

Immunotherapy of Cancer (Review)

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We present a review of modern methods of immunotherapy of cancer. The following main types of immunotherapy are considered: active and passive, specific and non-specific. Active non-specific immunotherapy of tumors is based on the use of cytokines, some bacterial products, synthetic molecules and hormones; active specific immunotherapy — on the use of vaccines on tumor-associated or viral antigens. The main approaches of passive non-specific immunotherapy are adoptive T cell therapy as well as the use of heat-shock proteins and lectins. Passive specific immunotherapy is based on the injection of monoclonal antibodies. Special attention is paid in the review to the mechanisms of the anti-tumor effects of immunotherapeutic agents: their effects on the cells of the immune system as well as their inhibition of tumor progression. The results of some *in vitro* and *in vivo* preclinical studies and of the clinical trials of different medications are presented. The prospects for the use of immunotherapy in the treatment of cancer are discussed.

Key words: cancer; tumor; immunotherapy; cytokines; vaccines; monoclonal antibodies; adoptive T cell therapy.

It has been found that oncological diseases are associated with impairment of the immune system and the immune surveillance of oncogenic viruses and anomalous cells.

Recently, the immunotherapy of tumors aimed at inhibition of tumor growth and the stimulation of the anti-tumor immune response of the body is being developed [1–3]. Immunotherapy is targeted at overcoming the suppression of immune surveillance, to allow recognition of tumor cells by the immune system and, as a result, the inhibition of tumor growth. Unlike classical methods of treatment of cancer immunotherapy is targeted at restoration of the ability of the immune system to fight the disease and not just at tumor removal.

Immunotherapy of tumors can be subdivided into four types: active and passive, specific and non-specific (See the Table).

Evasion of immunological surveillance by the tumor

There are a wide range of mechanisms that allow tumors to escape immunological surveillance [4–6].

Firstly, effector T lymphocytes can lose the ability

to recognize tumor cells due to low expression, and presentation or to mutation of the tumor antigens. In particular, tumor cells can lose the expression of one or several types of molecules of the main histocompatibility complex (MHC) class I (for example, HLA-A), required for the recognition of tumor antigens by cytotoxic CD8⁺ T lymphocytes. Furthermore, tumor cells may not express the molecules CD80 and CD86 (B7-1 and B7-2), recognized by co-receptor CD28 on the surface of CD8⁺ T lymphocytes. Without a signal from the co-

Methods of immunotherapy of malignant neoplasms

Immunotherapy	Active	Passive
Non-specific	Use of: cytokines; bacterial products; synthetic polymers; thymus hormones	Adoptive T cell therapy Use of heat-shock proteins
Specific	Use of vaccines: tumor-associated or viral antigens	Injection of monoclonal antibodies

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receptor during the presentation of tumor antigen CD8⁺ to the T lymphocytes they do not activate, but, by contrast, they lose their ability to perceive and react to any signal from the outside (anergy) [7, 8].

Secondly, tumor cells can produce different immunosuppression factors and cytokines, suppressing the immune response of the body: transforming growth factor β (TGF- β), interleukin-10 (IL-10), vascular endothelium growth factor (VEGF), interferon gamma (IFN- γ), prostaglandin E2 and others. The immunosuppressive effect of these factors is mainly aimed at the suppression of activation and differentiation of effector T lymphocytes, inhibiting maturation and the functions of antigen-presenting cells and reducing the expression of MHC molecules [9].

Thirdly, tumor cells may be more resistant to apoptosis due to over-expression of anti-apoptotic molecules or the suppression and mutation of pro-apoptotic factors. In particular, the following have been found: the phenomenon of weak expression, inactivation or mutation of cell death receptors such as CD95, TRAIL-R1 and TRAIL-R2, as well as the product of Apaf-1 gene initiating apoptosis, together with increased production of anti-apoptotic protein FLIP_{L,S} and factor Bcl-2 [10, 11].

It should be noted that in the tumor microenvironment there is an accumulation of cells having an immunosuppressive effect such as regulatory T lymphocytes and myeloid-dependent suppression cells (MDSCs), which produce further factors capable of suppressing the activation, proliferation and functions of effector T lymphocytes [12–14]. In particular, regulatory T lymphocytes can show a direct immunosuppressive effect by producing IL-10, TGF- β and adenosine. Accumulation of the latter in the extracellular environment suppresses the cytotoxic functions of CD8⁺ T lymphocytes. Moreover, regulatory T lymphocytes express a number of factors including Foxp3, CTLA-4, PD1, which inhibit the effect of effector T lymphocytes [12, 13]. The immunosuppressive effect of MDSCs is mediated by the formation of active forms of oxygen, the activation of arginase-1, and by the production of nitric oxide as well as stimulation of the regulatory T lymphocytes [14].

And finally, in the tumor microenvironment there is production of immunosuppressive metabolites such as tryptophan, adenosine, L-arginine or lactate [15, 16].

Thus, tumor cells have different mechanisms of protection from the actions of the immune system and to achieve an effective therapy against cancer it is necessary to overcome these mechanisms.

Active non-specific immunotherapy

This type of immunotherapy is based on the stimulation of a non-specific tumor response by antigen agents, which can be cytokines, some bacterial products, synthetic molecules and hormones.

The most frequently used agents are cytokines. They represent a group of proteins and peptides produced

by the cells of the immune system, and by other types of cells, and that take part in regulation of the growth, differentiation and life time of cells and in non-specific protection defenses in the body [17].

Cytokines such as TNF- α (tumor necrosis factor), GM-CSF (granulocyte-macrophage colony stimulating factor), IFN- α (interferon alpha), as well as some interleukins including IL-2, IL-7, IL-12, IL-15, IL-21 can act as agents for active non-specific immunotherapy [2, 18].

The effect of cytokines on the cells of the immune system can be mediated by different mechanisms, including the stimulation of proliferation, differentiation, the activation and tracking of effector CD4⁺ and CD8⁺ T lymphocytes and natural killers; the stimulation of proliferation and differentiation of progenitor cells of the hematopoietic system, which causes the formation of granulocytes, monocytes/macrophages and T lymphocytes; and the stimulation of synthesis by the immune system cells of IFN- γ and immunoglobulins. Furthermore, cytokines can contribute to malnutrition and vascularization of the tumor, to increase immunogenicity of the tumor cells and to reduce immunosuppression of the tumor [1, 17].

Successful preclinical *in vitro* and *in vivo* studies on animal tumor models of such cytokines as TNF- α , IFN- γ , GM-CSF, IL-4, IL-12, IL-15, IL-21, showed their ability to induce anti-tumor immune responses to different types of cancer [1, 2, 19].

Clinical studies have used cytokines for patients with different types of tumor. In particular, GM-CSF, IL-2, IFN- α -2b and IL-12 were tested on metastatic melanoma [20–23], IFN- α and GM-CSF — on myeloid leukemia [24, 25], and IFN- α -2b, IL-2 and IL-12 — on kidney cancer [22, 23, 26]. On the whole, the use of cytokines in anti-tumor immunotherapy demonstrated tumor regression, the prevention of metastasis formation, the development of immunological memory as well as a reduced risk of disease recurrence together with increased survival. However further clinical trials of some cytokines such as TNF- α , GM-CSF, IL-12, were strictly limited due to serious side-effects [25–27]. Nevertheless, therapy with cytokines (IL-2, GM-CSF, IFN- α) is being actively developed, including in the context of their combined treatment with chemotherapy or other approaches to immunotherapy [28–31].

The use of some cytokines has already been approved and they are being used successfully in clinical practice. So, the first cytokine, used for treating patients with leukemia and melanoma, was IFN- α [28, 32], and the second, for treating melanoma, was — IL-2 [31, 33].

Additionally, to enhance the immune response to a tumor, agents based on bacterial products can be used. Generally their action is aimed at the induction of an inflammatory reaction in the tumor microenvironment, and the activation of macrophages and normal killers.

Clinical studies are being performed on the local injection of BCG vaccines (tuberculosis vaccine containing nonpathogenic Calmette–Guerin bacillus) and *Corynebacterium parvum* (pseudo-diphtheroid bacteria). Their injection into the lesion creates a

local inflammatory reaction and, in combination with anti-tumor vaccines, contributes to tumor (in particular melanoma) regression [34, 35]. Although the use of these antigens has not shown such a high effectiveness as monotherapy, it is being successfully used in adjuvant therapy. Thus, in Russia, Imuron has been developed, based on BCG, and it is used as an immunomodulator for the prevention of recurrence of superficial bladder cancers as well as for the treatment of cancers *in situ* and for superficial bladder tumors [36]. Another agent typical of this type of immunotherapy is muramyl dipeptide (an active fragment of the cell wall of bacteria, responsible for an immune-stimulating effect), used in the case of treatment of lesions of the cervix caused by the human papillomavirus [37, 38].

Also different synthetic polymers, nucleotides and polynucleotides such as DEMA (divinyl ether-maleic anhydride), polyinosinic and polycytidylic acids, pyrimidines, and pyran copolymer can be used as agents for non-specific immunotherapy. Their action is targeted at the formation and secretion of interferons [39, 40].

And finally medication with the thymus hormones — thymosin, timalin and thymopoietin, affecting the T lymphocytes, are being used for the treatment of cancer [41–43].

Active specific immunotherapy

This type of immunotherapy is based on the use of specific antigenic preparations — vaccines. Such vaccines contain tumor-associated or viral antigens as a result of which induction of an immune response against the tumor is possible in the body. The action of these vaccines is aimed at increasing the efficiency of presentation of these antigens for effector T lymphocytes by the antigen-presenting cells, at the formation of specific effector T lymphocytes directed against these antigens, the development of immunological memory, and, in case of viral antigens, at the prevention of a full-blown infection [44–46].

Currently, prophylactic vaccines aimed at the prevention of the disease or its recurrence [47], and therapeutic vaccines aimed at fighting existing tumors in the patient's body [48] are being developed.

On the one hand, antigens from different viruses causing the occurrence of cancer can form the basis for the development of vaccines, especially prophylactic ones. Thus, the targets for preventive anti-tumor vaccination are HPV (human papilloma virus) causing cancer of the cervical cancer [49, 50], hepatitis B and C viruses capable of triggering liver cancer [51, 52], Epstein–Barr viruses) HTLV-1 (human T-cell leukemia virus) and HHV-8 (human herpesvirus type 8), connected with different kinds of lymphomas [53–55]. These vaccines can be used as therapeutic agents for the activation of an effective specific immunological response, resulting in the ability of effector T lymphocytes to destroy the cells carrying such viruses.

On the other hand, to obtain vaccines, tumor-

associated antigens can be used, and today this approach to cancer immunotherapy is the most developed [56, 57]. An example of a preventive vaccine of this type is a vaccine based on peptide E75 obtained from the protein HER2/neu, whose increased expression is typical of breast cancer. Clinical tests have shown the effectiveness of this vaccine, including when combined with GM-CSF, in the prevention of recurrent disease in patients with a high risk of this type of cancer [58, 59].

Therapeutic vaccines based on tumor-associated antigens contain either these particular antigens in the form of peptides of the proteins, or dendritic cells (DCs) loaded with tumor-associated antigens, or autologous or allogenic tumor cells carrying the complete set of tumor-associated antigens or a mixture of DCs and tumor cells [44, 45, 48].

Today, preclinical studies of different antiviral and antitumor vaccines are being undertaken. Thus, in preclinical studies, *in vivo* on mice with colorectal cancer, the effectiveness of a therapeutic vaccine against oncolytic measles virus has been shown [60]. A study of a synthetic vaccine against HPV has been performed on mice with cancer of the cervical cancer [61]. In work on mice with cancer of the prostate RM-1 *in vivo* a vaccine based on tumor-associated antigens modified by GM-CSF or TNF- α has been successfully tested [62, 63]. These encouraging results provide the prerequisites for further clinical studies.

Clinical studies of therapeutic vaccines with the use of tumor-associated antigens have shown mainly positive results. In phases I and II clinical trials involving patients with metastatic melanoma, vaccines based on peptides recognized by CD8⁺ T lymphocytes have been used [64, 65], and a vaccine based on gp100 peptide in combination with IL-2 contributed to enhanced survival, and this has given grounds for further developments [64], while vaccination based on tyrosinase-based peptides in combination with GM-CSF have shown limited clinical and immunological activity in patients with stage IV melanoma [65]. Furthermore, it has been found that vaccines based on DCs can cause complete and partial regression of neoplasms [66, 67].

Positive effects have been noted in patients with lung cancer when therapeutic vaccine containing epidermal growth factor (EGF) with added bacterial adjuvant was used, so this suggests the potential for future successful studies [68]. Therapeutic vaccines have been successfully tested in colorectal cancer (vaccines based on DCs and on tumor cells), kidney cancer and brain cancer (vaccines based on DCs and vaccines based on DCs and tumor cells), as well as in lymphoma, prostate cancer and bladder cancer (vaccines based on DCs) [69].

Preventive vaccines are being used in clinical practice against HPV and the hepatitis B virus [69]. Moreover, the therapeutic vaccine Sipuleucel-T (Provenge) based on DCs has been approved by the Food and Drug Administration (FDA, USA) for patients with metastatic prostate cancer [70].

Passive non-specific immunotherapy

The main method of passive non-specific immunotherapy is adoptive T cell therapy (ACT) based on the activation of effector cells outside the body and their subsequent injection into the patient [71, 72].

Agents for ACT include: lymphokine-activated CD8⁺ T lymphocytes (lymphokine-activated killer, LAK), obtained from peripheral mononuclear blood cells after cultivation *in vitro* in the presence of IL-2; CD8⁺ T lymphocytes obtained from peripheral mononuclear blood cells *in vitro* with the assistance of several factors including IL-2, IL-1, IFN- γ and anti-CD3 monoclonal antibodies (cytokine-induced killer, CIK); CIK, cultivated in the presence of DC (DC-CIK); and tumor-infiltrating lymphocytes (tumor-infiltrating lymphocyte, TIL), obtained from patients with tumors [2, 71].

Preclinical studies in this field started quite a long time ago. The effectiveness of ACT has been shown in preclinical studies *in vitro* on a number of lines of tumor cells such as cancer of colon, pancreas, adrenal glands, kidney, and esophagus (LAK) [73]; hepatocellular carcinoma (CIK) [74]; myeloma, chronic myelogenous leukemia and osteosarcoma (DC-CIK) [75–77].

In vivo LAK obtained from a human were injected into immunodeficient SCID mice with human colorectal cancer, and the effect of these cells contributed to the inhibition of tumor growth [78]. Other preclinical studies *in vivo* have shown effectiveness of LAK action against human lung cancer and head and neck cancer [79, 80], CIK — against hepatocellular carcinoma and B-cellular lymphoma [74, 81, 82], DC-CIK — against human lung cancer [83], and TIL — against metastases in the liver and lungs in mice [84].

The preclinical data that has been obtained suggests that ACT could be effective in treating patients. However, despite successful studies *in vitro* and *in vivo*, phase II and III clinical trials on the use of LAK undertaken on patients with different types of cancer (colorectal cancer, breast cancer, carcinoma of the lungs, ovary, pancreas and kidney) showed only a low effectiveness of LAK in such treatments [85–87]. Phase II and III clinical trials using CIK on patients with metastatic carcinoma of the kidneys and adenocarcinoma of the pancreas have shown their greater effectiveness compared to LAK, but this is not sufficient for tumor treatment [88, 89]. Clinical studies of DC-CIK in lung cancer, metastatic breast cancer, and leukemia have shown an increased survival rate and their significant effectiveness in combination with chemotherapy [90–92], indicating that DC-CIK is a promising method for treating cancer.

The first clinical studies of TIL for patients with metastatic melanoma were published in 1988 [93]. Today successful tests of TIL have been performed, including TIL in combination with IL-2, on patients with metastatic melanoma and lung cancer [94, 95]. It is supposed that ACT with TIL might be effective in respect of such patients and those with other tumors [2].

Besides ACT, the use of some other agents can also be referred to as passive non-specific immunotherapy.

Thus, for example, clinical trials of heat-shock protein are being performed for the treatment of metastatic melanoma and brain tumors [96–97]. Furthermore there is an anti-tumor drug Iscador, based on mistletoe lectins, that supports inflammatory processes in tumor tissue via immunomodulation and stimulation [98].

Passive specific immunotherapy

This type of therapy is based on the use of monoclonal antibodies (mAb) activated with tumor antigens [99, 100].

MABs belong to an individual cell clone developed by the cells of the immune system against a particular antigen, and bind to it specifically.

The injection of mAbs inhibits the effects of the receptors that take part in tumor progression. Inhibition of the following receptors can lead to a positive effect in the fight with cancer: EGFR — epidermal growth factor receptor, an important regulator of cellular proliferation and malignant transformation; VEGF-A — a receptor for vascular endothelium growth factor stimulating the proliferation of endothelial cells and enhancing the permeability of vessels; IL-2Ra (CD25) — expressed by regulatory T lymphocytes; PD-1 (programmed cell death-1) — a receptor playing a role in the proliferation and differentiation of immune cells; CTLA-4 — receptors on the surface of effector T lymphocytes that “turn on” their cytotoxic function; HER-2 — receptors for human epidermal growth factor playing an important role in the pathogenesis and progression of breast cancer; and CD20 — a co-receptor on the surface of B lymphocytes with a high level of expression in the case of non-Hodgkin’s lymphoma [99, 101].

It has been shown that immunotherapy with the use of mAbs targeted at the inhibition of receptors causes a reduced proliferation of tumor cells and their death, together with reduced tumor vascularization and permeability of the vessels. Furthermore this therapy contributes to overcoming immunological surveillance and leads to restoration of the anti-tumor effect of effector CD8⁺ T lymphocytes [100, 101].

In phases I, II and III clinical trials the effectiveness of using mAbs has been demonstrated on melanoma (anti-CTLA-4 and anti-PD-1 mAbs) [102–104], non-small-cell lung cancer (anti-CTLA-4, anti-PD-1 and anti-VEGF-A mAbs) [102, 105–107], colorectal cancer (anti-VEGF-A, anti-EGFR and anti-PD-1 mAbs) [107–109], renal cell carcinoma (anti-VEGF-A and anti-PD-1 mAbs) [102, 103, 110], squamous cell carcinoma of the head and neck, prostate cancer and ovarian cancer (anti-CTLA-4 mAbs) [111–113] and metastatic breast cancer (anti-HER-2 and anti-CD25 mAbs) [114–115].

To date, FDA (USA) has approved Cetuximab based on anti-EGFR mAb for treating patients with colorectal cancer [116] and head and neck cancer [117], and Bevacizumab based on anti-VEGF-A mAb for the treatment of colorectal cancer, non-small cell lung cancer, glioblastoma, renal cell carcinoma, and breast cancer as well as in combination with chemotherapy

for treating cancer of the cervical cancer, epithelial ovarian, fallopian tube and primary peritoneal cancer [118, 119]. For the patients with breast cancer Trastuzumab (Herceptin) based on anti-HER-2 mAb [120] has been approved, and for the treatment of melanoma — Ipilimumab, based on anti-CTLA-4 mAb [121]. Moreover, Rituximab (Rituxan) based on anti-CD20 mAb has been approved for treating patients with B-cell non-Hodgkin's lymphoma and for chronic lymphocytic leukemia [122].

In general the use of monoclonal antibodies indicates increased survival rates, reduced risk of recurrent disease, extensive tumor necrosis with leukocyte infiltration and tumor cell death from apoptosis.

Conclusion

Immunotherapy is a promising method for the treatment of malignant neoplasms. For its further development and enhancement of its effectiveness it is important to understand the mechanisms of action of each type of immunotherapeutic agent as well as the ways that tumors evade the surveillance of the immune system. Active immunotherapy includes the use of cytokines, some bacterial products, synthetic molecules and thymus hormones, anti-viral and anti-tumor vaccines. Passive immunotherapy is based on adaptive immunotherapy and the use of monoclonal antibodies. Combinations of the methods of activation of specific and non-specific immunity can be considered to be a promising direction in the development of tumor immunotherapy. This approach helps not only effectively to destroy tumor cells in the body, including metastases, but can also considerably reduce the risk of recurrence of the disease, as a result of the development of immunological memory.

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