Ministry of Health of the Russian Federation

PATIENT INFORMATION SHEET
GUIDELINES FOR THE USE OF AN INDIVIDUAL BIOMEDICAL CELL PRODUCT

"HUMAN ANTI-CD19 CAR-T CELLS FOR AUTOLOGOUS USE"

2026

Introduction part

CAR-T-cell therapy (Chimeric Antigen Receptor T-cells) is one of the most promising and rapidly developing areas of immuno-oncology and gene therapy. This innovative treatment method is based on the use of the patient's own T-lymphocytes, which are genetically modified in the laboratory to express a chimeric antigen receptor (CAR)that can recognize tumor antigens. Returned to the patient's body, these "armed" cells acquire the ability to effectively recognize and destroy malignant cells, which opens up a new era in the treatment of refractory and recurrent forms of cancer. This therapy has shown particular value in the treatment of B-cell malignancies, such as refractory acute lymphoblastic leukemia, where other treatments have proved unproductive. The most well-known targets for CAR-T cells are most often B-cell antigens in multiple myeloma and CD19 B-cell antigen in various recurrent or refractory B-cell lymphoid tumors, including B-cell leukemias and certain types of lymphomas.

The constant or temporary presence on the surface of CAR immune cells gives them the ability to activate, grow and differentiate when interacting with tumor cells. T-lymphocyte expressing CAR - CAR-T-lymphocyte. CAR-T lymphocytes are historically the first and most advanced forms of medical use of CAR.

The first clinical results of CAR-T cell therapy were published in 2013 in a clinical case report and were confirmed in a number of clinical studies. The use of this type of treatment allows to achieve clinical and hematological remission in 70-90% of cases within 1 month after the infusion, while in 80% of patients remission persists for 1 year after therapy. The survival rate of patients 1 year after treatment varies from 50% to 60%. The main side effects associated with this type of therapy are a decrease in the level of B-lymphocytes and hypogammaglobulinemia. The key complications are the development of cytokine release syndrome (SVC), immune cell-related neurotoxicity syndrome (HT), and a long-term decline in the overall blood count. Severe forms of such complications were observed in almost 50% of cases and in some cases led to the death of patients.

The final decision on CAR-T cell therapy will be made by the Medical Commission by unanimous consensus. Payment for treatment is made as part of the quota for provision of high-tech medical care or as part of provision of paid services with the patient's voluntary consent. The therapeutic plan will be based on stratification of patients depending on the mass of the tumor.

What procedures will be performed if you agree to IBMCP therapy?

Description of the CAR-T therapy procedure.

This is a method of treating oncohematological diseases, in which the patient's own T-lymphocytes are genetically modified to recognize and destroy tumor cells. A patient's treatment is based on an individual biomedical cell product (hereinafter referred to as IBMCP) made from genetically modified T cells that target a specific antigen (target), for example, CD19 in B-cell lymphomas.

Main stages of obtaining a CAR-T product

1. Collecting T cells. A blood sample is taken from the patient (venous blood in tubes with an anticoagulant or using apheresis-a technology that allows to divide blood into components and get a certain number of lymphocytes).
2. Genetic modification. In the laboratory, a chimeric antigen receptor (CAR) is inserted into T-lymphocytes. Its extracellular part is a single-stranded variable antibody fragment that recognizes a specific antigen on the surface of a tumor cell (for example, CD19). The lentiviral vector is often used for modification.
3. Reproduction of modified cells. The resulting CAR-T cells are cultured and propagated in vitro in a cytokine-rich medium.
4. Quality control. Cells are checked for safety and functionality before being administered to the patient.

Features of carrying out some of the procedures involved in the therapy:

Patient preparation.

Before the introduction of CAR-T cells, the patient undergoes lymphodepleting therapy - a course of chemotherapy aimed at reducing the activity of remaining "normal" T cells. The aim is to reduce the number of lymphocytes in the peripheral blood to reduce the risk of rejection of IBMCP and improve the effectiveness of treatment.

Patients with low tumor burden receive lymphodepletion therapy with fludarabine-Flu (total dose 120 mg /^{m2}) and cyclophosphamide-Cph (total dose 750 mg/^{m2}) for 5 days, from day -6 to day -2. On day 0, IBMCP is administered once at a dose of 0.01-6.0 x 10^8 CD3+/anti-CD19 CAR+ cells.

Patients with a high tumor burden receive lymphodepletion therapy consisting of fludarabine-Flu (total dose 120 mg /^{m2}), cyclophosphamide-Cph (total dose 750 mg/^{m2}), cytarabine-Ara-C (total dose 900 mg/^{m2}) and etoposide-VP-16 (total dose 450 mg /^{m2}), dexamethasone (total dose 30 mg /^{m2}) for 5 days, from day -6 to day -2. On day 0, IBMCP is administered once at a dose of 0.01-6.00 x 10^8 CD3+/anti-CD19 CAR+ cells. Infusion of IBMCP is recommended to be performed 2-14 days after the completion of lymphodepleting chemotherapy. Lymphodepleting chemotherapy may not be performed if the patient has significant cytopenia, for example, the number of white blood cells in the one week before the infusion is ≤ 1000 cells/μl. If the time interval between the completion of lymphodepletion chemotherapy and the infusion of IMBCP is less than 4 weeks, and the number of white blood cells

is> 1000 cells/μl, then the patient should undergo lymphodepletion chemotherapy again before receiving the IMBCP infusion.

Rules for the administration of drugs during therapy

Premedication.

To minimize potential acute infusion reactions, premedication with acetaminophen/paracetamol and diphenhydramine or another histamine H1 receptor blocker is performed 30-60 minutes before the infusion of modified patient T-lymphocytes with a chimeric anti-CD19 antigen receptor.

During the first 10 days after IBMP administration, patients are monitored daily for signs and symptoms of cytokine release syndrome, neurological disorders, and other types of toxicity. It is necessary to stay within a distance of a 2-hour walk from the medical facility where the therapy was performed, for at least 4 weeks after the infusion. The number of white blood cells, platelets and red blood cells in the blood may be low, which may require repeated transfusions of blood components. Inpatient treatment is carried out until the optimal values of blood parameters are restored, at which outpatient observation is possible;

Discharge from the hospital will be possible only after the blood counts are restored to optimal values and after the necessary medical measures that require observation in a hospital setting, including in the intensive care unit and intensive care unit are completed.

Introduction of the drug

Before administration, the patient is identified and checked for compliance with the identifier on the IBMP tube. If the information does not match, the drug is not administered. Before the infusion, the test tube with IBMCP should be examined for cracks and damage, as well as the uniformity of the contents and the absence of clots. If the test tube is damaged or clots remain after careful mixing, the infusion of IBMCP is not performed. Before administration of the drug, it is necessary to flush the catheter with 10-20 ml of 0.9% sodium chloride solution. The drug is administered intravenously slowly through a peripheral or central venous catheter at a rate of 1-2 ml per minute. Upon completion of the drug administration, the system is flushed with 10-30 ml of 0.9% sodium chloride solution intravenously slowly at a rate of 1-2 ml per minute.

Your responsibilities:

- mandatory implementation of all hygiene measures and taking all medications prescribed by the attending physician during treatment in round-the-clock and day hospitals, as well as in outpatient settings;
- compliance with the dietary requirements and the necessary daily routine.

Possible use of other medication and other restrictions on the duration of therapy

For the duration of lymphodepletion therapy and CAR-T-cell therapy, standard treatment of the disease is suspended due to its ineffectiveness.

For the duration of CAR-T therapy, it is strictly forbidden to be a donor of blood, organs, tissues or cells for transplantation. Live vaccination is not recommended for at least 6 weeks before the start of lymphodepletion chemotherapy, during IBMCP therapy, or until immunological parameters are restored after IBMCP infusion. The use of antiplatelet agents is not prohibited. Systemic corticosteroids and non-steroidal anti-inflammatory drugs should be avoided, as they may affect the activity of CAR-T lymphocytes.

Pregnancy and breast-feeding are strictly contraindicated during treatment, and therefore the use of contraception is recommended for the duration of therapy and for several months after it. For 8 weeks after the infusion, it is recommended to refrain from driving or performing dangerous activities, such as working with heavy or potentially dangerous mechanical tools.

In which cases the decision to stop therapy is made?

Possible reasons for discontinuing or suspending CAR-T cell therapy:

Life-threatening conditions	Severe infections, multiple organ failure, active bleeding,exacerbation of concomitant disease
Serious side effects	Severe cytokine release syndrome ,neurotoxicity, anaphylactic shock
Disease progression	Progression of the main disease
Loss of target	Loss of CD19+ antigen on tumor cells
Lack of T cells	Not possible to create the required product
Decision of the medical commission	Decision on the inexpediency of continuing therapy due to high risk of fatal outcome or lack of prospects for a response to treatment

Expected risks and disadvantages of IBMCP therapy, possible adverse reactions

Possible main complications:

- Nausea and vomiting.
- Neutrotoxicity.

- Cytokine reactions.
- Possible skin changes (dryness, local pigmentation, darkening, etc.) and hair loss.
- Development of infectious complications. Infectious complications are caused by a decrease in the number of white blood cells (especially granulocytes – a subclass of white blood cells that performs a protective function, primarily against bacterial and fungal infections) during bone marrow engraftment. Infectious complications can be caused by various infectious agents - bacteria, viruses and fungi that can affect various organs and systems: infections of the bloodstream (sepsis), respiratory system (bronchitis, pneumonia, pleurisy), gastrointestinal tract (gastritis, enterocolitis), urinary system (nephritis, pyelonephritis, cystitis, urethritis) central nervous system (meningitis, encephalitis), etc.
- Reactivation of viral infections of the herpetic group, chronic viral hepatitis B, C, and other viral infections can also develop.
- Bleeding, which is associated with a decrease in platelet levels and the occurrence of disorders in the blood coagulation system. This can be manifested by nasal, gingival bleeding, hemorrhages in the sclera of the eyes, uterine, gastrointestinal bleeding, hemorrhages in internal organs.
- Microvascular complications. Thrombotic microangiopathy develops in 5-15% of patients and is manifested by anemia, pronounced general weakness, impaired function of internal organs, especially the central nervous system and kidneys. Veno-occlusive liver disease develops in approximately 1-2% of patients and is manifested by an increase in bilirubin levels, an increase in liver size, pain in the right hypochondrium, weight gain, and fluid accumulation in the abdominal cavity.
- Impaired reproductive function. Chemotherapy courses have an impact on the male and female reproductive systems, which significantly reduces the reproductive function and may lead to infertility, especially in women. Pregnancy status should be determined before starting IBMCP therapy in women with preserved reproductive potential. For patients receiving lymphodepleting chemotherapy, the information about the need for effective methods of contraception indicated in the instructions for medical use of drugs used in the lymphodepleting chemotherapy should be taken into account. There are insufficient data on the use of IBMCP, on the basis of which it would be possible to make recommendations on the duration of contraception after its use. There are no data on the use of IBMCP in pregnant women. No animal studies have been conducted to assess whether IBMCP may cause harm to the fetus if used in pregnant women. It is not known whether IBMCP can affect fetus through placenta and whether it can cause toxic effects in the fetus,

,including a decrease in the level of B-lymphocytes. IBMCP is not recommended for pregnant women and women with preserved reproductive potential who do not use contraceptive methods. Pregnant women should be warned about possible risks to the fetus. The possibility of pregnancy after IBMCP therapy should be discussed with the patient's doctor. Hypogammaglobulinemia may occur in pregnant women who have received IBMCP. Newborns whose mothers have been treated with IBMCP will have to be tested for concentration of immunoglobulins. It is not known whether the cells included in IBMCP affect breast milk. The risk to a breastfed baby cannot be excluded. Women who are breast-feeding should be warned about the possible risk to the breastfed baby. After the introduction of IBMCP, the issue of breastfeeding should be discussed with the attending physician. There are no data on the effect of IBMCP on fertility. In animal studies, the effect of IBMCP on fertility of both sexes was not evaluated.

- Impaired renal function. Courses of chemotherapy and other medications can affect renal function, causing acute or chronic renal failure.
- Impaired liver function. Some patients may develop toxic hepatitis and liver failure due to high-dose chemotherapy.
- It is also possible to damage any organ of the nervous, cardiovascular, respiratory, endocrine system, gastrointestinal tract, musculoskeletal system, etc.
- Since the treatment may cause neurological disorders, including altered mental state or seizures, patients may experience changes or decreases in their level of consciousness and coordination within 8 weeks of administration. Therefore, it is recommended that patients refrain from driving or performing dangerous activities, such as working with heavy or potentially dangerous mechanical tools, for 8 weeks after the introduction of IBMCP.

- Patients may develop secondary malignancies. T-cell malignancies occurred after treatment of hematological malignancies with BCMA-and CD19-directed genetically modified autologous T-cell immunotherapy. T-cell malignancies from mature cells, including CAR-positive tumors, can appear as early as a few weeks after administration and can be fatal. These patients should be monitored throughout their lives for secondary malignancies, including those of T-cell origin. If a secondary malignancy occurs, contact a representative of the registration card holder for instructions regarding the collection of patient material for tests.

• Relapse of the disease may occur after the introduction of autologous anti-CAR-T lymphocytes, especially in high-risk patients.

What are the benefit of IBMCP therapy?

The benefits of IBMCP therapy are due to the proven effectiveness of this type of treatment and the possibility of achieving a response to therapy.

Are other types of treatment available?

Other available treatments may be used in accordance with national clinical guidelines.

Compensation for possible damages related to IBMCP therapy

Compensation for possible damage associated with IBMCP therapy is carried out within the framework of current legislation.

Access and processing of medical information containing your personal data

Access and processing of medical information containing your personal data in accordance with Federal Law No. 152-FZ of 27.07.2006 "On Personal Data" and Article 13 of the current Federal Law No. 323-FZ of November 21, 2011 "On the Fundamentals of Public Health Protection in the Russian Federation".

What happens if you change your mind

In accordance with Article 20 of the current Federal Law No. 323-FZ of November 21, 2011 "On the fundamentals of public health protection in the Russian Federation", you will be informed by your attending physician about the risks associated with refusing this medical intervention.

Informing your attending physician (full name)

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Contact Information

If you have any questions, please contact your doctor at 8 (846) 374-91-00 or by e-mail to SamSMU Clinics clinica@samsmu.ru

I have read the information provided in this document, I received all the necessary explanations, I understand the information contained in this document and answers to all my questions have been given.

_____/_____ **(patient's signature, transcript)**

Date_____