Colorectal Cancer Immunotherapy: Current State and Prospects (Review)

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Currently, new knowledge on immunotherapy in solid tumors is being intensively accumulated and new promising techniques are originating. The most advanced are those in the field of searching for new immune checkpoints, development of highly efficient immune adjuvants based on recombinant viruses to improve the effect of anticancer vaccines, as well as design engineering of chimeric receptors of T cells used for adoptive immunotherapy. We have presented some clinical trial results of immunotherapeutic approaches, as well as experimental studies on animal models, which offer new prospects for colon cancer treatment.

Key words: colorectal cancer; immunotherapy; monoclonal antibodies; adoptive cellular therapy; anticancer vaccine; cytokines.

For the first time the existence of immune surveillance in malignant tumor growth was suggested by Paul Ehrlich in 1909. However, a fundamental theory postulating that all cells undergoing neoplastic alterations are recognized by the immune system and destroyed by cytotoxic T lymphocytes was created in the middle of the twentieth century by Burnet and Thomas [1, 2]. Despite the inconsistency of the postulates, which were promoted by the authors, experimental evidences were obtained long after. The experiments on nude mice with induced oncogenesis revealed no significant increase in tumor incidence compared to immunologically of normal mice [3]. The lack of accomplishment of the first experiments could be due to the fact that athymic nude mice are still not deprived of T cells, as it was demonstrated soon after [4, 5].

It was not until the beginning of the twenty-first century that the concept of immune surveillance in malignant tumor growth was proved experimentally by Shankaran [6]. The research was performed on mice with complete loss of lymphocytes due to mutation switching off a recombination activating gene 2 (*RAG2*) necessary for their differentiation. It was the model that was used to demonstrate for the first time a significant increase in tumor incidence in chemically induced carcinogenesis. The following research intensification in the area of cancer immunotherapy proved the phenomenon of tumor immune editing which means that at early stages of tumor growth, due to the elimination of highly immunogenic clones, predominant accumulation of low immunogenic and even immunosuppressive clones occurs. The tumor ability to avoid the effect of immune system factors is implemented through a number of mechanisms, among them, for example: low expression, or shedding of tumor antigens, molecules of major histocompatibility complex (MHC), co-receptors, induction of $CD4^+CD25^+FoxP3^+$ regulatory T lymphocytes ($CD8^+$ and $CD4^+$) suppressing effector lymphocytes, the production of immunosuppressive mediators and autocrine growth factors by the cells of a tumor and of its microenvironment, dysmaturation of dendritic cells (DC), etc. Thus, by the moment of tumor clinical manifestation, natural antitumor mechanisms, as a rule, appear to be suppressed [7].

According to a current concept, immunotherapy is a complex of therapeutic measures aimed at the abolishment of blockade, and the enhancement of antitumor response using the factors of innate and adaptive immunity. The present review contains the term "immunotherapy" in this interpretation.

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Currently, the colon cancer treatment is based on surgical resection of a tumor combined with adjuvant chemotherapy [8, 9]. The protocol of rectal cancer treatment also includes pre- and postoperative radiotherapy [8]. Despite the fact that the use of target agents blocking epidermal growth factor receptor (EGFR) and vascular endothelial growth factor receptor combined with cytostatic drugs is able to provide some contribution to the enhancement of survival indices for some forms of metastatic colorectal cancer, this type of treatment for colon cancer has not spread widely yet [10–13], therefore the search for new immunotherapeutic agents for colorectal cancer is still relevant.

The present review presents the current clinical trial results of immunotherapeutic approaches, as well as experimental studies on animal models opening new prospects in colon cancer treatment.

Monoclonal antibodies in of colon cancer immunotherapy

In the absence of *Ras* gene mutations it is recommended to treat metastatic colon cancer with EGFR-based therapies (cetuximab, panitumumab) [9]. Modern literature describes in detail the principles of their antitumor action [14], it is important to highlight the ability of cetuximab, in addition to direct EGFR inhibition, to induce congenital mechanisms of antibody-dependent cellular cytotoxicity by interacting with FcγRIII (CD16) receptors of natural killers (NK), enhancing their tropism to tumor cells with membrane EGFR [15]. Clinical significance was confirmed by potentiation of the effect when cetuximab was administered along with CD137 agonist — NK co-stimulatory molecule increasing their proliferation [16]. Moreover, even the efficacy of cetuximab in colorectal cancer can depend on a patient's allelic variant *FcγRIIIa* [17, 18].

In cetuximab, an immunomodulatory effect appeared to be unintended; however, it is likely to induce partially its antitumor effect. The attempts to use targeted monoclonal antibodies for attraction of cytotoxic cells to colon tumor tissue are still rare. The application of mouse monoclonal antibodies anti-EpCAM (edrecolomab), despite most promising results of preliminary clinical trials on patients with colorectal carcinoma [19], phase III of clinical research study did not show significant advantage compared to conventional chemotherapy [20].

There is a relatively new concept that can be referred to immunotherapy, which is based on the same principle of molecular recognition antigen–antibody, i.e., engineering design of chimeric proteins, which have double or multiple specificity for both cancer antigens, and membrane receptors of immune cells. The obtained constructions are vastly superior to monospecific antibodies in efficacy, and have already demonstrated encouraging results in experiments on cell lines and animal models of colorectal carcinoma. Hence, the application of bispecific antibodies

of anti-CD3/anti-Her2 resulted in the stimulation of CD8+ lymphocyte cytotoxicity to tumor cells *in vitro* compared to an antibody anti-Her2 (Herceptin), and inhibited the growth of human colon adenocarcinoma xenograft [21]. Attraction of NK into tumor by means of binding of bispecific antibody to antigens CD16 and CD133 typical for stem cells of colorectal carcinoma Caco-2 promoted *in vitro* cytotoxicity enhancement [22]. The promoting of nonspecific response in colorectal carcinoma tissue was achieved also using the interaction of NKG2D receptor expressed on the surface of NK and some T cells and its ligands. Typically, NKG2D are expressed only on the surface of senescent or malignized cells providing their elimination by the immune system [23]. However, due to the immunoediting, the expression of NKG2D ligands in a tumor is often suppressed [24]. Therefore, the recovery of the interaction so important for tumor elimination by introducing NKG2D ligand associated with the antibody against tumor antigen can be a promising therapeutic method. The efficacy of the technique was demonstrated in a xenograft model of colorectal cancer using a chimeric protein consisting of ULBP2 — NKG2D ligand — and an antibody against a carcinoembryonic antigen (CEA) [25]. No clinical trials of chimeric immunoligands in colorectal cancer have been carried out yet.

High efficiency in the treatment of a number of oncologic diseases was shown by a new group of immunotherapeutics based on antibodies, which target key molecular pathways controlling immune response: the so called immune checkpoints (ICP) [26]. The most extensively studied now are ICP associated with the expression of cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) on a membrane of cytotoxic T lymphocytes, and a programmed cell death receptor 1 (PD-1). Protein CTLA-4 is produced in T lymphocytes after their activation, and serves as a natural inhibitor of a cytotoxic response under normal conditions aimed to restrict autoimmune responses [27]. PD-1 receptor is also expressed on the membrane of activated T lymphocytes, and by interacting with its ligand (PD-L1) causes their apoptosis [28]. PD-L1 molecule is expressed on the surface of various cells, and often its concentration in tumor tissue is increased; that is considered to be one of the main mechanisms to escape an immune response [29].

First significant breakthroughs in administration of the agents based on antibodies to CTLA-4 (ipilimumab) and PD-1 (nivolumab), as well as to PD-L1 in patients with melanoma and non-small cell lung carcinoma [30–33] have inspired numerous studies on the efficacy of antibody and ICP therapy in other types of oncopathologies including colorectal cancer. Though the role of ICP described is considered universal, characteristics of a solid tumor can have an effect on immunotherapy by such antibodies agents. In particular, in literature there is contradictory information on ICP effect in colorectal cancer. On the one hand, according to the information on an increased underlying risk for

colon cancer in patients carrying single nucleotide polymorphisms in PD-1 gene, one might assume that the interaction between PD-1 and PD-L1 participates in colorectal carcinoma growth [34, 35]. Moreover, immune histochemical study showed an increased level of PD-L1 expression in colorectal carcinoma tissues to be associated with the absence of tumor-infiltrating lymphocytes, which correlates with the poorest survival prognosis [36]. Nevertheless, the first studies on the efficiency of antibodies blocking PD-1 and PD-L1 interaction did not demonstrate a significant therapeutic effect in patients with colorectal cancer [30, 32]. Later, it was suggested that a positive response on PD-1 and PD-L1 blockade interaction can be expected only in tumors with microsatellite instability [37] that was confirmed by the following work by Le et al. [38].

The study found the relation of single nucleotide polymorphisms with the predisposition to colon cancer for *CTLA-4* gene like for PD-1 [34]. However, the first study of human anti-CTLA-4 monoclonal antibody (tremelimubab) in patents with chemotherapy-resistant types of colon cancer did not yield positive results [39].

Further studies required to determine what treatment regimens switching CTLA-4 and PD-1/PD-L1 blocking would be the most effective in colorectal cancer, and identify new ICP, inhibition or stimulation of which would result in the induction of tumor-specific immune response in each kind of oncopathology. T cell immunoglobulin- and mucin-domain-containing molecule-3 (Tim-3) can be held up as an example of a potential candidate for the blockade. It takes part in the suppression of type 1 T helper and CD8^{+} lymphocytes function, its concentration was found to be increased both in blood and tumor tissue of patients with colorectal carcinoma [40]. Besides, it can be effective to use the blockers of lymphocyte activating gene 3 (*LAG-3*) involved in a negative control of proliferation of a variety of immunocompetent cells, and demonstrating high expression in colorectal carcinoma tissue [41].

In addition to immunosuppressive ICP blocking, the stimulation of activated T lymphocytes by agonistic antibodies of OX40 receptor promoting their survival can appear to be promising, since there was described a direct relationship of its expression in tumor tissue with a more favorable prognosis in patients with colorectal cancer [42]. Despite the fact that modern therapy of malignancies using ICP blockers and agonists is at the beginning of its development, there is no doubt about the prospects and great potential of the development and implementation of new promising therapeutic decisions for colon cancer.

Anti-tumor vaccines as a tool for colon cancer immunotherapy

The ultimate objective of vaccination is to induce an effective immune response on tumor providing a long-term control over tumor growth and dissemination.

Currently, there can be distinguished four main vaccination strategies against cancer: 1) application of tumor cell preparations, 2) administration of isolated peptide antigens, 3) use of viral/bacterial vectors, and 4) vaccination using DC. To create a vaccine based on tumor cell preparations implies lysis or radiation of a tumor sample with its following administration to a patient. To enhance immunogenicity of whole cell vaccines, preliminary contamination of tumor cells before radiation is possible including that by recombinant viral vectors expressing co-stimulating molecules, or the combined administration of inactivated tumor material with infectious agents, which could play a role of an immune adjuvant [43]. The strategy was used in a randomized clinical study stage III performed in 50 metastatic colorectal cancer patients to assess the efficiency of vaccination by tumor cells infected by NDV (Newcastle disease virus). In addition, a significant increase in total and recurrence-free survival for patients with colon cancer was found [44].

One of the disadvantages of tumor cell-based vaccines is their low immunogenicity against proper cancer antigens, since tumor tissue contains only a small number of antigens associated with malignant growth, which are significantly exceeded by antigens' amounts and variety expressed in the normal cells.

Increased induction of specific immunity against tumor antigens can be achieved by using a certain peptide or peptide mixture as an agent for vaccination, because the relation between the peptides and malignized tissue was found. Tumor specific antigens were studied for colorectal cancer immunotherapy. According to various researches, the expression of the antigens is increased in colorectal carcinoma tissue, and associated with the poorest prognosis. The increased expression of such antigens as CEA [45], mucin 1 (MUC1) [46], β-human chorionic gonadotrophin (β-HCG) [47], survivin-2B [48], A2-type ephrin receptor (EphA2) [49], squamous cell carcinoma antigen (SART3) [50] was found in the nucleus and cytosol of adenocarcinoma cells. Positive results of clinical trials were shown after application of vaccine based on β-HCG, which caused the formation of specific antibodies in 56 of 77 patients, and resulted in total survival growth [51]. The vaccine against MUC1 demonstrated a preventive effect on transplantable tumor model [52] that inspired to search the ways of its application to prevent colorectal cancer growth. The first researches in the field have already shown encouraging results in clinical trials in patients with pre-malignancies in colon inducing a marked humoral response in 43.6% of them [53].

Despite the immunogenicity of peptide vaccines is higher than of whole cell ones, it is still rather low. The possibility of its increase depends on the use of adjuvants, such as Freund adjuvant, nanoparticles of different origin, alum, and other agents enhancing peptide delivery to DC and/or stimulating pre-immune inflammation in tissues. The development of molecular

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engineering techniques has contributed to the rise of a new high-efficient strategy of combining vaccine with an immune adjuvant — tumor antigen built in a non-replicating infectious vector. Assuming that a viral particle is a strong immunostimulant agent by itself, the molecules enhancing immunocyte response can be additionally built in it. One of the first studies was carried out on colorectal cancer using ALVAC-CEA/B7.1 vaccine created on the basis of a non-replicating virus: canarypox expressing CEA along with antigen B7.1 responding to the lymphocyte stimulation [54, 55]. Vaccination combined with chemotherapy was found to cause 2.4-fold amount increase of CEA-specific T cells in 31% patients, an objective clinical response being observed in 40%. CEA/TRICOM vaccine presents a recombinant viral vector expressing CEA, as well as three co-stimulating molecules: B7.1, intercellular cell adhesion molecule-1 (ICAM-1) and lymphocyte function-associated antigen-3 (LFA-3). It showed high efficiency in mouse colon cancer model and the possibility to be administered safely in patients with metastatic colorectal cancer [56, 57].

Alternatively to the attempt to add co-stimulating signals to cell or peptide vaccines, some researchers turned directly to key elements responsible for the formation of adaptive cell immunity, i.e. to dendritic cells. The process for making dendritic cellular vaccines includes the isolation of DC from patient's blood, the induction of their maturation *ex vivo* and sensibilization either by tumor cell lysate, or by synthetic tumor-specific peptides, recombinant vectors, tumor DNA or RNA. Dendritic cell vaccine loaded with antigens of tumor lysate was shown to be able to cause a marked T cell tumor-specific response in patients with metastatic colorectal cancer [58–60].

In addition to autologous tumor preparations, allogenic lysates are also used in colon cancer treatment using dendritic cell vaccines [61, 62]. Since an increased CEA expression is frequently observed in colorectal cancer, dendritic cell vaccines against this tumor are made using CEA peptide, or the CEA-expressing vectors [63, 64]. The most patients of the referent clinical trials demonstrated a marked CEA-specific T cell response, and some patients also demonstrated tumor growth stabilization.

Thus, it may be concluded that the administration of anticancer vaccines to patients with colorectal carcinoma, as a rule, induces marked immune response to a certain antigen, and in some cases it also results in the improvement of survival indices; the examples are given in the review. However, ambitious meta-studies of the efficiency of vaccines of different origin in colorectal cancer treatment showed that an induced immune response is rarely accompanied by the survival indices improvement [65, 66]. Therapeutic vaccines are likely to be more effective as a part of a combined immunotherapy aimed at both immune response stimulation, and elimination of immunosuppressive tumor effect.

Application of cytokines in colon cancer immunotherapy

Cytokines are biologically active substances, which are the products of immunocompetent cells with auto- and paracrine regulatory mechanisms of their activity through specific receptors. All the variety of cytokines is conditionally divided into three main groups: growth (colony-stimulating) factors controlling the production of immunocompetent cells; pro-inflammatory providing mobilization and activation of cells — participants of inflammation, and anti-inflammatory with opposite effects: limiting inflammation development, regulating cellular and humoral immunity. Cytokines also regulate the processes of angiogenesis, regeneration, proliferation, apoptosis, metabolism, etc. [67]. The main cells producing pro-inflammatory cytokines are activated monocytes, macrophages, DC, NK, T lymphocytes; anti-inflammatory — T cells, primarily $CD3^+CD4^+CD8^-$ (Th1 and Th2). However, cytokines can be produced not only by immunocompetent cells, but also by the cells of a tumor and its microenvironment [68]. Potential high efficiency of therapeutics based on cytokines enables to consider it as a promising field of research in colon cancer immunotherapy.

A significant work was carried out in Rostov Research Institute of Oncology to study the cytokines' ratio of a tumor and non-malignized colon tissue. The tissue content of such cytokines as IL-6, IL-8, IL-1α and others in colorectal malignant tumor was found to be significantly higher than in the peritumoral area and in the resection margin, as well as in tissue of benign tumor (adenoma) [69, 70]. Tissue cytokine status in primary multiple colorectal cancer, in particular, in metachronic tumors, has some variations from single tumors; differences in the content of some cytokines (TNF-α, IL-1α) in metachronous and synchronous tumors also involve peritumoral area and a resection margin. The differences found indicate a key role of tissue immune and inflammatory responses in colon cancer pathogenesis.

The data on experimental studies of cytokine application as a part of a combined therapy for colorectal carcinoma seemed to be inspiring [71–74]; however, clinical trials have shown contradictory results. Initially high expectations in colon cancer treatment were related to the use of interferons, since they have a direct and indirect (mediated via immunocompetent cells) anti-tumor effect: suppression of tumor cell proliferation, induction of their apoptosis, increased of MHC class I molecules expression, stimulation of NK and cytotoxic cells, anti-angiogenic effect [75]. However, long-term clinical trials of interferon therapy capabilities of this oncopathology showed ambiguous results. On the one hand, there has been demonstrated the efficacy of adding IFN-α chemotherapy on colorectal carcinoma cell lines [73, 74]; furthermore, there are evidences in favor of the fact that polymorphism in

interferon signal pathway genes is associated with high susceptibility to colon cancer [76, 77]. However, clinical trials of combining IFN-α with 5-fluorouracil [78], with 5-fluorouracil and levamisole [79], as well as the combinations with 5-fluorouracil IFN-β [80] and IFN-γ [81] yielded no favorable results, and showed the toxicity of such combined treatment.

The studies on using IL-2 as a part of a combined therapy in colorectal cancer appeared to be more successful. It causes apoptosis of tumor cells, stimulation of T, B and NK lymphocytes and also is able to produce anti-angiogenic effect [75]. The results of recent clinical trials have shown that granulocyte macrophage colony-stimulating factor (GM-CSF) and IL-2 (GOLFIG mode) supplemented to conventional chemotherapy results in an increase of total and progressive-free survival in colon cancer patients [82, 83]. Moreover, the experience of Russian researchers has shown that recombinant IL-2 (Roncoleukin) included in a complex therapy of advanced colorectal cancer enables to reach a positive effect in 77.2% patients when combined with conventional chemotherapy, as well as results in growth delay of liver metastases and the decrease of their size when the it is combined with regional arterial chemoembolization [84–86].

Generally, the activity of cytokines *in vivo* is confined by a small area, and has a short period of time; however, their therapeutic application is related to a continuous administration of high doses that can cause adverse reactions due to systemic inflammation [87]. To avoid side effects of the drug and to enhance its efficiency, strategy of local delivery of cytokines into tumor was developed by inserting the genes encoding synthesis of cytokines in recombinant vectors of viral particles or agents of non-viral nature. The first advances were demonstrated in preclinical trials on animal models. The administration of a modified NDV expressing IL-2 resulted in tumor growth inhibition up to total regression in most tumor-bearing mice with a grafted CT26 [88]. The same model was used to demonstrate the more effective (compared to a non-modified virus) reduction of liver metastases when animals are infected with herpes simplex virus of type 1 (HSV-1) expressing IL-2 or GM-CSF [89], as well as the enhancement of an anti-tumor immune response in the administration of vesicular stomatitis virus expressing IL-15 [90]. However, it is unknown if there are successful clinical trials on targeted delivery of anticancer cytokines in colorectal carcinoma.

Since many interleukins were found to have both immunomodulatory properties, and growth stimulating activity [91], the presence in adenoma and colorectal carcinoma tissue of IL-6, IL-17A, IL-22, TNF-α and a number of other cytokines, as well as growth factors is considered to provide such key features of tumor cells as apoptosis resistance, abnormal growth and proliferation, genetic instability induction, development of blood vessels, invasion and metastasis [92–95].

Thus, the presence of numerous pro-oncogenic cytokines in colorectal carcinoma tissue implies that both cytokine and anti-cytokine therapy can be suggested to gain more success in tumor treatment. First advances were achieved on experimental models. So, IL-6/STAT3 signal way blocking resulted in a significant decrease of tumor incidence on a murine model associated with chronic colitis oncogenesis [96]. Another trial on a similar model of induced oncogenesis showed the blocking of granulocyte colony stimulating factor (G-CSF) activating growth and migration in colorectal carcinoma culture cells that resulted in reduced incidence of tumor and immune response enhancement [97]. The results of our research [98] showed a positive clinical effect and immune status dynamics when a combined treatment of patients with colorectal cancer included the combinations of Mexidol and Galavit inhibiting an increased synthesis of TNF-α, IL-1, IL-6 and other pro-inflammatory cytokines.

A great obstacle on the way of a combined therapy using cytokines and immunotherapy in general, is the effect of chemotherapeutics on immune system activity, which is unclear to a full degree so far. Some of them are able to impair such parameters as number and composition of released tumor antigens and to trigger various transformations of tumor microenvironment, which will influence the immune system behavior producing either stimulation or inactivation of cytokines' effect [99]. Further study development on the interaction of cytokine net with colon tumor tissues and the effect of conventional chemotherapy and the development of new ways to reduce cytokine therapy toxicity, will enable to develop and introduce a great number of new high-efficient anti-cancer immune preparations and combined therapy modes in the future.

Adoptive immunotherapy of colon cancer

A principle of adoptive immunotherapy consists in *ex vivo* activation of lymphocytes, isolated from patient's blood or tumor tissue, by cytokines with their further administration to the patient. Lymphokine-activated killer (LAK) cells were first used for cancer therapy by Rosenberg and colleagues in the middle of 80s of the last century [100]. They originate from NK cells of patient's blood; *ex vivo* IL-2 stimulation causes the enhancement of their cytolytic activity and broadening of a target-cell spectrum; however, they remain innate immunity factors, and have no antigen-specificity. Later on cytokine-induced killer (CIK) cells were obtained. They are circulating lymphocytes, stimulated by INF-γ, IL-1, IL-2 and antibodies to CD3, which exhibit the properties of both kinds of killer lymphocytes: NK and T cells providing the recognition of target cells expressing and non-expressing MHC class I molecules [101].

Tumor infiltrating lymphocytes (TILs) contain various subsets including T cells, which were in contact with tumor antigens; therefore, some authors consider them to be the best material for cytokine-induced tumor-specific killer cells, the main difficulty being due to

a limited availability of TILs compared to circulating lymphocytes [102]. The application of cytokine-induced TILs demonstrated a positive effect in the treatment of metastatic melanoma — a tumor exhibiting high immunogenicity compared to other malignancies [103]. To overcome insufficient immunogenicity of other tumors, some researchers tried to modify autologous circulating T lymphocytes providing them with T cell receptors (TCR), which with high specificity to cancer antigen. However, the function of such receptors depends on haplotype of a major histocompatibility complex, and therefore, cannot be used universally. Therefore, chimeric receptors were developed consisting of a heavy chain of monoclonal antibody recognizing the antigen linked to signal intracellular domains initiating cytotoxic reactions typical for T cells [104]. Since antibodies are able to recognize a specific antigen MHC-unlinked class I protein, therapeutics based on T cells with chimeric receptors can be used regardless patients' immunogenetic properties.

Currently, there is no evidence of successful application of LAK in colon cancer therapy. The colorectal carcinoma therapy using cytokine-induced killer cells catches greater interest and the contemporary data indicate potentially high efficiency of using CIK in combination with conventional chemotherapy [105]. Positive results of a combined immunotherapy, namely, CIK used along with dendritic cell vaccine sensibilized by autologius tumor lysate, as a supplement to conventional postoperative adjuvant chemotherapy in colorectal cancer is also described [106–108]. All researches show immunotherapy included in an anticancer treatment course to result in a significant increase of total survival. Good acceptability of the therapy and improved clinical indices of patients has been demonstrated.

The application of antigen-specific and chimeric receptors for additional modification of autologous circulating T cells in patients with colon cancer has not yet given a significant advantage, and, moreover, not infrequently it was accompanied by marked side effects. The 1st phase of clinical trial of human T cells expressing CEA-specific mouse TCR was carried out [109]. The research results showed all patients to have a significant decrease of circulating CEA level; however, the treatment was accompanied by the development of acute colitis. Serious side effects were also found in metastatic colon cancer when studying a therapeutic effect of T cells expressing Her2-specific chimeric receptor [110].

Thus, the analysis of data gathered showed the necessity to undertake further studies to increase the efficacy and safety of adoptive immunotherapy for colon cancer. Furthermore, the series obstacles in the development of adoptive immunotherapy are still its high labor intensity and high cost.

Conclusion

Currently, new knowledge on immunotherapy of solid tumors is being intensively accumulated and new promising techniques are being originated. The most advanced are those in the field of searching new immune checkpoints, development of highly efficient the immune adjuvants based on recombinant viruses to enhance the effect of anticancer vaccines, as well as design engineering of T cells' chimeric receptors to improve adoptive cellular therapy by giving it an antigen-specific constituent. However, even now it is clear that the development of any universal immunotherapeutic, which could have been used as monotherapy with high efficiency is unfeasible. Achievements in treating malignancies including colon cancer depends on a combined application of both: recent developments in immunotherapy, and also conventional cures for oncologic diseases — surgical resection of a tumor, the use of cytostatics, radiation, etc. The application of different immunotherapeutic methods in an adjuvant mode to eliminate residual tumor cells implies an anti-relapsing effect and the enhancement of total and progressive-free survival of patients. A critical goal is to optimize the selection of immunotherapy variant, as well as its place in combined treatment, which would enable to achieve the potentiation of the effect by means of application of new and known approaches to cancer treatment.

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