Universe
Scientific Publishing

Tumor Vaccine Based on Targeted Neoantigen: A Powerful Immunotherapy Weapon in Acute Myeloid Leukemia

Shuwei Liu

Shenyang Pharmaceutical University, Shenyang 110016, China.

Abstract : Acute myeloid leukemia (AML) is a common type of leukemia. The existing chemotherapy regimens and hematopoietic stem cell transplantation can not achieve the ideal treatment effect, and more efficient treatment methods are needed in the clinical treatment of AML patients. As a star method of immunotherapy, tumor vaccines have attracted much attention. Choosing neoantigen as the target antigen in vaccine is a new and exploreable design plan for AML. In this review, we will carefully summarize the current neoantigen-related vaccine research progress, reasonably speculate its application prospects in AML, and put forward the key challenges and risks in the research.

Keywords: Tumor Vaccine; Neoantigen; Immunotherapy; Acute Meyroid Leukemia

Introduction

1. Acute myeloid leukemia: the most common but intricate leukemia

As the most common diagnosed leukemia (1), acute myeloid leukemia (AML) is mainly characterized by the uncontrolled proliferation of primitive myeloid progenitor cells. These cells are not capable to further differentiate into normal mature leukocytes in vivo (2).

Chemotherapy is a common clinical treatment for AML. Moreover, according to the patient's physical fitness and chemotherapeutic drug sensitivity, adjuvant radiotherapy can be treated to enhance the therapeutic effect of the induction phase (3). In the consolidation period, the current clinical treatment is also to use high-dose cytarabine and other drugs combined with chemotherapy for consolidation therapy (4). In addition, hematopoietic cell transplantation (allo-HCT) is approved to treat patients with certain high-risk cytogenetic characteristics (such as FLT3-ITD without NPM1) and refractory patients or patients with relapsed AML achieving CR2 after re-induction therapy (5). In short, the traditional treatment of acute myeloid leukemia is often combined with sequential chemotherapy.

2. Tumor vaccine: a powerful weapon in immunotherapy

2.1 Tumor vaccine is an emerging active immunotherapy regime

In traditional concepts, vaccines refer to biological products made with various microorganisms for the prevention of infectious diseases. In tumor treatment programs, tumor vaccines are not only limited to preventive vaccines, but also include therapeutic vaccines, and most of them are used to reduce cancer recurrence after chemotherapy or surgery (6). In this review, we will only discuss therapeutic vaccines. This type of vaccine mainly refers to injecting specific cells or molecules into the patient's body, regulating the immune microenvironment in the peripheral blood, and inducing the body to actively amplify or produce a specific response (7). The goal of therapeutic cancer vaccines is to induce tumor regression, eradicate minimal residual disease, and ultimately establish a long-term anti-tumor memory to increase the patient's long-term disease-free survival rate (DFS) (8). There are two types of tumor vaccines: cellular vaccines and molecular vaccines. Cell vaccines include whole tumor cell vaccines and dendritic cells (DCs) vaccines. Peptide vaccines and granulocyte-macrophage-colony stimulating factor (GM-CSF) vaccines belong to molecular vaccines (9). So far, tumor vaccines have become a research hotspot in solid tumors. They have been used in ovarian cancer, lung cancer, melanoma, brain cancer, kidney cancerand other

cancers (10-16). Even in the development direction of cervical cancer, different from the preventive vaccines that have been on the market, cervical cancer therapeutic vaccines have been reported to be shown to induce a systemic immune response in patients, resulting in a reversion of immunosuppression in the tumor microenvironment (17).

3. Neoantigen tumor vaccine: Bringing dawn to the treatment of AML

For the current tumor vaccine target antigens for AML, most of the projects are based on TAAs， such as NY-ESO-1 vaccine and DCP-001 vaccine (18-19). Moreover, based on the high specificity and safety of neoantigen discussed above, the development of effective tumor vaccines based on various neoantigens in AML has become a new and valuable direction.

3.1 Two examples of neoantigen vaccines in AML

3.1.1 Vaccination with dendritic cell/tumor fusions

A research team has developed a multiple bone marrow vaccine in 2013. After injecting vaccine, the patient's auto-derived tumor cells and auto-dendritic cells can be fused to produce a variety of tumor genetic antigens, including neoantigens. It effectively captures tumor heterogeneity (20). In a phase I/II clinical trial, the median age of AML patients who received chemotherapy was vaccinated at 63 years. The result was that 71% of vaccinated patients were still in remission during the 5-year follow-up (21). With the research of this new personalized DC/AML fusion vaccine, after vaccination, checkpoint blockade leads to the enhancement of genes that regulate memory and effector T cell activation and proliferation, and enhances the diversity of T cell clones (22).

3.1.2 New OCV-501 peptide vaccine

The expression of WT1 gene (Wilms tumor gene1) in normal tissues in the body is extremely low and can be ignored, but it has extremely high expression in 96% of AML cells, producing a large amount of WT1 peptide. Moreover, WT1 is an oncogenic protein, and it does inhibit the growth of tumor cells, so WT1 is an ideal neoantigen for AML (23). OCV-501 is a synthetic peptide composed of natural sequences derived from the WT1 gene product protein without any modification or combination with other peptide sequences. It is an HLA II restricted WT1 adjuvant peptide therapeutic cancer vaccine (26).

Discussion

Based on the detailed discussions on neoantigens and vaccines for AML in our review, the analogy study of personalized neoantigen pulsed cancer vaccines in AML is reasonable. Compared with solid tumors that have been extensively studied, AML has a relatively low tumor burden. But neoantigen vaccine still has a prominent therapeotic potential.

In short, the personalized tumor vaccine based on neoantigen can be a potential treatment strategy for AML patients in the future, which can cure patients more accurately, efficiently, and with little harm. Especially， it may will reduce AML relapse rate after chemotherapy treatment or allo-HSC. Combination with this new type of vaccine with other immunotherapies is also a desirable idea (25-26).

References

[1] Burd, A., Levine, R.L., Ruppert, A. S., et al. Precision medicine treatment in acute myeloid leukemia using prospective genomic profiling: feasibility and preliminary efficacy of the Beat AML Master Trial.[J] .Nat Med, 2020, 26: 1852-1858.

[2] Tefferi, A,Vardiman, J.W., Myelodysplastic syndromes. [J] .N Engl J Med, 2009, 361: 1872-85.

[3] Tallman, M.S.,Wang, E.S., Altman, J.K., et al. Acute Myeloid Leukemia, Version 3.2019, NCCN Clinical Practice Guidelines in Oncology.[J] .J Natl Compr Canc Netw, 2019, 17: 721-749.

[4] Elsayad, K., Oertel, M., Haverkamp, U., et al. The effectiveness of radiotherapy for leukemia cutis.[J] .J Cancer Res Clin Oncol, 2017, 143: 851-859.

[5] Leukemia & Lymphoma Group, Chinese Society of Hematology, Chinese Medical Association,[Chinese guidelines for diagnosis and treatment of adult acute myeloid leukemia (not APL) (2017)].[J] . Zhonghua Xue Ye Xue Za Zhi, 2017, 38: 177-182.

[6] Chevallier P., Mohty, M., Lioure, B., et al. Allogeneic hematopoietic stem-cell transplantation for myeloid sarcoma: a retrospective study from the SFGM-TC. [J] .J Clin Oncol, 2008, 26: 4940-3.

[7] Creutzig, U.,van den Heuvel-Eibrink Marry M,Gibson, B. et al. Diagnosis and management of acute myeloid leukemia in children and adolescents: recommendations from an international expert panel.[J] .Blood, 2012, 120: 3187-205.

[8] Saxena, M., van der Burg Sjoerd H, Melief, C. J. M., et al. Therapeutic cancer vaccines.[J] .Nat Rev Cancer, 2021, 21: 360-378.

[9] Arribillaga L., Echeverria, I., Belsue, V., et al. Bivalent therapeutic vaccine against HPV16/18 genotypes consisting of a fusion protein between the extra domain A from human fibronectin and HPV16/18 E7 viral antigens.[J] . J Immunother Cancer, 2020, 8: undefined.

[10]Kim, C.G., Sang, Y.b., Lee, J.H., et al. Combining Cancer Vaccines with Immunotherapy: Establishing a New Immunological Approach.[J] .Int J Mol Sci, 2021, 22: undefined.

[11]Cheever, M.A., Higano, C. S., PROVENGE (Sipuleucel-T) in prostate cancer: the first FDA-approved therapeutic cancer vaccine.[J] .Clin Cancer Res, 2011, 17: 3520-6.

[12]Rocconi, R.P., Grosen, E.A, Ghamande, S.A., et al. Gemogenovatucel-T (Vigil) immunotherapy as maintenance in frontline stage III/IV ovarian cancer (VITAL): a randomised, double-blind, placebo-controlled, phase 2b trial.[J] .Lancet Oncol, 2020, 21: 1661-1672.

[13]Kalli, K.R., Block, M.S., Kasi, P. M., et al. Folate Receptor Alpha Peptide Vaccine Generates Immunity in Breast and Ovarian Cancer Patients.[J] .Clin Cancer Res, 2018, 24: 3014-3025.

[14]Dammeijer, F., Lievense, L.A.,Veerman, G.D., Marijn et al. Efficacy of Tumor Vaccines and Cellular Immunotherapies in Non-Small-Cell Lung Cancer: A Systematic Review and Meta-Analysis.[J] .J Clin Oncol, 2016, 34: 3204-12.

[15]Ott, P.A., Hu-Lieskovan, S.W.,Chmielowski, B., et al. A Phase Ib Trial of Personalized Neoantigen Therapy Plus Anti-PD-1 in Patients with Advanced Melanoma, Non-small Cell Lung Cancer, or Bladder Cancer.[J] .Cell, 2020, 183: 347-362.e24.

[16]Sahin, U., Oehm, P., Derhovanessian, E., et al. An RNA vaccine drives immunity in checkpoint-inhibitor-treated melanoma.[J] .Nature, 2020, 585: 107-112.

[17]Weller, M., Roth, P., Preusser, M., et al. Vaccine-based immunotherapeutic approaches to gliomas and beyond.[J]. Nat Rev Neurol, 2017, 13: 363-374.

[18]Pal, S.K., Agarwal, N., Dizman, N., et al. Vaccine therapy in renal cell carcinoma: attempting to leap over a rising bar.[J] .Lancet Oncol, 2016, 17: 1477-1478.

[19]Che, Y.X.,Yang, Y., Suo, J.G., et al. Induction of systemic immune responses and reversion of immunosuppression in the tumor microenvironment by a therapeutic vaccine for cervical cancer.[J] .Cancer Immunol Immunother, 2020, 69: 2651-2664.

[20]Griffiths, E.A., Srivastava, P., Matsuzaki, J., et al. NY-ESO-1 Vaccination in Combination with Decitabine Induces Antigen-Specific T-lymphocyte Responses in Patients with Myelodysplastic Syndrome.[J] .Clin Cancer Res, 2018, 24: 1019-1029.

[21]van de, Loosdrecht Arjan A,van Wetering Sandra,Santegoets Saskia J A M et al. A novel allogeneic off-the-shelf dendritic cell vaccine for post-remission treatment of elderly patients with acute myeloid leukemia.[J] .Cancer Immunol Immunother, 2018, 67: 1505-1518.
[22]Rosenblatt, J., Avivi, I., Vasir, B., et al. Vaccination with dendritic cell/tumor fusions following autologous stem cell transplant induces immunologic and clinical responses in multiple myeloma patients.[J] .Clin Cancer Res, 2013, 19: 3640-8.
[23]Rosenblatt, Jacalyn., Stone, Richard, M, Uhl, L., et al. Individualized vaccination of AML patients in remission is associated with induction of antileukemia immunity and prolonged remissions.[J] .Sci Transl Med, 2016, 8: 368ra171.
[24]Stroopinsky, D., Liegel, J., Bhasin, M., et al. Leukemia vaccine overcomes limitations of checkpoint blockade by evoking clonal T cell responses in a murine acute myeloid leukemia model.[J] .Haematologica, 2021, 106: 1330-1342.
[25]Dombret, H., Gene mutation and AML pathogenesis.[J] .Blood, 2011, 118: 5366-7.
[26]Fujiki, F., Oka, Y., Tsuboi, A., et al. Identification and characterization of a WT1 (Wilms Tumor Gene) protein-derived HLA-DRB1*0405-restricted 16-mer helper peptide that promotes the induction and activation of WT1-specific cytotoxic T lymphocytes.[J] .J Immunother, 2007, 30: 282-93.