of immunotherapy for clinical impact is now firmly investigated. The integration of new modality into standard clinical practice must adapt to rational design of combinations of immunotherapy and conventional therapy. When we work together for the sake of remarking any types of immune therapy strategies, we have to definitely assemble the challenges described here and select immune therapy to facilitate immune response.

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