Revisiting of cancer vaccine?—Specific immunotherapy comes to field with the biomarker

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Coley *et al*., advocated a hypothesis of immune response against malignant tumors and he applied his concept by providing patients with the first cancer immunotherapy in 1906 (1). A few decades later, Bacillus Calmette-Guerin was introduced as a tumor immunotherapy by Old *et al*. (2). These non-specific immunotherapies have been promising cancer therapies, however, they were not widely accepted because of the unstable efficacy and a lack of understanding of the mechanisms of action. After understanding tumor-associated antigens and after discovering dendritic cells, the cancer immunotherapies primarily studied were specific cancer immunotherapies, such as cancer vaccines and dendritic cell vaccines.

In 1991, van der Bruggen *et al*., first reported the melanoma-associated antigen gene as a cancer antigen in a human melanoma cell line (3). Following Bruggen's report, numerous studies on cancer vaccines have been published. However, no immunotherapy, such as a cancer vaccine, shows clear efficacy for lung cancer. For instance, tecemotide (L-BLP25) is a liposomal-based therapeutic cancer vaccine that targets Mucin 1 antigen, and patients with non-small cell lung cancer (NSCLC) did not have a statistically better overall survival (OS) than the control group in a randomized phase 3 trial (4). In addition, using melanoma-associated antigen-A3, which is expressed in about 35–40% of NSCLCs, as an adjuvant did not improve the disease free interval in a phase 3 trial (5). A phase 2 study of belagenpumatucel-L, a transforming growth factor beta-2 antisense gene-modified allogeneic tumor cell vaccine, induced a better OS in NSCLC patients than the control (6), however, it is still under evaluation in a further large scale clinical trial. TG4010 is also a cancer vaccine composed of a modified vaccinia Ankara virus that expresses both Mucin 1 and interleukin 2, and it is currently the only promising vaccine for NSCLC. Although a randomized phase 2 study of TG4010 showed no statistical difference in the progression free survival (PFS) compared with patients treated with sequential platinum-based chemotherapy (7), a phase 2b/3 trial combining TG4010 immunotherapy with a first-line chemotherapy for advanced NSCLC was reported in *Lancet Oncology* in 2015 (8). In this report, which is the focus of this editorial, CD16, CD56 and CD69 triple-positive activated lymphocytes (TrPAL) were analyzed as a biomarker to predict treatment efficacy. This trial indicated that TG4010 combined with chemotherapy improved the PFS of patients relative to placebo plus chemotherapy, and fewer TrPAL was associated with a statistical reduced PFS and OS in both treatment groups. Therefore, TrPAL were a predictive biomarker in this study. This report highlights two important issues for cancer vaccination, which are biomarker analysis and combination therapy. In our past study of multiple peptide vaccines for patients with NSCLC, we observed that the specific CTL responses against one or more epitopes could be a prognostic biomarker (9). Like this study, most immunotherapy studies were focused on CTL responses as a prognostic biomarker, however, there has not been a predictive biomarker for cancer vaccination before treatment. Thus we have to identify a more definite predictive biomarker, and TrPAL is an interesting possibility that requires further study. The second important point regards combination therapies that incorporate a cancer vaccine. To date, there has been no pivotal study showing the efficacy of a cancer vaccine used in a combination therapy.

As mentioned above, immunotherapies with specific targets have been difficult, but immune-checkpoint inhibitors have been launched with promising results. Leach *et al*., reported that blocking cytotoxic T-lymphocyte antigen 4 (CTLA-4) in mice with cancer resulted in tumor regression (10). In 2010, the OS of metastatic melanoma was better with ipilimumab, a blocking antibody for CTLA-4, than with the glycoprotein 100 peptide vaccines (11). In other phase 3 trials, the OS, objective response rate and PFS for patients with NSCLC were better with nivolumab, an antibody against PD-1, than with docetaxel (12,13) In addition, pembrolizumab, an antibody against PD-1, prolonged the OS of patients with previously treated PD-L1-positive NSCLC (14). Although the survival was statistically superior with the antibody treatments in these studies, the limited responses were concerning (13). Therefore, a clinically useful biomarker and more effective combination therapies are required. Furthermore, the benefits remain unknown in patients with targetable driver mutations, and the efficacy of using PD-L1 expression as a biomarker remains controversial (15). A biomarker to predict the efficacy of immune-checkpoint inhibitors is currently been researched at multiple institutes, and a phase 1 biomarker study of nivolumab and nivolumab plus ipilimumab for the treatment of advanced melanoma is ongoing (NCT01621490).

The use of cancer vaccines and immune checkpoint inhibitors in a combination therapy is promising and clinical trials assessing this combination are underway. Although ipilimumab, with or without a glycoprotein 100 peptide vaccine, as compared with glycoprotein 100 alone, improved the OS in patients with previously treated metastatic melanoma. A phase 1/2 trial evaluating the safety and efficacy of the combination of a 6MHP peptide vaccine and PD-1 blockade with pembrolizumab for melanoma is ongoing (NCT02515227). Another pilot phase 1 study to test the safety of BMS-93558, an anti-PD-1 antibody, with or without a peptide vaccine, such as MART-1 or NY-ESO-1 targeting vaccines, for patients with stage 3/4 melanoma (NCT01176461) is underway.

Additionally, oncolytic viruses have also demonstrated some benefit in combination with immune-checkpoint inhibitors. Talimogene laherparepvec (T-VEC) is an oncolytic virus, and T-VEC has been tried in combination with CTLA-4 and PD-1 blockade. In a phase 1b trial, the combination of T-VEC and ipilimumab was well tolerated, and immune-related grade 3 or 4 adverse events only occurred in two of 18 patients with unresectable melanoma (16). In addition, objective responses were seen in 56% of patients and complete responses was seen in 33%, so the efficacy was promising. A phase 2 trial of ipilimumab with or without T-VEC for unresectable melanoma is currently recruiting participants. In addition, a phase 1/2 study of T-VEC combined with pembrolizumab for the treatment of unresectable melanoma is enrolling patients (NCT02263508). There are also some ongoing studies into combination therapies using immune-checkpoint inhibitors and other cancer immunotherapies. A phase 1/2 study of nivolumab plus GM.CD40L vaccination for adenocarcinomas of the lung will be open in a few months (NCT02466568). In addition, a phase 1/2 study of nivolumab plus viagenpumatucel-L is ongoing and under analysis (NCT02439450).

In 2004, Rosenberg mentioned the unsuccessful results of immunotherapies up to that point, but he clearly described that it was not a pessimistic story. In this report, he said "the lack of clinical effectiveness of currently available cancer vaccines should not be interpreted to mean that cancer vaccine approaches are at an investigational 'dead end' (17)". Various combination therapies that include immunotherapies are expected to be developed more rapidly. The effect of treatment with a combination consisting of an immune-checkpoint inhibitor and a tumor vaccine may be promising if a suitable biomarker for these therapeutic agents is identified. Immunotherapy will open the door to possibility improve the prognosis of patients who have unresectable or recurrent lung cancer.

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Footnote

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References

1. Coley WB. The treatment of malignant tumors by repeated inoculations of erysipelas. With a report of ten original cases. 1893. Clin Orthop Relat Res 1991;(262):3-11.

2. Old LJ, Clarke DA, Benacerraf B, et al. Effect of prior splenectomy on the growth of sarcoma 180 in normal and Bacillus Calmette-Guerin infected mice. Experientia 1962;18:335-6.
3. van der Bruggen P, Traversari C, Chomez P, et al. A gene encoding an antigen recognized by cytolytic T lymphocytes on a human melanoma. Science 1991;254:1643-7.
4. Butts C, Socinski MA, Mitchell PL, et al. Tecemotide (L-BLP25) versus placebo after chemoradiotherapy for stage III non-small-cell lung cancer (START): a randomised, double-blind, phase 3 trial. Lancet Oncol 2014;15:59-68.
5. Cuppens K, Vansteenkiste J. Vaccination therapy for non-small-cell lung cancer. Curr Opin Oncol 2014;26:165-70.
6. Nemunaitis J, Dillman RO, Schwarzenberger PO, et al. Phase II study of belagenpumatucel-L, a transforming growth factor beta-2 antisense gene-modified allogeneic tumor cell vaccine in non-small-cell lung cancer. J Clin Oncol 2006;24:4721-30.
7. Ramlau R, Quoix E, Rolski J, et al. A phase II study of Tg4010 (Mva-Muc1-Il2) in association with chemotherapy in patients with stage III/IV Non-small cell lung cancer. J Thorac Oncol 2008;3:735-44.
8. Quoix E, Lena H, Losonczy G, et al. TG4010 immunotherapy and first-line chemotherapy for advanced non-small-cell lung cancer (TIME): results from the phase 2b part of a randomised, double-blind, placebo-controlled, phase 2b/3 trial. Lancet Oncol 2016;17:212-23.
9. Suzuki H, Fukuhara M, Yamaura T, et al. Multiple therapeutic peptide vaccines consisting of combined novel cancer testis antigens and anti-angiogenic peptides for patients with non-small cell lung cancer. J Transl Med 2013;11:97.
10. Leach DR, Krummel MF, Allison JP. Enhancement of antitumor immunity by CTLA-4 blockade. Science 1996;271:1734-6.
11. Hodi FS, O'Day SJ, McDermott DF, et al. Improved survival with ipilimumab in patients with metastatic melanoma. N Engl J Med 2010;363:711-23.
12. Brahmer J, Reckamp KL, Baas P, et al. Nivolumab versus Docetaxel in Advanced Squamous-Cell Non-Small-Cell Lung Cancer. N Engl J Med 2015;373:123-35.
13. Borghaei H, Paz-Ares L, Horn L, et al. Nivolumab versus Docetaxel in Advanced Nonsquamous Non-Small-Cell Lung Cancer. N Engl J Med 2015;373:1627-39.
14. Herbst RS, Baas P, Kim DW, et al. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. Lancet 2016;387:1540-1550.
15. Melosky B, Chu Q, Juergens R, et al. Pointed Progress in Second-Line Advanced Non-Small-Cell Lung Cancer: The Rapidly Evolving Field of Checkpoint Inhibition. J Clin Oncol 2016. [Epub ahead of print].
16. Hellmann MD, Friedman CF, Wolchok JD. Combinatorial Cancer Immunotherapies. Adv Immunol 2016;130:251-77.
17. Rosenberg SA, Yang JC, Restifo NP. Cancer immunotherapy: moving beyond current vaccines. Nat Med 2004;10:909-15.

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