УДК [61+615.1](06)(043.2)
ББК 5+52.81
А 43
ISBN 978-985-21-1569-8

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CHIMERIC ANTIGEN RECEPTOR T CELLS AS A CANCER THERAPY

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For decades surgery, chemotherapy, and radiation therapy have been the backbone of cancer treatment. These remain the most important basic methods, but new groups of medicines have helped change the pattern of treatment for cancer patients. The 2000s were notable for the introduction of targeted therapies – medicines that find and destroy cancer cells by targeting specific molecular changes seen predominantly in those cells. And over the past decade, immunotherapy has become vital in treating cancer.

Immunotherapy is a therapy that engages and enhances the ability of a patient's immune system to attack tumors. For instance, immune checkpoint inhibitors are already widely used to treat people with many types of cancer. Another form of immunotherapy is chimeric antigen receptor (CAR) T cell therapy. The principle of chimeric antigen receptor technology is to replace the main receptor complex of human cytotoxic T-lymphocytes, which nonspecifically recognizes foreign cells, with an artificial CAR specific to a particular type of cancer. They are called chimeric because they are "assembled" into a single molecule from components (a single chain variable fragment, a spacer domain, a transmembrane domain, and one or more cytoplasmic domains) of different origins, each of which contributes towards the proper activation, functionality, and persistence of CAR T cells.

To produce CAR T lymphocytes, the cytotoxic T lymphocytes are taken from the patient's blood, the CAR gene is inserted into them using a viral vector. The resulting CAR-expressing cells are injected back into the patient body. These individually produced ex vivo CAR T lymphocytes are called autologous. At present, work is underway to obtain allogeneic cells. These are the same T lymphocytes but taken from a healthy donor. They have their T cell receptor turned off, which reduces the risk of their attack on the patient's cells carrying MHC molecules to which this receptor may be specific. This approach makes it possible not to make cells individually for each patient, but to have a ready-made cell preparation, which is much easier and more convenient.

Most CARs are being developed and tested for the treatment of different forms of blood cancer, including diffuse large B cell lymphoma (DLBCL), B cell acute lymphoblastic leukemia (B-ALL), and multiple myeloma (MM), with FDA approvals. This is because leukocytes have a relatively small number of highly specific antigens, so it is easier to develop an effective and safe chimeric receptor for them. With various cancers of other tissues is more difficult – they have more antigens, and many of them are present on healthy cells. In addition, such tumors are often heterogeneous in antigenic composition due to high levels of cell mutations. Nevertheless, CARs are created for them as well. Studies are also ongoing to find new applications for CAR T lymphocytes (e.g., treatment of viral infections, combating cellular aging) and to increase their effectiveness.