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Modern Approaches to Enterovirus-Based Oncolytic Immune Virotherapy of Malignant Diseases

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The aim. The review presents the analysis of publications on modern approaches to oncolytic viral immunotherapy of malignant diseases which is predominantly based on usage of enteroviruses.

Materials and methods. Electronic data bases — PubMed, Scopus, Web of Science, Google Scholar, eLibrary, and other accessible datasets were used for gathering and analyzing appropriate publications for the following keywords: oncolytic virotherapy, oncolytic viruses, enteroviruses, *poliovirus, coxsackievirus, echovirus,* preclinical and clinical trials. The research included the time interval from 1990 till 2024.

Results. The data present the properties of wild type and gen modified viruses — the supposed basis for development of the drugs, as well as their action mechanisms. The described mechanisms include direct cytolysis caused by the intracellular reproduction of the virus, activation of antitumor immunity of the host body (viral recipient) due to presentation of the tumor-associated antigens from the damaged cells to dendritic cells for their further maturation, presentation of these antigens to T-lymphocytes and activation of cytotoxic lymphocytes, modulation of tumor microenvironment due to immunostimulation, and transition of "cold" tumor and its environment into "hot" state. It has been noticed that the most pronounced therapeutic efficacy is observed in immunosensitive tumors. This observation correlates with the action mechanism of the oncolytic viruses. Clinical trials of viral drugs still have not led to superior results in therapeutic efficacy but they have demonstrated the synergistic efficacy with other methods of conservative therapy. According to the results of preclinical and clinical trials, enteroviruses demonstrate a favorable toxic profile. Factors which reduce the efficacy of virotherapy were evaluated. They include non-targeted and non-specific absorption of viruses by tumor cells, weak endocytosis and reproduction followed by distribution in the body, preexisting immunity against the concrete viruses and induction of antiviral antibody expression during viral therapy, and lack of sensitivity of the tumor and its microenvironment to the virus.

Conclusion. Enterovirus-based oncolytic therapy is a promising therapeutic option but its efficacy needs to be enhanced using mechanisms of its therapeutic impact.

Keywords: oncolytic virotherapy; oncolytic viruses; enteroviruses; *poliovirus; coxsackievirus; echovirus;* preclinical and clinical trials

Abbreviations: APCs — antigen-presenting cells; DCs — dendritic cells; CAR-T — chimeric antigen receptor; CD — cluster of differentiation; CXADR — coxsackie-adenovirus receptor; DAMPs — damage associated molecular patterns; EM — extracellular matrix: HSV — herpes simplex virus; IFN — interferon; IL — interleukin; MDSC — myeloid-derived suppressor cells; NOAEL — no-observed-adverse-effect level; NOD-SCID — non-obese diabetic / severe combined immunodeficiency; PAMPs — pathogen associated molecular patterns; $TCID_{50}$ — Tissue Culture Infectious Dose; TME — tumor microenvironment; TNF — tumor necrosis factor; MN — malignant neoplasm; CTs — clinical trials; MHC — major histocompatibility complex; ICAM-1 — intercellular adhesion molecule 1.

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Современные подходы к онколитической иммуновиротерапии онкологических заболеваний на основе энтеровирусов

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Цель. Представить обзор современных подходов к онколитической вироиммунотерапии онкологических заболеваний с применением энтеровирусов по данным мировой научной литературы.

Материалы и методы. Для сбора и анализа сведений использованы электронные базы данных PubMed, Scopus, Web of Science, Google Scholar, библиотечная база данных (eLibrary.ru) и другие доступные ресурсы. Поиск проведён по публикациям за 1990–2024 гг. по ключевым словам: «онколитическая виротерапия», «онколитические вирусы», «энтеровирусы», «*poliovirus*», «*coxsackievirus*», «*echovirus*», «доклинические исследования», «клинические испытания».

Результаты. Представлены данные о свойствах онколитических вирусов дикого типа и геномодифицированных вирусов, на которых основан выбор вируса для разработки лекарственного препарата, и о механизмах их действия. Они включают прямое цитолитическое действие, обусловленное внутриклеточным размножением вируса; активацию противоопухолевого иммунитета организма — реципиента вируса за счет презентации опухоль-ассоциированных антигенов дендритным клеткам с последующим их созреванием, презентацией антигенов Т-лимфоцитам и активацией цитотоксических лимфоцитов; модуляцию опухолевого микроокружения окружения в результате иммуностимуляции и перехода «холодной» опухоли и окружающей ткани в «горячее» состояние. Отмечено, что наиболее выраженный терапевтический эффект наблюдается в отношении иммуночувствительных опухолей, что коррелирует с механизмом действия онколитических вирусов. Клинические испытания лекарственных препаратов пока не привели к прорывным результатам по терапевтическому действию, но показали синергизм по эффективности с другими видами консервативной терапии. По результатам доклинических и клинических исследований, энтеровирусы проявляют благоприятный профиль токсичности. Оценены факторы, снижающие эффективность виротерапии: недостаточно целенаправленное попадание вируса в опухолевые клетки, неактивный эндоцитоз и размножение с последующим распространением в организме; предсуществующий в организме иммунитет против конкретного вируса и индукция выработки антител к нему в процессе виротерапии; отсутствие чувствительности самой опухоли и ее микроокружения к вирусу.

Заключение. Онколитическая виротерапия на основе энтеровирусов перспективна, но эффективность ее необходимо повышать, опираясь на механизмы действия.

Ключевые слова: онколитическая виротерапия; онколитические вирусы; энтеровирусы; *poliovirus; coxsackievirus; echovirus;* доклинические и клинические исследования

Список сокращений: АПК — антиген-презентирующие клетки; ДК — дендритные клетки; CAR-T — химерный антигенный рецептор Т лимфоцитов; CD — кластер дифференцировки; CXADR — Коксаки-аденовирусный рецептор; DAMPs – молекулярный фрагмент, ассоциированный с повреждениями; ECM — внеклеточный матрикс; HSV — вирус простого герпеса; IFN — интерферон; IL — интерлейкин; MDSC — миелоидные супрессорные клетки; NOAEL — уровень отсутствия наблюдаемых побочных эффектов; SCID — тяжёлый комбинированный иммунодефицит; PAMPs – патоген-ассоциированные молекулярные паттерны; $TCID_{50}$ — инфекционная доза тканевой культуры; TME — опухолевое микроокружение; TNF — фактор некроза опухолей; ЗНО — злокачественное новообразование; КИ — клинические исследования; ГКГС — главный комплекс гистосовместимости; ICAM-1 — молекула межклеточной адгезии 1.

INTRODUCTION

Malignant diseases remain to be one of the major death causes over the world despite the obvious progress in the development of both surgical and conservative treatment methods [1, 2]. It is well-known that tumor cells use various methods to successfully fight with chemo- and target drugs, as well as inhibit the immunity of tumor-bearing body [3–5].

It should be admitted while evaluating modern state-of-art in oncology, that one of the major advances of the XXI century is understanding that tumor node is formed not only by malignant cells but presents a huge dynamically developing network containing both transformed and non-transformed cells tightly connected with each other, as well as soluble mediators which form tumor microenvironment (TME) [6].

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TME provides the niche for tumor growth and accumulation of metastatic cells using the extracellular matrix, maintains vitality of tumor stem cells, provides functioning of the procarcinogenic mediator signal systems and forms a barrier that prevents penetration of both endogenous and exogenous anticancer agents to the malignant node. It means that antitumor therapy should be targeted not only to malignant cells but provide a complex impact on the whole TME.

Oncolytic antitumor virotherapy has been actively developed during the last decades. Its therapeutic action is based on various mechanisms which impact multiple components of malignant processes [7, 8].

The wild type viruses with oncolytic potency not only damage the tumor cells due to direct destroying their structure but also affect various TME elements inducing both cell death and prolonged activation of immune reactions. That is why treatment including viruses with oncolytic potency has been named oncolytic viral immunotherapy and oncolytic viruses have been recognized as immunotherapeutic agents [9, 10].

Initially at the beginning of virotherapy era, when only wild type viruses were used as therapeutic agents, the results were contradictory and doubtful. The development of gene engineering technology and understanding of the serious role of TME brought back the interest to oncolytic virotherapy. Nowadays we possess a great set of both wild type and gene modified viruses which form the basis for creating medicines aimed at oncolytic immune therapy. Many of them have reached various stages of clinical trials (CTs) and 4 of them have been registered as drugs for treatment of different malignant diseases [11, 12].

Their efficacy was demonstrated in the treatment of patients with melanoma, glioma, and squamous head and neck cancer. But soon it was elucidated that monotherapy with virus drugs did not cause the cure of patients or the significant therapeutic efficacy. The combined therapy including radio- or chemotherapy, as well as immune checkpoint inhibitors or CAR-T- cell therapy, proved to be more efficient. More than 100 CTs for the evaluation of this approach have been initiated, or are under study, or have been completed recently in many countries worldwide. No oncolytic viral drugs are registered for treatment of cancer patients in Russia, so the development and registration of the original drugs are important for Russian medicine.

THE AIM. The aim of this review is to present modern approaches to enterovirus-based anticancer oncolytic viral immunotherapy using the research data from worldwide publications.

MATERIALS AND METHODS

Electronic data bases (PubMed, Scopus, Web of Science, Google Scholar, library dataset (eLibrary), and other available resources were used for collection and analysis of information. The search was performed through the publications from 1990 till 2024 using the following keywords: “oncolytic viruses”, “enteroviruses”, “*poliovirus*”, “*coxsackie virus*”, “*echovirus*”, “preclinical study”, and “clinical trials”.

RESULTS AND DISCUSSION

Selection of oncolytic virus

Before selecting a virus — the future basis of the supposed antitumor oncolytic drug — it is important to study its biological properties and genetics in order to decide if it would be relevant to use it as a wild type virus or if its genome should be modified for safety and efficacy of the therapy.

The ideal oncolytic virus for antitumor viral therapy should possess the following properties:

- be able to replicate and produce active offspring after accumulation in malignant cells;
- be oncolytically active in the infected tumor cells which could excrete viral offspring into extracellular area after their damage;
- be immunogenic, that is be able to induce the immune response;
- not cause the development of chronic or infectious disease;
- not integrate into human genome;
- be safe for various cohorts of people;
- be available for genetic modification aimed to enhance immunogenicity or stimulation of targeted antitumor impact.

From the very beginning of antitumor viral immunotherapy and early CTs the development of medicines has been performed using various DNA and RNA viruses of both wild type and gene modified ones. These are: *Adenovirus, Herpes simplex virus type 1, Parvoviruses,* and *Poxviruses* (*vaccinia virus* и *myxoma virus*) of the DNA-viruses [13, 14] and *Coxsackie virus, Seneca Valley virus, Maraba virus, Measles*

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virus, Newcastle disease virus, Vesicular stomatitis virus, Sindbis virus, and *Poliovirus* type 1–3 of the RNA-viruses [15].

Genome stability and the possibility to insert large transgenes into DNA-viruses without the loss of viral infectivity and the ability to replicate are undoubtedly their advantages. The advantages of the RNA-viruses are absence of integration into recipient genome and their higher immunogenicity in some cases. But smaller volume of the genome in comparison to DNA-viruses is their disadvantage because it limits the size of the inserted transgene.

A serious problem in selecting a virus for oncolytic therapy is its tropism to tumor cells. Constructing recombinant viruses is aimed to enhance their ability to interact and penetrate the tumor, but not the normal, cells. Tropism of wild type viruses to malignant cells depends on many factors, presence of the receptors on the cell surface being one of them. They provide tight connection of the virus with a tumor cell and endocytosis of the virus in some cases. So, CD46, CD155, α2β1, CD55, CXADR (coxsackie-adenovirus receptor) molecules are often overexpressed on tumor cells of various histogenesis and provide the linking of the *measles virus, poliovirus, echovirus, adenovirus, coxsackievirus* [16–19].

Other molecules promoting tumor growth and progression of malignant process may also serve as receptors for various oncolytic viruses [20, 21]. But it should be noted that not all tumor cells possess enough receptors for efficient linkage and penetration of the viruses. Moreover, the expression of viral receptors may be seen not only on the tumor cells. Normal cells sometimes also express these receptors though less intensively, so we cannot consider that virus-receptor interactions on tumor cells would be extremely selective regarding normal cells.

Metabolic cell status and the ability of the virus to overcome antitumor immune reactions and intracellular signal pathways independently or with the help of auxiliary incentives are also very important [22–24].

Cancer is a complex heterogeneous disease with many genetic mutations which induce various alterations in antiviral signal pathways thus creating excellent conditions for viral replication. For instance, cells often sacrifice some elements of their congenial antiviral defense system provided by cytokines — interferons I or II (IFNs), tumor necrosis factor (TNF), or some others [25].

Apart from the ability to infect tumor but not normal cells which is determined by the defective IFN signal pathway in malignant cells, there are some other innate antiviral defense pathways. They help normal cells to identify and block viral replication, and play a crucial role in the ability of oncolytic viruses to infect and replicate selectively in tumor cells. For instance, tumor-specific aberrations in *RAS, TP53, RB1, PTEN, EGFR, WNT, BCL-2*, and other related genes provide the predispositions of malignant cells to viral infections [21, 22, 26].

The main advantage of genetic editing or engineering is a possibility of genetic modification of natural viruses by rational elimination of viral genes responsible for virulence and by insertion of tumor-specific promotors or sequences — targets for miRNA, thus selectively enhancing viral gene expression only in tumor cells.

Vise versa it is possible to put genes which are critical to viruses under the control of miRNA weakly expressed in tumor cells. Then viruses would not be able to replicate in normal cells where ordinary expressed miRNA would prevent high production of viral genes important for replication.

Gene engineering methods give opportunity to construct viruses which are able to infect cells only with abnormal content of some genes. In order to provide the selective infection of tumor cells some proteins of viral shell may be especially modified for further viral interaction only with tumor specific receptors.

The usage of antibodies targeted to tumor antigens can also enhance the specificity of viral therapy [27]. This approach results in the viral ability to damage tumor but not normal cells providing high selectivity of antitumor viral therapy [28].

Mechanisms of antitumor oncolytic viral immunotherapy

The main components of the oncolytic virus antitumor impact are intracellular viral replication, cell destruction due to induction of various death mechanisms (apoptosis, necrosis / necroptosis, piroptosis, autophagia, and others), elimination of immunogenic components from the damaged cells, and stimulation of innate and adaptive antitumor immunity.

The death pattern of malignant cells depends on the characteristics of oncolytic virus and tumor cell type

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because some genes inhibiting/stimulating apoptosis, necrosis, or autophagia may express in these cells [12]. Gene engineering helps to obtain viruses which induce a particular kind of cell death resulting in the increase of immunogenicity of viral therapy.

It is quite obvious now that after linking with and accumulation in the tumor cells oncolytic viruses use various mechanisms for destroying these cells which may depend or not depend on viral replication in them. It is assumed that antitumor viral activity is based on the following mechanisms:

1) A virus may selectively accumulate in malignant cells inducing cytolytic effect (oncolysis). The exact mechanism of viral oncolysis is not fully studied but it is known that it may greatly vary between the viruses as well as the types of tumor target cells. 2) There may appear indirect effects of cell death (for instance, apoptosis-like and necrosis-like effects) in infected, non-infected and endothelial cells of intratumoral blood vessels which decrease angiogenesis. 3) Activation of systemic antitumor and antiviral immunity as well as recruitment of activated immunocompetent cells into TME may happen [29–31].

As it was noted above, all mechanisms greatly depend on the viral type and interactions between oncolytic virus, TME, and immune system of the recipient — tumor-bearing body [32, 33]. But commonly virus infected malignant cells die due to activation of cell death pathways or virus induced damage of their integrity.

It has been proved that TME is the pool of elements with abnormal metabolic pathways — stromal and immune cells, blood vessels, extracellular matrix, and others which actively stimulate proliferation and metastasis of malignant cells due to local cytokines, chemokines, and signal intracellular chains. At the same time tumors may be classified in most cases as immunologically “cold” structures because of low level of tumor antigens, tumor infiltrating suppressor immune cells, and signal molecules.

Oncolytic viruses become a potent immunotherapeutic weapon due to their ability to destroy immunosuppressive TME and create a “hot” environment which promotes development of prolonged tumor-specific immunity providing opportunity of control over the “surveillance against relapse” [11, 34–36].

One of the major characteristics of oncolytic therapy is its ability to induce immunogenic cell death (apoptosis, necrosis / necroptosis, pyroptosis). It results in release of molecular structures demonstrating cell damage (DAMPs — damage associated molecular patterns) — calreticulin, heat shock proteins, ATP, uric acid, and others, together with pathogen-associated molecular structures (PAMPs — pathogen associated molecular patterns) — double-stranded DNA, double- and single-stranded RNA, glycoproteins, lipoproteins, and membrane viral components, as well as cytokines (IFN-γ, IFN-α, TNFα, IL-1, IL-6, IL-8, IL-12) and tumor-associated antigens [37]. These components act as danger signals and induce immune responses to viral infection – initially local (activation of dendritic cell (DC), infiltration, and their maturation) and then systemic adaptive antitumor immunity which is the second effective impact of viral immunotherapy.

DCs are rarely presented in tumors but they are especially potent as antigen-presenting cells (APCs) which fulfil the linkage between the systems of innate and adaptive immunity [38]. Immature DCs are able to migrate easily whereas mature DCs activate T-lymphocytes expressing both specific linkage molecules for T-lymphocytes and co-stimulating molecules. Regulation of DC pool in TME is of great importance for obtaining efficient antitumor immunity. Oncolytic viruses are not only able to induce the outflow of new antigens into circulation and consequently their presentation to DC, but also to prepare TME for easy infiltration by DCs, their maturation, and T-lymphocyte activation. Moreover, enhancing the expression of cytokines in TME after the infection with oncolytic virus stimulates both infiltration of TME by CD4+ and CD8+ T-lymphocytes and their activation. The increase of antitumor cytokine expression in TME pronouncedly impacts malignant cells and many TME components: immune cells, blood vessels, tumor-associated fibroblasts, metabolic processes, and extracellular matrix. As a result, activation of innate and adaptive immunity and prolonged tumor suppression are observed.

Despite the proof of the dual viral impact on the development of tumor structures and total malignant process, the treatment using Oncorine (H101; (E1B/E3 deficient adenovirus), one of the registered drugs, has shown that viral therapy with a single oncolytic virus is not much efficient. This is why recent studies are

mostly concentrated on constructing oncolytic viruses with inserts of genes producing immune components — cytokines and chemokines, or supplied with monoclonal antibodies (targeting them) targeted to malignant cells [39–41].

This approach provides the delivery of cytokines and chemokines to TME with the help of an oncolytic virus, localize**s** the immune reactions near the tumor node, and decrease**s** the toxic reactions of the treatment. Moreover, the replication of oncolytic viruses in tumor cells determines constant production of the cytokines encoded in recombinant viral genome [41].

The usage of recombinant viruses with inserted cytokine genes has demonstrated that after intratumoral administration they provide a more pronounced abscopal effect (regression of distant metastases) than similar viruses of wild type without cytokine production which can only stimulate cytokine expression due to lysis of malignant cells [39–41].

A most important antitumor viral impact is their influence on M1 and M2 macrophages populations in TME. Macrophage plasticity is very high and it is realized in continuum of transfer from M1 to M2 populations in TME. It is well-known that M2 macrophages in tumor node are a prognostic factor of poor survival for various malignant processes. It has been shown that oncolytic viral therapy induces repolarization of immunosuppressive intratumoral M2 macrophages to M1 phenotype expressing anti-inflammatory cytokines and chemokines, for example, IFNγ, CXCL10, IL-6, IL-2, IL-12, and IL-21, which enhance antitumor impact of TME immune complexes [42]. Thus, oncolytic therapy is an efficient control mechanism of M1 / M2 ratio in TME [43]. Besides, in estimation of the genomodified HSV1716 mechanism it was demonstrated that the infection induced not only the stimulation of macrophage polarization into M1 phenotype. Macrophages determine viral amplification due to its accumulation, replication, and elimination of the next generation in TME, thus providing oncolytic efficacy of the treatment [44].

Natural killers (NK) play an important role in antitumor fight, realizing cytotoxic functions as well as remodeling TME. Dendritic cells produce cytokines (IFN-1, IL-12, and IL-18) which enhance the NK cytotoxicity in TME. Other signal mediators — IL-15 and IL-21 produced by myeloid cells also promote their efficacy. Oncolytic viral therapy activates NK indirectly due to stimulation of cytokine and chemokine production [45, 46]. There are data that viruses change the expression of the activating and inhibiting NK ligands including MHC-1 on the malignant cells [9].

One of the important factors in maintaining TME immunosuppressive role is the population of highly suppressive myeloid-derived suppressor cells (MDSC) which significantly increases during tumor progression. These cells not only inhibit the tumor response to the immune impact but also stimulate tumor invasion by engaging various non-immune mechanisms. Besides, it was proved that MDSC decrease the efficacy of modern antitumor therapeutic methods — chemo-, radio-, and immunotherapy [47]. Viral impact on these cells is ambiguous. It was shown that both accumulation of MDSC in TME and remodeling of this population to phenotype destroying tumor tissue took place due to the enhanced NO production after the infection [48]. The efficacy of oncolytic viruses is not yet elucidated regarding the T-regulatory cells (Treg) — another population of immunocompetent cells in TME which possesses a pronounced immunosuppressive activity [49].

Despite the discovery of numerous antitumor mechanisms of oncolytic wild type viruses by which they damage malignant cells or inhibit their growth it came out in practice that the efficacy of viral monotherapy is quite restricted due to several reasons. 1) Antiviral neutralizing antibodies may be present in blood stream either as a factor of preexisting immunity because of previous contacts with the viruses or as the newly formed due to the therapy using systemic administration of oncolytic viruses (intravenous, intraarterial). They can prevent the intracellular viral replication and consequently the tumor cells' lysis [50, 51]. 2) Mechanisms of antivirus resistance including complement activation, antiviral cytokines and macrophages may improve oncolytic virus elimination [52, 53]. These antiviral immune reactions become a serious obstacle decreasing efficacy of viral antitumor therapy. While by now the whole range of immune impacts *pro* and *contra* of oncolytic viruses is not fully known, there is a possibility that the suppressive action against viruses may be overcome due to their local and abscopal effects.

3) Extracellular matrix, fibrosis, necrosis, and interstitial hydrostatic pressure may form an insurmountable physical barrier for linking the oncolytic

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virus with cell receptors which would cause serious decrease of viral endocytosis and consequently its replication, amplification, and antitumor efficacy [50, 54].

Understanding the oncolytic viral immunotherapy peculiarities based on natural wild type viruses led to the necessity to produce the modified viruses by directed change of their properties by inserting genes responsible for synthesis of target proteins. Gene modification helps to improve various viral characteristics**:** their tropism to malignant cells, selectivity of linking with particular receptors, expression of cytokines and chemokines, ability to recruit immunocompetent cells to TME, and increase their antitumor activity. But gene modified viruses possess their own disadvantages. The expression of transgenes or modification of the virus aimed to increase its selectivity can worsen its suitability for therapy due to decrease of replication and its oncolytic activity. Expression of transgenes may prevent participation of the virus in immune reactions significant for realization of the antitumor effect [55]. Therefore, it seems justified to create complex medicines including several viruses both wild type and recombinant.

As a result, such properties of non-pathogen viruses with oncolytic potency as direct cytolysis of malignant cells,-recruitment of immunocompetent cells, activation of antitumor immune reactions, TME modulation, antiangiogenesis, and ability to use metabolic and specific signal in tumor cells have engaged the researchers in developing medicines for antitumor viral immunotherapy [10].

Preclinical study of safety and efficiency of oncolytic enteroviruses

Conservative treatment of cancer patients is often accompanied by severe adverse reactions. So, at the stage of development of new drugs great attention should be paid to evaluation of their safety and tolerability during preclinical study according to the modern guidelines which tightly restrict the study pattern for registration of original medicines. Preclinical studies of toxicity of various oncolytic viruses using experimental animals which are presented in research literature demonstrate the acceptable toxicity profile of oncolytic viruses and prospects for further promoting the antitumor viral immunotherapy [56].

As it was noted, the arsenal of oncolytic viruses promising for antitumor therapy is rather large now and includes viruses of different nature, both DNA- and RNA-viruses. Understanding viral nature and biology is crucial for planning the study of the viral therapy safety because it is well-known that DNA-viruses unlike RNA-viruses integrate into genome of recipient which may cause undesirable consequences. Therefore, only RNA-viruses may be used in their wild type for creation of a drug. DNA-viruses should be modified by exchange of the genes responsible for integration to transgenes producing “useful” proteins, for instance, cytokines or chemokines.

RNA viruses of the *Picornaviridae* family *Enterovirus* genus have attracted the researchers. So, several of them have become the basis for medicines developed in some countries which have reached the initial stages of CTs.

ECHO 7 is the active pharmaceutical substance in Rigvir (Latvia, 2004), the first official drug registered for oncolytic therapy of patients with melanoma, local skin melanoma metastasis, and for prophylaxis of melanoma recurrence after radical surgery [57]. The drug was used in 2 mL dose with the concentration $\geq 10^6 TCID_{50}$ (Tissue Culture Infectious Dose).

The cytolytic efficacy of Rigvir was initially shown using various lines of human tumor cells: FM-9 (melanoma), RD (rabdomiosarcoma), AGS (gastric adenocarcinoma), A549 (lung carcinoma), HPAF II (pancreatic carcinoma), MSC (mesenchimal stem cells from human bone marrow), and uveal melanoma lines — MP41, Mel-202, 92-1 [58, 59].

The toxicity study of Rigvir was performed according to the regulations of Good Laboratory Practice (GLP) in Han-Wistar rats at multiple administration of the drug during 4 weeks with a consequent follow up period for the next 4 weeks. The drug was administered in three doses of 2×10^6, 1×10^7, and 2×10^7 $TCID_{50}$ on the 1–3, 8–10, 15–17, and 22–24 days. Neither deaths nor adverse clinical reactions were observed. Body mass, ophtalmoscopia, clinical pathological parameters, analyses, and organ mass remained unchanged during the observation period. Only eosinophil level increased a little bit but it was normalized towards the end of observation. Rigvir has been detected both in blood samples and spleen during 48 h after the administration. But in spleen samples of 2 animals which were administered the highest dose the drug it was detected on the 29 day of the follow up period. Therefore, it may be resumed that Rigvir reaches spleen

in intact animals. It is quite justified taking into account the immune competency of this organ and the detected increase in eosinophil content which reflects the impact of the drug on the immune system [60].

Non-intensive cell infiltration has been detected in the injection site which characterizes the development of weak inflammation confirmed by increased quantity of lymphocytes in regional lymph nodes. The majority of adverse effects were reversible and only the lymphocyte content remained increased during the whole follow up period. The highest tested dose which did not induce the detected adverse impact on animal health was 2×10^7 $TCID_{50}$ (NOAEL, no-observed-adverse-effect level) [60].

As a result, good Rigvir tolerability was observed which was a proof of the favorable toxicity profile of *ECHO* 7 in animals. Further this conclusion was confirmed by the results of the Rigvir CTs in patients with melanoma as well as by its post-registration usage [60].

Wild type enterovirus *Coxsackievirus* A21 (CVA21) is an active pharmaceutical substance of CAVATAK (Viralytics Ltd., Australia). It predominantly links with tumor cells through ICAM-1 (intercellular adhesion molecule 1) or CXADR (coxsackie-adenovirus-receptor) [61, 62]. The lytic effect of CVA21 was initially detected on human melanoma cell lines, then the study was enhanced using cell lines and xenografts of multiple melanomas, breast, pancreatic, lung, and non-muscle invasive bladder cancer [61, 62].

In vivo study using xenografts has shown the viral ability to spread in the animal body. The NOD-SCID (non-obese diabetic / severe combined immunodeficiency) mice bearing melanoma xenografts were injected one dose of CAVATAK (10^3 or 10^5 $TCID_{50}$) using various administration paths: intratumoral, intravenous, and intraperitoneal. Efficient spread of the virus and inhibition of the ME4405 melanoma xenograft growth were observed in each case. Oncolysis took place even in tumors located far away from the site of administration. Moreover, the fact that viral blood concentration got 10^5–10^6 $TCID_{50}$ titer confirmed the efficient viral replication [63].

The combination of CVA21 with DAFv and ECHO-*1* in the single doses of 7.5×10^5; 1.8×10^7, and 7.5×10^5 $TCID_{50}$ was studied in the PC-3 prostate adenocarcinoma model in SCID-BALB/c immune deficient mice. In the LNCaP human prostate adenocarcinoma model various doses of ECHO-1 (10^7, 10^5, and 10^3 $TCID_{50}$) were infused intravenously to mice. CVA21 and CVA21-DAFv in high titers were detected in mouse blood till the time of euthanasia (the 35th day after the infusion) whereas ECHO-1 titer significantly decreased in a week [56].

Serious adverse reactions — paralysis of the hind limbs and myositis of varying severity — were observed in SCID mice with breast cancer and multiple myeloma xenografts which were infected intravenously with CVA21 in 10^7 $TCID_{50}$ dose [64] but such reactions did not develop in immunocompetent patients [65]. Viral murine blood concentration varied in the range of 10^5–10^7 $TCID_{50}$ during the experiment. Viremia was observed in some mice. It is quite possible that this phenomenon was determined by the animal immune deficient status, and, respectively, inability to fight successfully the viral burdens or viral replication in muscle tissue which often occurs in immune deficient mice [64].

Recombinant *poliovirus* 3 (Sabin) attracted attention of the researchers with a prospect to use it for treatment of glioblastoma — the most malignant brain tumor [66]. But p*oliovirus* 3 (Sabin) acquires some properties that determine its neurotoxicity, and so its safety and tolerability should be evaluated in detail. Normally the effective replication of *poliovirus* is limited to two areas: gastrointestinal tract with associated lymphocytic components and motor neurons of medullar areas of spinal marrow [67]. These replication areas correspond to localization of cells with maximum expression of CD155 — the main receptor which links with *poliovirus* and provides its accumulation in the cells. *Poliovirus* replication in gastrointestinal tract does not cause enteropathology and normally is not clinically active. But viral tropism to motor neurons is the cause of paralytic poliomyelitis, it is in fact the pathognomonic signature of *poliovirus,* and as such raises serious biosafety concerns [66].

The clinically safe but replicative competent *poliovirus* should be completely deprived of its neurovirulent potency. Ideally the safety characteristics of oncolytic *poliovirus* must meet the following requirements: a virus should possess the ability to replicate in malignant cells, be devoid of neurovirulent properties inherent in it, and the viral genotype attenuated in the neurovirulent potency should be stable for a long period.

Sequencing genome of neuroattenuated poliovirus

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(Sabin) strains which were obtained by prolonged selection has elucidated that single point mutations in the IRES (internal ribosomal entry sites) critical zone are the major safety mechanism for all three strains of poliovirus (Sabin, type 1–3), whereas genetic reversal of these mutations to wild type sequence brings it back to neurovirulency [68]. This led to the creation of recombinant *poliovirus* PVSRIPO with IRES of human *rhinovirus* type 2 which is the most studied up to now [69]. It is true that substitution of IRES in *poliovirus*-1 caused significant decrease of neurovirulent viral action which excluded development of poliomyelitis, meningitis, and encephalomyelitis at intracerebral administration of attenuated recombinant virus to primates of Old World in a WHO standard model for evaluation of these infectious diseases [70]. These complications were not observed in patients in phase I of CTs [67].

High expression of CD155 in tumor cells of various histogenesis is very important for realization of viral oncolytic potency because this protein is the major *poliovirus* receptor determining endocytosis and intracellular accumulation of the virus [71, 72]. It has been found out recently that CD155 serves as an immune control point due to its ability for tight linking to T-cell immune receptor expressed in natural killers and T-cells. Though the CD155 physiological properties are not fully known they may include modulation of immune response [73, 74].

It is well-known that *enteroviruses* that include *poliovirus* induce the development of pronounced antitumor response determined by the innate interferon system. This may come to be the main factor of PVSRIPO immunogenic mechanism [75]. Besides, the viral infection causes a large spectrum of inflammatory reactions which promote significant immunocompetent cell invasion into TME. Post-infectious processes resemble the development of a classic response to the inflammation induced with a pathogen and are very important in the context of antitumor therapy [76, 77].

Intratumor pathway for PVSRIPO administration is the most efficient for realization of its impact on the antitumor immune system [76]. Systemic infusion of recombinant *poliovirus,* as well as other oncolytic viruses, leads to the need for the virus to overcome various obstacles on the way to the tumor including the blood-brain barrier, the circulating neutralizing antibodies, and the complement system. Moreover, it is quite difficult to provide targeting virus to tumors and their environment at systemic infusion and**,** consequently, accumulation of the virus in high concentration in the targeted structures [76].

An original drug has been developed in the Institute of Molecular Biology named after Engelhardt RAS together with National Medical Research Radiology Center on the basis of 4 active pharmaceutical substances — viruses of *Picornaviridae* family *Enterovirus* genus. Safety and efficacy of the drug were studied in preclinical trials using experimental animals. The obtained results bear evidence of good prospects for its further study in CTs.

Clinical trials and clinical usage of oncolytic viruses-based drugs

Only 4 drugs on the basis of various oncolytic viruses have been registered in the world, among them wild type viruses (*Enteroviruses*) and gene modified viruses (*adenovirus*, *herpes simplex virus* type I) [12].

The first drug on the basis of non-modified *Picornaviridae* (*ECHO* 7), Rigvir, has been registered for melanoma treatment in Latvia in 2004**,** and then in Georgia, Armenia, and Uzbekistan [57, 78]. But it has not spread further because of its poor therapeutic efficacy. The next drug named Oncorine (H101) was developed on the basis of gene-engineered *adenovirus* with deletion of the *E1B* gene. It was approved in China in 2005 for treatment of squamous cell head and neck and esophageal cancer [79]. But its efficacy also came to be rather poor because it was mostly provided by oncolysis, and not by active stimulation of antitumor immunity [54]. The third was the gene-engineered attenuated *herpes simplex virus type I* (HSV-1) with *GM-CSF* transgene (granulocyte-macrophage colony stimulating factor), Talimogene Laherparepvec (T-VEC, Imlygic), which was sequentially approved in 2015 in USA and Europe, and then in Australia and Israel for local treatment of the unresectable skin melanoma, as well as the subcutaneous and lymphatic nodes in patients with recurrent melanoma after surgical extinction of primary tumor [80–83]. Delytact (teserpaturev/G47Δ) is one more drug based on the modified *herpes simplex virus* type I registered in Japan in 2021 as a medicine for treatment of brain tumors including glioblastoma [84–86]. Increase of survival and favorable toxicity profile were observed in patients with residual tumor or relapse of glioblastoma against the background of viral immunotherapy. But these results are

preliminary and the registration of the drug has still a conditional status.

Therefore, only Talimogene Laherparepvec (T-VEC, Imlygic) keeps a strong position at the moment in the arsenal of therapeutic antitumor medicines.

Still, it is interesting to note that no transgenes have been included into the *HSV-1* genome of Delytact. So, a question arises: is genome modification through transgenesis necessary for improving therapeutic efficacy? Since it was shown that *GM-CSF* can stimulate MDSCs [87] and, respectively, decrease innate and adaptive antitumor responses in tumors of various genesis after administering virus with this gene, another question arises: is it expedient to insert *GM-CSF* gene in the *HSV-1* genome**,** as it was done for Talimogene Laherparepvec?

These questions together with many other concerning rational designs of oncolytic viral medicines, dosages, usage regimen both individually and in combination with other methods of conservative antitumor therapy, safety, and efficacy, would be answered by the results of CTs which grow geometrically and now exceed three hundred.

More than half of CTs now are being performed according to phase I, ¼ — according to phase II, and not more than 5% — according to phase III [54]. Undoubtedly, viral immunotherapy as an individual treatment method is more interesting than the combined methods but unfortunately its efficacy leaves much to be desired though the safety profile is favorable for most viruses.

Data on T-VEC treatment of 436 patients with melanoma were published in 2019. Patients were randomized in 2 groups: group 1 — 295 patients were treated using T-VEC and group 2 — 141 patients were treated using *GM-CSF*. The differences revealed by comparative statistical data processing were quite striking: the objective response was 31.5% (group 1) and 6.4% (group 2); complete response — 16.9% (group 1) and 0.7% (group 2); 88.5% of patients with complete response were alive at a 5-year assessment of the results [83].

The results of other T-VEC CTs in melanoma patients were also rather promising [81, 88]. The enterovirus-based oncolytic viral immunotherapy in patients with advanced melanoma was efficient too. The Phase I CTs of *coxsackievirus* V937 (CVA21) provided a 12-months survival without progression in 32.9% cases and general survival in 75.4% cases during this observation period [89]. The PVSRIPO phase I CTs in similar patients led to analogous results [90].

The fact that melanoma is one of the tumors most sensitive to immunotherapy**,** this being proved by good results of the oncolytic viral therapy, bears indirect evidence of the induction of antitumor immune processes at viral application. It is also noted in the review by Lin et al [54] that the most immunogenic tumors can be easier cured than malignancies which do not respond to immune impacts.

Some CTs concern administration of oncolytic viruses in patients with stage IV of gliomas. It seems that G47Δ and G207 (HSV-1) are the most promising viral medicines [86, 91, 92]. The Phase II CT of G47Δ has shown that 1-year survival of patients with residual or recurrent glioblastoma reaches 84.2% and general survival median — 20.2 months after the treatment initialization. It is interesting to note that G47Δ and G207 have not been modified by insertion of exogenous genes into the viral genome.

The Phase I CTs of PVSRIPO recombinant non-pathogenic virus has demonstrated that its intratumoral injection to 61 patients with IV stage of malignant glioma caused no signs of neurovirulent potency even at dose escalation from 10^8 $TCID_{50}$ till 10^{10} $TCID_{50}$: no poliomyelitis, meningitis, or encephalomyelitis were observed in the treated patients [93]. Only one dose limiting toxic effect was revealed during the treatment using PVSRIPO: at the maximum dose of 10^{10} $TCID_{50}$, immediately after removal of the catheter, hemorrhage was noted which did not cause serious complications after removal of the hematoma and the patient's life span was as long as 57 months.

Comparison of survival of patients treated by oncolytic virus and patients in the control group has demonstrated that survival in the experimental group reached a plateau of 21% by 24 months and this level was kept for 36 months, whereas in the control group it was only 14 % by the same period and decreased to 4% by 36 months.

Many other CTs of various oncolytic viruses for treating cancer patients have been initiated recently and some of them have reached Phase III.

Table 1 presents CTs of *enteroviruses* which are performed now [94].

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Table 1 – Clinical trials of oncolytic viruses of *Picornaviridae* family Enterovirus genus

Oncolytic virus	Virus type	Phase No., NCT No., state of trials	Monotherapy/ combination	Pathways for virus administration
PVSRIPO	*Picornavirus Poliovirus* Lerapolturev	I	Monotherapy	Intratumoral
		NCT01491893 (active, not recruiting patients)		
		NCT03564782 (recruiting patients)		
		NCT03043391 (active, not recruiting patients)		
		NCT03712358 (II phase, active, not recruiting patients)		
		NCT02986178 (active, not recruiting patients)		
		NCT04479241 (recruiting patients)		
			Pembrolizumab	Intratumoral
CVA21	*Picornavirus Coxsackievirus* CAVATAK® Gebasaxturev	I/II	Monotherapy/ combination	Intravenous Intratumoral Intravesical
		NCT04303169 (recruiting patients)	Pembrolizumab	Intratumoral
		NCT04521621 (recruiting patients)	Pembrolizumab	Intratumoral
		NCT04152863 (active, not recruiting patients)	Pembrolizumab	Intratumoral
		NCT02824965 (active, not recruiting patients)	–	Intravenous
		NCT00235482 (completed)	–	Intratumoral
		NCT00438009 (completed)	–	Intratumoral
		NCT01227551 (completed)	–	Intratumoral
		NCT01636882 (completed)	–	Intratumoral
		NCT02307149 (completed)	Ipilimumab	Intratumoral
		NCT02565992 (completed)	Pembrolizumab	Intratumoral
		NCT02043665 (completed)	–	Intravenous
		NCT03408587 (completed)	Ipilimumab	Intravenous
		NCT00636558 (completed)	–	Intravenous
		NCT02316171 (completed)	Mitomycin C	Intravesical

The results obtained up to now are presented in scientific medical literature only for 5 CTs of enteroviruses: NCT01491893 (PVSRIPO) [94], NCT03712358 (PVSRIPO) [90], NCT01636882 (*coxsackievirus* A-21, previous name CAVATAK®, modern name Gebasaxturev) [89], NCT03408587 (*coxsackievirus* A-21) [95, 96], and NCT02316171 (*coxsackievirus* A-21) [61].

All of these CTs were performed according to Phase I, so, the primary control point was evaluation of safety of the oncolytic viruses-based medicines.

Almost all researchers mention that the most frequent adverse reactions of the applied oncolytic viruses of *Picornaviridae* family *Enteroviridae* genus, as well as other, were chills, fever, nausea, flu-like syndrome, weakness, and pain at the injection site. Still, it is noted that overall, the safety profile of these viruses is more favorable than that of other immunotherapeutic medicines.

To sum up, the oncolytic viruses demonstrate a better toxicity profile not only in preclinical studies but also in CTs completed up to now.

CONCLUSION

Oncolytic viruses have recently attracted a close attention of the oncologists because of the positive results of preclinical evaluation using cultured malignant cells demonstrating their high cytotoxic activity. Further elucidation of antitumor impact of the most active viruses using models of human tumors in immune deficient animals has proved that there are good prospects for developing medicines on the basis of selected viruses.

Four preparations for oncolytic immunotherapy

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have been registered up to now in several countries, and some more medicines have reached Phase III CTs. The results of CTs were rather promising because they demonstrated the efficacy of oncolytic viral therapy in patients with several types of malignant processes which were resistant to common antitumor treatment as well as favorable toxicity profile of the studied medicines.

Evaluation of oncolytic virus impact mechanisms characterized some major aspects in their therapeutic action: direct cytolitic impact, determined by intracellular viral replication; activation of antitumor immunity of the viral recipient due to presentation of tumor--associated antigens from the damaged cells to antigen presenting dendritic cells with their further maturation and consequent presentation of the antigens to T-lymphocytes with activation of cytotoxic lymphocytes; modulation of the tumor microenvironment as a result of immunostimulation and transfer of the "cold" tumor and TME into the "hot" state; antiangiogenic viral impact; changing both signal pathways and metabolic processes in virus infected tumor cells.

The ability to modify viral genome appears to be a great advantage of the oncolytic viruses. It gives us an opportunity to change their properties through eliminating genes responsible for virulence and inserting genes coding the functionally active proteins which are able in their turn to enhance targeting viruses to malignant cells, stimulate immunity, and modify TME.

But despite the obvious progress in viral immunotherapy, there are many aspects in design, creation, and application of viral medicines that still do not fully satisfy the specialists of various profiles. There are some barriers that significantly decrease the efficacy of viral therapy.

First of all, this is defected targeting of the virus to malignant cells, endocytosis, accumulation, and replication in them with further spread in the body. Preexisting immunity against the particular virus and induced production of antibodies during the viral therapy also decrease the tumor damage. Presence or absence of the sensitivity of the tumor and its TME to the virus play, of course, the crucial role in the response and are determined by the concrete properties of the tumor and recipient body. It was observed that immune sensitive tumors showed the most pronounced sensitivity to oncolytic viruses which well correlated with viral action mechanism.

It is obvious that viral immunotherapy efficacy directly depends on the balance between the antitumor immunity induced in the tumor-bearing body by the oncolytic virus and the antiviral immunity of this body. But the biologic mechanisms influencing this balance are not yet revealed and, respectively, the pathways for improving it are not clear.

As it is, the researchers worldwide are developing methods aimed to enhance antitumor efficacy of viral oncolytic therapy, are creating various medicines aimed to improve their therapeutic properties, and are studying various schemes of combined application of viruses and other conservative therapeutic methods.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHORS' CONTRIBUTION

Elena R. Nemtsova — development of the concept, search and analysis of sources, interpretation of the data obtained, writing the final version of the article, final approval of the version for publication;
Ekaterina A. Plotnikova — search and analysis of sources, interpretation of the data obtained, writing the layout of the article. All authors made an equivalent and equal contribution to the preparation of the publication.
All authors confirm that their authorship meets the international ICMJE criteria (all authors made a significant contribution to the development of the concept and preparation of the article, read and approved the final version before publication).

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