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Editorial
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Cancer Immune Therapy in Clinic: 2016

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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 trail 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].

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)

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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-L1antibody, 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) simulates 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, α2protein, 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-α2a, IFN-α2b 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.

References

1. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. CA Cancer J Clin. 2015; 65: 87-108.
2. Maloney DG, Grillo-Lopez AJ, White CA, Bodkin D, Schilder RJ, Neidhart JA, et al. IDEC-C2B8 (Rituximab) anti-CD20 monoclonal antibody therapy in patients with relapsed low-grade non-Hodgkin's lymphoma. Blood. 1997; 90: 2188–2195.
3. Whiteside TL. Immune cells in the tumor microenvironment: Mechanisms responsible for functional and signaling defects. Adv Exp Med Biol. 1998; 451: 167-171.

4. Ferris RL. Progress in head and neck cancer immunotherapy: Can tolerance and immune suppression be reversed? ORL J Otorhinolaryngol Relat Spec. 2004; 66: 332-340.

5. Kuss I, Hathaway B, Ferris RL, Gooding W, Whiteside T. Decreased absolute counts of T lymphocyte subsets and their relation to disease in squamous cell carcinoma of the head and neck. Clin Cancer Res. 2004; 10: 3755-3762.

6. Bauernhofer T, Kuss I, Henderson B, Baum AS, Whiteside TL. Preferential apoptosis of CD56dim natural killer cell subset in patients with cancer. Eur J Immunol. 2003; 33: 119-124.

7. Nishikawa H, Sakaguchi S. Regulatory T cells in tumor immunity. Int J Cancer. 2010; 127: 759-767.

8. Kammertoens T, Schüler T, Blankenstein T. Immunotherapy: Target the stroma to hit the tumor. Trends Mol Med. 2005; 11: 225-231.

9. Ferris R, Whiteside TL, Ferrone S. Immune escape associated with functional defects in antigen-processing machinery in head and neck cancer. Clin Cancer Res. 2006; 12: 3890-3895.

10. Bates GJ, Fox SB, Han C, Leek RD, Garcia JF, Harris AL, et al. Quantification of regulatory T cells enables the identification of high-risk breast cancer patients and those at risk of late relapse. J Clin Oncol. 2006; 24: 5373-5380.

11. Petersen RP, Campa MJ, Sperlazza J, Conlon D, Joshi MB, Harpole DH Jr, et al. Tumor infiltrating Foxp3+ regulatory T-cells are associated with recurrence in pathologic stage I NSCLC patients. Cancer. 2006; 107: 2866-2872.

12. Gao Q, Qiu SJ, Fan J, Zhou J, Wang XY, Xiao YS, et al. Intratumoral balance of regulatory and cytotoxic T cells is associated with prognosis of hepatocellular carcinoma after resection. J Clin Oncol. 2007; 25: 2586-2593.

13. Marshall JL, Gulley JL, Arlen PM, Beetham PK, Tsang KY, Slack R, et al. Phase I study of sequential vaccinations with fowlpox-CEA(6D)-TRICOM alone and sequentially with vaccinia-CEA(6D)- TRICOM, with and without granulocyte-macrophage colony-stimulating factor, in patients with carcinoembryonic antigen-expressing carcinomas. J Clin Oncol. 2005; 23: 720-731.

14. Morse MA, Niedzwiecki D, Marshall JL, Garrett C, Chang DZ, Aklilu M, et al. A randomized phase II study of immunization with dendritic cells modified with poxvectors encoding CEA and MUC1 compared with the same poxvectors plus GM-CSF for resected metastatic colorectal cancer. Ann Surg. 2013; 258: 879-886.

15. Cathcart K, Pinilla-Ibarz J, Korontsvit T, Schwartz J, Zakhaleva V, Papadopoulos EB, et al. A multivalent bcr-abl fusion peptide vaccination trial in patients with chronic myeloid leukemia. Blood. 2004; 103: 1037-1042.

16. Banchereau J, Palucka AK. Dendritic cells as therapeutic vaccines against cancer. Nat Rev Immunol. 2005; 5: 296-306.

17. Coosemans A, Vergote I, Van Gool SW. Dendritic cell-based immunotherapy in ovarian cancer. Oncoimmunology. 2013; 2: e27059.

18. Akiyama S, Abe H. Cancer Vaccine. In: Öner Özdemir, editor. Current Cancer Treatment-Novel Beyond Conventional Approaches. Croatia: INTECH; 2011. p.429-442.

19. Dammeijer F, Lievense LA, Veerman GD, Hoogsteden HC, Hegmans JP, Arends LR, et al. The Efficacy of Tumor Vaccines and Cellular Immunotherapies in Non-Small Cell Lung Cancer: A Systematic Review and Meta-Analysis. J Clin Oncol. 2016; 34: 3204-3212.

20. Davila ML, Bouhassira DC, Park JH, Curran KJ, Smith EL, Pegram HJ, et al. Chimeric antigen receptors for the adoptive T cell therapy of hematologic malignancies. Int J Hematol. 2014; 99: 361-371.

21. Ahmed N, Brawley VS, Hegde M, Robertson C, Ghazi A, Gerken C, et al. Human Epidermal Growth Factor Receptor 2 (HER2) -Specific Chimeric Antigen Receptor-Modified T Cells for the Immunotherapy of HER2-Positive Sarcoma. J Clin Oncol. 2015; 33: 1688-1696.

22. Nishimura H, Okazaki T, Tanaka Y, Nakatani K, Hara M, Matsumori A, et al. Autoimmune dilated cardiomyopathy in PD-1 receptor-deficient mice. Science. 2001; 291: 319-322.

23. Topalian SL, Hodi FS, Brahmer JR, Gettinger SN, Smith DC, McDermott DF, et al. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. N Engl J Med. 2012; 366: 2443-2454.

24. Hamid O, Robert C, Daud A, Hodi FS, Hwu WJ, Kefford R, et al. Safety and tumor responses with lambrolizumab (anti-PD-1) in melanoma. N Engl J Med. 2013; 369: 134-144.

25. McDermott DF, Sosman JA, Sznol M, Massard C, Gordon MS, Hamid O, et al. Atezolizumab, an Anti-Programmed Death-Ligand 1 Antibody, in Metastatic Renal Cell Carcinoma: Long-Term Safety, Clinical Activity, and Immune Correlates from a Phase Ia Study. J Clin Oncol. 2016; 34: 833-842.

26. Kiessling R, Klein E, Pross H, Wigzell H. "Natural" killer cells in the mouse. II. Cytotoxic cells with specificity for mouse Moloney leukemia cells. Characteristics of the killer cell. Eur J Immunol. 1975; 5: 117-121.

27. Orleans-Lindsay JK, Barber LD, Prentice HG, Lowdell MW. Acute myeloid leukaemia cells secrete a soluble factor that inhibits T and NK cell proliferation but not cytolytic function – implications for the adoptive immunotherapy of leukaemia. Clin Exp Immunol. 2001; 126: 403-411.

28. Conlon KC, Lugli E, Welles HC, Rosenberg SA, Fojo AT, Morris JC, et al. Redistribution, hyperproliferation, activation of natural killer cells and CD8 T cells, and cytokine production during first-in-human clinical trial of recombinant human interleukin-15 in patients with cancer. J Clin Oncol. 2015; 33: 74-82.

29. Ishikawa E, Tsuboi K, Saijo K, Harada H, Takano S, Nose T, et al. Autologous natural killer cell therapy for human recurrent malignant glioma. Anticancer Res. 2004; 24: 1861-1871.

30. Pegram HJ, Jackson JT, Smyth MJ, Kershaw MH, Darcy PK. Adoptive transfer of gene-modified primary NK cells can specifically inhibit tumor progression *in vivo*. J Immunol. 2008; 181: 3449-3455.

31. Taniguchi M, Harada M, Dashtsoodol N, Kojo S. Discovery of NKT cells and development of NKT cell-targeted anti-tumor immunotherapy. Proc Jpn Acad Ser B Phys Biol Sci. 2015; 91: 292-304.

32. Inui T, Amitani H, Kubo K, Kuchiike D, Uto Y, Nishikata T, Mette M. Case Report: A Non-small Cell Lung Cancer Patient Treated with GcMAF, Sonodynamic Therapy and Tumor Treating Fields. Anticancer Res. 2016; 36: 3767-3770.

33. Sim GC, Martin-Orozco N, Jin L, Yang Y, Wu S, Washington E, et al. IL-2 therapy promotes suppressive ICOS+ Treg expansion in melanoma patients. J Clin Invest. 2014; 124: 99-110.

34. Prenen H, Guetens G, de Boeck G, Debiec-Rychter M, Manley P, Schoffski P, et al. Cellular uptake of the tyrosine kinase inhibitors imatinib and AMN107 in gastrointestinal stromal tumor cell lines. Pharmacology. 2006; 77: 11-16.