Editorial

From the era of ineffective tumor vaccines to a future with effective immunotherapy

Wolter Igor Quincy de Waard, Michel Maria van den Heuvel

Department of Thoracic Oncology, The Netherlands Cancer Institute, Amsterdam, The Netherlands

Correspondence to: M.M. van den Heuvel, MD PhD. The Netherlands Cancer Institute, Plesmanlaan 121 1066 CX Amsterdam, The Netherlands. Email: m.vd.heuvel@nki.nl.

Submitted Jun 20, 2016. Accepted for publication Jun 24, 2016.
doi: 10.21037/jtd.2016.07.04
View this article at: http://dx.doi.org/10.21037/jtd.2016.07.04

Immunotherapy has become an attractive therapeutic option (1). A hundred years ago Dr. William B. Coley created inspiration by his description of the anti-cancer effects of a streptococcal vaccine (2). Since then many vaccination trials were started but few succeeded. Cancer vaccines most often introduce tumor associated antigens (TAAs) that trigger the immune responses against cancer cells (3). To be effective immunotherapeutic targets the TAAs have to have three features (4). Expression of TAAs has to be in tumor tissue, but not (or very restricted) in normal tissues. They should induce T-cell immune responses. Finally they should have biologically oncogenic characteristics. Melanoma antigen A3 (MAGE A3) was thought to be an ideal candidate TAA.

Vansteenkiste *et al*. used MAGE A3 that is expressed in 30–50% of NSCLCs (5). The MAGRIT trial, the biggest-ever adjuvant trial in lung cancer, was performed to investigate whether the MAGE A3 vaccine could improve overall survival. In a phase 3 trial 2,272 patients with stage IB-III NSCLC were randomized, following resection with or without adjuvant chemotherapy, to receive the vaccine or a placebo. Unequivocally, there was no improvement in any of the endpoints. Rarely trials did show such an overlap of survival curves. Not a single subgroup showed advantage.

This makes us wonder why this vaccine has failed. The strong induction of an anti-MAGE A3 antibody-response suggests that there is no problem in the antigen presentation or lack of necessary signals delivered by CD4 T-cells. Alternative explanations might be that the CD8 T-cell activation was not sufficient. However, this is also unlikely, as this large trial did not even show the slightest signal of activity. More likely, the answer will lie in the complex interaction between tumor cells, inflammatory cells and the stroma. Both recent insights in immune-oncology following the arrival of the immune checkpoint inhibitors and the prognostic data of the intra-tumor inflammatory cells underline the importance of local intra-tumor processes that prevent an efficient immune response (6,7).

We need to find a way to improve vaccination therapy without decreasing safety due to autoimmunity. Data on biomarkers such as PD-L1 expression, mutational load and interferon signatures suggest that personalized vaccination strategies will be needed (8-10). By using next generation sequencing techniques the individual neoantigen spectrum can be determined in tumors and thus personalized vaccines can be engineered (11). Another possibility might be to remove the operative immune checkpoints that hinder the vaccine's antitumor capability (11). Another option is the use of adoptive cell therapy in which tumor infiltrating lymphocytes (TIL) are expanded in vitro and then given back to the patient (11).

Although these and other measures could improve immunotherapy, there are still many hurdles to take. However, we have learned from our failures and given the recent successes within the field of immune-oncology we know that the future is bright.

Acknowledgements

None.

Footnote

Provenance: This is an invited Editorial commissioned by

the Section Editor Long Jiang (Second Affiliated Hospital, Institute of Respiratory Diseases, Zhejiang University School of Medicine, Hangzhou, China).

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Cite this article as: de Waard WI, van den Heuvel MM. From the era of ineffective tumor vaccines to a future with effective immunotherapy. J Thorac Dis 2016;8(8):1916-1917. doi: 10.21037/jtd.2016.07.04