

Oncolytic virotherapy for human malignant mesothelioma: recent advances

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Abstract: Cancer virotherapy is an attractive alternative to conventional treatments because it offers a wide range of antitumor effects due to 1) the diversity of the oncolytic viruses that are now available and 2) their multifaceted activities against both tumor cells and tumor vessels, in addition to their ability to induce antitumor immune responses. In this review, we summarize preclinical and clinical data regarding the targeting of malignant mesothelioma (MM) by oncolytic viruses. We also discuss the potential of other oncolytic viruses that have already shown antitumor effects against several malignancies in advanced clinical trials but are yet to be tested against MM cells. Finally, we review how the activation of the immune system and combinations with other types of anticancer treatments could support the development of oncolytic virotherapy for the treatment of MM.

Keywords: oncolytic viruses, cancer virotherapy, malignant mesothelioma, antitumor immune responses, immunotherapy

Introduction

Oncolytic viruses are either naturally occurring or genetically engineered viruses that are able to target tumor cells preferentially over healthy cells.¹ Such viruses have been shown to exert antitumor activity against numerous types of human cancers, and several are currently being tested in the final phases of clinical trials. Their ability to not only kill cancer cells specifically but also both impair abnormal vasculature and stimulate different types of immune effectors makes them potent therapeutic agents that are adapted to a variety of clinical situations. One can expect that some of these oncolytic viruses will be routinely used to treat clinically challenging malignancies within a few years.

Questions remain regarding treatment modalities, eg, when deciding the route of administration or the number of injections that would be necessary to achieve significant antitumor responses. One of the major pending issues relates to the ability of the oncolytic vectors to escape from antiviral mechanisms – such as neutralizing antibodies that are present in body fluids or type I interferon pathways – that could dampen their antitumor efficacy. When applicable, the use of intratumor or intracavity injections may be advocated, which are expected to increase the probability of contact between the virus and the tumor cells while limiting neutralization of the viral particles before they reach the tumor site. As an example, patients with advanced ovarian cancers who were immune to measles virus (MV) were shown to be efficiently treated by intraperitoneal injections of an oncolytic strain of MV.^{2,3} Other malignancies that

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are known to arise in or metastasize to body cavities thus make good candidates for similar approaches.

In this review, we discuss the aspects that make virotherapy a good alternative to conventional treatments for malignant mesothelioma (MM), an aggressive cancer that affects the cells delineating different body cavities and for which an efficient treatment is yet to be designed. We summarize data that have been collated over the past 2 decades in order to support further investments for the development of virotherapeutic strategies for patients with MM.

Malignant mesothelioma

Asbestos exposure has been known for several decades to cause various respiratory diseases. One of the most illustrative pathologies related to occupational asbestos exposure is malignant pleural mesothelioma (MPM), an incurable cancer affecting pleural mesothelial cells.^{4,5} These cells are normally constitutive of the two membranes – the parietal pleura and the visceral pleura – that surround and protect the lungs. MM can also, rarely, arise from mesothelial cells delineating the pericardium (heart), the peritoneum (abdomen), or the tunica vaginalis testis and tunica serosa uteri (reproductive organs).

MPM is characterized by pleural thickening, the formation of pleural plaques and the accumulation of pleural fluid – known as pleural effusion – between the two layers of the pleura. This malignancy is commonly diagnosed several decades after exposure to asbestos, with symptoms that can be mistaken for those of invasive lung cancer or of pleural metastases from other types of cancers.⁶ It is an extremely aggressive neoplasm, resistant to conventional treatments including surgery, chemotherapy, and radiotherapy. Outcomes for this disease are extremely poor, with a survival rate of approximately 40% 1 year after diagnosis and only 10% after 5 years.⁷

These clinical hurdles make MM a suitable candidate for innovative therapeutic approaches such as oncolytic virotherapy, with the aim of improving its clinical management. Because the treatment of pleural effusion indeed requires access to the pleural cavity, local injections of oncolytic viruses into the pleural or the peritoneal cavities could be envisioned.

Herpesvirus

Several DNA viruses from the Herpesviridae family have been investigated for their oncolytic properties.¹ The most advanced, talimogene laherparepvec (T-Vec), previously known as OncoVEX^{GM-CSF}, is an oncolytic herpesvirus (HSV) that showed significant antitumor activity after intratumoral

injection in a recent Phase II clinical trial for the treatment of melanoma.⁸ This virus is currently being tested in a Phase III study and is expected to be shortly approved for clinical use by the US Food and Drug Administration.

T-Vec has not yet been used in patients with MM, but other strains of HSV have been studied for their ability to target and specifically kill mesothelioma cells. In 1997, it was first shown that replication-restricted HSV-1716 could eliminate human MM cells both in vitro and in immunodeficient mice.⁹ In the following years, Adusumilli et al published several articles in which they showed that different oncolytic HSV vectors were relevant therapeutic agents to target human MM, alone or in combination with other types of anticancer treatments.^{10–13} HSV-1716 is currently being investigated in a Phase I/IIa trial to determine the safety and efficacy of single or multiple intrapleural administrations of the virus in patients with MPM (Table 1).

Other strains of oncolytic HSV, such as G207, NV1020, and NV1066, that code for fluorescent proteins have also been used to treat and image primary tumors and metastases of mesothelioma in vivo.^{12–14} This alternative use of oncolytic viruses identified minimal residual disease and lymph node metastases in animal models. Such an approach could participate in improving the clinical management of MM.

Poxvirus

JX-594, also known as pexastimogene devacirepvec (Pexa-Vec), is another oncolytic virus expected to be tested in a Phase III clinical trial for patients with hepatocellular carcinoma. In the prior Phase II study, regression of both the injected tumors and tumors distant from the injection site were observed, suggesting the induction of an antitumor immune response.¹⁵ Interestingly, half the patients were seropositive for vaccinia virus prior to the treatment, but the therapy was efficient in all patients independent of their immune status.

In the corresponding Phase I study that was conducted in patients with different types of solid tumors, a single patient with metastatic MPM was included and showed partial remission for more than 10 weeks after a single intravenous injection of the virus.¹⁶ Another Phase I trial is underway for patients with malignant pleural effusions of different origins, including those with MPM (Table 1). This group of researchers previously showed that such an oncolytic virus could specifically target human MM cells in vitro and in an orthotopic animal model.^{17–19} Another vaccinia virus was also recently shown to treat MM efficiently in vivo in association with cytoreductive surgery.²⁰ In 2000, a first study showed that a recombinant vaccinia virus encoding the interleukin-2

Table 1 Completed and ongoing clinical trials of virotherapy for malignant mesothelioma treatment

Virus	Phase	Patients	Treatment modalities	Results	Reference
Adenovirus					
Ad.HSVtk	I	21 MPM	No previous therapy Intraleural injection ($\geq 1.5 \times 10^{13}$ particles) + systemic ganciclovir	Well tolerated Antitumor antibodies 2 long-term survivors (>6.5 years)	55
Ad.hIFN- β (BG00001)	I	7 MPM 3 metastatic pleural effusions (ovary, lung, MPM)	No previous therapy Single intraleural injection (9×10^{11} – 3×10^{12} particles)	Antitumor immune response in 7/10 patients Clinical response (SD) in 4/10 patients	35
Ad.hIFN- β (BG00001)	I	10 epithelioid MPM 7 metastatic pleural effusions (ovary, lung, breast)	2 intraleural injections (7-day interval) (3×10^{11} – 1×10^{12} particles)	Well tolerated Antibody responses against tumor antigens 1 PR, 2 SD, 7 with survival >18 months	36
Ad.hIFN- $\alpha 2b$ (SCH 721015)	Pilot	9 MPM	2 intraleural injections (3-day interval) (3×10^{11} – 1×10^{12} particles)	Well tolerated Neutralizing antibodies 1 PR and 2 SD	34
Ad.hIFN- $\alpha 2b$ (SCH 721015)	I/II	MPM	2 intraleural injections + 4–6 cycles of chemotherapy	Ongoing	NCT01119664 ^a
Ad.hIFN- $\alpha 2b$ (SCH 721015)	I	MPM	2 intraleural injections (3-day interval)	Ongoing	NCT01212367 ^a
Ad5-D24-GMCSF	Unspecified	2 MPM	After chemotherapy Single intraleural injection (2.5×10^{11} – 3×10^{11} particles)	Well tolerated Tumor-specific and virus- specific immunity 1 SD and 1 PD	54
Ad5/3-D24-GMCSF (ONCOS-102)	I	1 MPM	After chemo-/radiotherapy 4 intratumoral injections (3×10^{11} particles) + cyclophosphamide (daily)	T CD8 ⁺ tumor infiltration Th1 polarization	65
Poxvirus					
VV-IL2		6 MPM	Intratumoral injection	Well tolerated No tumor regression PR over 10 weeks	21
JX-594 (pexastimogene devacirepvec)	I	1 metastatic MPM	After chemotherapy Single intravenous injection (1.5×10^7 particles)		16
GL-ONCI	I	Malignant pleural effusions (primary, metastases, and MPM)	Intraleural injection	Ongoing	NCT01766739 ^a
Reovirus					
Reolysin	I	1 MPM	Pretreatment with docetaxel Intravenous injection (1×10^9 – 3×10^{10} TCID ₅₀) Up to 8 cycles (every 21 days) of 5 daily injections	Minor response 23% size decrease for 1 invaded lymph node	48
Measles virus					
MV-NIS	I	MPM	Intraleural injections Up to 6 cycles (every 28 days)	Ongoing	NCT01503177 ^a
Herpesvirus					
HSV-1716	I/IIa	MPM	Single/multiple intraleural injections	Ongoing	NCT01721018 ^a

Note: ^aNCT references can be viewed at <https://clinicaltrials.gov/>

Abbreviations: Ad, adenovirus; GM-CSF, granulocyte-macrophage colony-stimulating factor; IL2, interleukin-2; MPM, malignant pleural mesothelioma; PD, progressive disease; PR, partial remission; SD, stable disease; VV, vaccinia virus; TCID, tissue culture infective dose.

gene could be safely delivered to the pleural cavity to target tumor cells and was then able to attract immune cells to the tumor site.²¹

As with HSVs, oncolytic vaccinia viruses can be used for imaging purposes by using vectors recombinant for

radioelement transporters.^{17,18} This facilitates the detection of orthotopic tumors in mice by scintigraphy, positron emission tomography, or single-photon emission computed tomography. This could be of great value when monitoring tumors in patients treated by virotherapy.

Adenovirus

Adenoviral vectors have been widely used in viral gene therapy experiments because of the possibilities they offer for genetic engineering. As a consequence, oncolytic adenoviruses come in many varieties that were created to display specific antitumor properties against different types of human tumors. The first oncolytic virus to be approved for clinical use was the adenovirus H101 for the treatment of head and neck cancer in the People's Republic of China in 2006.²²

Several approaches have been developed to exploit tumor alterations that could favor specific replication of adenoviruses in MM cells compared with the surrounding healthy tissues. These approaches mainly rely on the use of tumor-specific, promoter-regulated adenoviruses using promoters such as those of the survivin,²³ *CREBBP/EP300 inhibitory protein 1*,²⁴ *telomerase*,²⁵ and *midkine*^{26–28} genes that can be highly active in MM cells. The use of specific promoters guarantees the safety of oncolytic adenoviruses that are then unable to replicate in nonmalignant cells. A similar strategy was used with an adenovirus dependent on a mesothelin promoter that showed specific antitumor activity in ovarian cancer, but to date, this virus has not been tested against mesothelioma cells.²⁹

Other types of viral therapy have been developed against MM, eg, by inserting genes encoding tumor suppressors or immunostimulatory molecules into adenoviral vectors. Some reports show that such vectors can be used to exploit the p53 status of MM cells. An E1B-55 kDa-defective adenovirus can thus activate p53 in p53-mutated MM tumors to promote killing of the tumor cell,³⁰ while an adenovirus encoding p53 was shown to activate apoptotic pathways in MM cells.³¹ Similar strategies were used to reexpress *p14* or *p16* tumor suppressor genes.^{32,33} These do not qualify as “oncolytic virotherapy” per se, but such approaches have allowed scientists and clinicians to test the safety and efficacy of intrapleural gene delivery to treat MM in the clinical setting (Table 1).^{34–36} These different studies showed that intrapleural delivery of viral vectors is well tolerated and also provides specific modes of action that can be beneficial for the treatment of MM, especially by activating the antitumor immune response.³⁷

RNA viruses

Several attenuated RNA viruses have been shown to exert oncolytic activity against a wide variety of human tumor types. Among these, vesicular stomatitis virus (VSV), MV, Sendai virus, Newcastle disease virus, reovirus, and even retroviruses have been specifically investigated for their ability to target and kill human MM cells.

VSV encoding the *IFN-β* gene specifically replicates in tumor cells deficient for the type I interferon pathways and shows anti-MM effects.^{38,39} Alterations of type I interferon pathways in human MM cells should also be considered when planning oncolytic virotherapy strategies with other viruses in patients with MM. Indeed, we recently described – in tumor cells derived from 22 patients with MPM – how type I interferon deficiencies could discriminate between patients who would be susceptible to oncolytic MV virotherapy and those who would be resistant to this type of treatment (Achard et al, unpublished data, 2015). Nonetheless, we had previously shown that MV was able to target and kill human mesothelioma cells,⁴⁰ which was then confirmed by another team at the Mayo Clinic.⁴¹ A Phase I clinical trial is thus in progress to investigate intrapleural delivery of MV in patients with MPM (Table 1).

MV was also shown to be an excellent platform to express different reporter transgenes such as the carcinoembryonic antigen^{3,42} or a sodium-iodide symporter⁴³ that allow for better monitoring of oncolytic MV targeting and replication in patients, which could be applied to MM. Data from MV are believed to be translatable to canine distemper virus, which could be a valuable vector to test oncolytic virotherapy in dog models of MM.⁴⁴ Sendai virus, another paramyxovirus related to MV, has also been shown to specifically target human MM in a xenograft model.⁴⁵ From the same family, Newcastle disease virus showed similar antitumor activity against numerous human MM cell lines.⁴⁶

Reoviruses, in particular Reolysin, which has been successfully tested in a Phase II trial for patients with metastatic melanoma,⁴⁷ are other promising oncolytic agents. So far, only one patient with metastatic MPM has been included in a clinical trial using Reovirus, and this showed that this tumor type could be targeted by the virus. Indeed, infected MPM cells showed strong viral protein production, and a decrease of the size of an invaded lymph node was also observed in this patient after six cycles of docetaxel/reovirus combination.⁴⁸

Finally, retroviral replicating vectors have been shown to efficiently transduce human MM cells both in vitro and in vivo in subcutaneous xenograft models.^{49,50} The vectors that were used in this study encode a prodrug activator gene that sensitizes tumor cells to the prodrug, 5-fluorocytosine. Tumor cells and their healthy counterparts were reported to exhibit different expression levels of the retrovirus receptors, which could account for the oncolytic potential of retroviruses against MM.

Antitumor immune responses

Specific lysis of tumor cells is a fundamental feature of oncolytic viruses. Nevertheless, these viruses can exert their antitumor activity through additional mechanisms such as the targeting of tumor vessels^{51,52} or the activation of immune cells. This ability to induce tumor-specific immune responses is now believed to be essential for the antitumor effects that have been observed in patients.⁵³ Most of the viruses that are currently being tested in advanced clinical trials are thus designed to activate immune responses that can help their antitumor properties. For instance, Pexa-Vec and T-Vec viruses are engineered to express the human granulocyte–macrophage colony-stimulating factor that is necessary for the antitumor effects that have been reported in clinical trials.^{8,15} Likewise, an oncolytic adenovirus coding for human granulocyte–macrophage colony-stimulating factor showed immune activation abilities in a Phase I trial on different types of solid tumors, even though only one of the two patients with MPM included showed disease stabilization, while the other patient exhibited progressive disease.⁵⁴

Back in 2005, Sterman et al hypothesized that the antitumor effects they observed in patients with MPM after intrapleural injection of an oncolytic adenovirus were due to the induction of an antitumor immune response characterized by the production of tumor-specific antibodies.⁵⁵ This was then confirmed with adenoviral vectors encoding the type I interferon genes that were able to activate cytotoxic T cells, natural killer cells, and humoral responses in the pleural cavity.^{34,35} As discussed earlier, activation of the type I interferon response by oncolytic viruses is a double-edged sword; these interferons have a strong antiviral activity, mainly due to their ability to shut down protein synthesis and to activate cell death programs in infected and neighboring cells. However, they are also strong inducers of the innate immune response that can subsequently initiate specific antitumor responses, and thus synergize with the direct cytotoxic effects of the viruses.⁵⁶

VSV is one of the major oncolytic viruses for which the antitumor immune response is believed to have a central role. Actual oncolytic activity (ie, viral replication in tumor cells) of VSV is not always observed after systemic treatment of animals *in vivo*, but this virus is extremely efficient in activating specific adaptive immune responses when reaching immune cells in the lymphoid organs. It has been shown that VSV-mIFN β encoding the murine *interferon- β* gene is able to induce general CD8 T-cell activation against MPM cells after locoregional delivery of the virus.³⁸ Such a mechanism could be exploited to improve the antitumor efficacy of VSV against MM. However, VSV-induced immune responses will

need further characterization as the same research group subsequently showed that the virus can also induce a transforming growth factor- β -dependent suppressive activity mediated by myeloid-derived suppressor cells in a different tumor model.⁵⁷

A critical feature for oncolytic viruses lies in their ability to kill tumor cells by inducing cell death exhibiting immunogenic properties. Different types of immunogenic cell death have been identified, including programmed necrosis – also known as necroptosis – pyroptosis or a specific type of immunogenic apoptosis, most of which are induced by anticancer treatments.⁵⁸ Oncolytic viruses are powerful inducers of tumor cell death and can definitely provide signals bearing immunogenic properties.^{53,59} As an example, we previously showed that MV was able to induce immunogenic cell death in infected human MPM cells. This allows for the activation of central immune cells such as myeloid⁴⁰ and plasmacytoid⁶⁰ dendritic cells that are then able to cross-prime tumor-specific cytotoxic T-cell responses.⁶¹ There has been a recent interest in stimulating plasmacytoid dendritic cells for the treatment of cancer⁶² that could be largely exploited by developing oncolytic virotherapy for cancers such as MM.

A recent Phase I trial described systemic antitumor effects after MV treatment of two patients with multiple myeloma, which strongly suggests the involvement of the immune system.⁶³ This same group previously reported that MV encoding the *interferon- β* gene induced immune cell infiltration – mainly macrophages – into human MM xenografts and the associated microenvironment.⁴¹ Another study showed that MV is an appropriate vector for immunotherapy when used in combination with anti-PD-L1 or anti-CTLA-4 antibodies.⁶⁴ One recent study also reported the induction of different antitumor immune mechanisms after intratumoral injection of an oncolytic adenovirus (Ad5/3-D24-GMCSF or ONCOS-102) in one patient (Table 1).⁶⁵ These findings require further research to determine how they can be applied to the treatment of MM in patients, but they confirm that viral vectors and oncolytic viruses can be used in antitumor vaccine strategies. One can thus anticipate the use of oncolytic vectors coding for tumor antigens to mount specific immune responses against MM tumors, a strategy that has already been developed for other malignancies.⁶⁶

Treatment combinations

To date, cancer virotherapy has shown extremely promising results both in preclinical studies and in clinical trials. However, further combinations of oncolytic viruses with other types of cancer treatments could again improve its efficacy.

In addition, combination studies are of great value because virotherapy is usually tested as a second-line or third-line therapy and it would be interesting to determine how other anticancer therapies could impact – positively or negatively – on its efficacy in patients.

Combined treatment with cisplatin plus pemetrexed – also known as Alimta – has become the standard of care for MM even though its mild clinical efficacy only accounts for an increased survival of approximately 3 months.⁷ Different studies have been performed to determine whether these chemotherapies can synergize with oncolytic viruses to improve the efficacy of both approaches. It was first shown that the stress response induced by cisplatin in cell lines derived from epithelioid, sarcomatoid, or biphasic MM could potentiate the replication and cytotoxicity of the oncolytic HSVs NV1066 *in vitro*.¹⁰ The same group reported that the DNA damage response induced by radiation could also synergize with NV1066 for increased antitumor activity.¹¹ It was also shown that the use of a replication-competent adenovirus deficient for E1B-55kDa, or encoding p53, sensitized MM cells to apoptosis and cytotoxicity induced by cisplatin or pemetrexed.^{30,31} These results are extremely interesting because they show that oncolytic viruses could benefit from the chemotherapeutics already used in patients with MM to achieve their antitumor effects.

The antitumor effects of epigenetic drugs have been widely demonstrated for the treatment of hematological cancers, but more work is needed to define their use for solid tumors. Nonetheless, this class of drugs has shown promising results for the treatment of MM^{67,68} and also exhibits different types of actions that could enhance or interfere with oncolytic virus activities. Indeed, inhibitors of histone deacetylases have been demonstrated to synergize with certain oncolytic viruses such as VSV to infect refractory primary tumors by dampening the type I interferon response.⁶⁹ Valproic acid was also shown to enhance HSV replication in tumor cells by a similar mechanism.⁷⁰ Analogous studies were carried out with different types of oncolytic viruses and showed a variety of mechanisms, such as anti-angiogenic actions, proapoptotic effects, and upregulation of viral receptors, leading to antitumor activity.^{71,72} Such an approach should thus be considered when designing combinatorial therapeutic strategies using oncolytic viruses for the treatment of MM.

Conclusion

MM is an aggressive cancer for which there is an urgent need for the development of efficient, innovative therapeutic strategies to improve its clinical management. Cancer virotherapy

is currently one of the most promising alternatives, with several studies having already shown that human MM cells are sensitive to many different oncolytic viruses by direct killing or by immune-mediated mechanisms. Nonetheless, extensive research is necessary to better define the modalities of treatment and to anticipate how experimental data can be applied to the clinical situation in patients. There is a critical need for exclusive MM trials in order to clinically address the specificities of this cancer, which is often included in studies for patients with “solid tumor”, with a limited number of actual patients with MM evaluated. Because MM is a relatively rare cancer, it may be difficult to incorporate a large number of patients in a single study, but this effort would ensure the clinical validation of oncolytic virotherapy for this specific malignancy and would hopefully provide a brighter prospect for patients afflicted with this incurable disease.

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FT, MG, and JFF own patents on the use of attenuated MV for antitumor virotherapy. Other authors report no conflicts of interest in this work.

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