Head and Neck SCC

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Oncolytic virus (OV) therapy selectively infects tumor cells with a low-pathogenic virus, lyses tumor cells by the cytopathic effects of the virus, and induces anti-tumor immunity to destroy tumors by the action of immune cells. In OV therapy for head and neck squamous cell carcinoma (HNSCC), viruses, such as herpes simplex virus type 1 (HSV-1), vaccinia virus, adenovirus, reovirus, measles virus, and vesicular stomatitis virus (VSV), are mainly used. As the combined use of mutant HSV-1 and immune checkpoint inhibitors (ICIs) was successful for the treatment of melanoma, studies are underway to combine OV therapy with radiation, chemotherapy, and other types of immunotherapy. In such therapy, it is important for the virus to selectively replicate in tumor cells, and to express the viral gene and the introduced foreign gene in the tumor cells. In OV therapy for HNSCC, it may be useful to combine systemic and local treatments that improve the delivery and replication of the inoculated oncolytic virus in the tumor cells.

Keywords: oncolytic virotherapy ; head and neck cancer ; immunogenic cell death ; virus delivery ; virus replication ; tumor antigen ; tumor microenvironment

1. Introduction

Head and neck cancer refers to cancers developing in the oral cavity, pharynx, and larynx. It is the sixth most common disease, with an annual morbidity of 550,000 and 300,000 deaths worldwide [1][2][3][4][5]. The majority of head and neck cancer is squamous cell carcinoma (SCC). Its etiology is related to smoking and drinking, but in recent years, many oropharyngeal cancers are caused by human papillomavirus (HPV) infection, and when HPV is positive, the prognosis of head and neck SCC (HNSCC) is better than when it is negative [6][7]. The combination of surgery, radiation, and chemotherapy is the standard treatment for HNSCC. However, although there have been advances in these therapies, 5-year survival rates remain 40–50% [1].

In recent years, immunotherapy for cancer has attracted attention as an advanced treatment [8]. In immunotherapy, multifunctional cytokines, such as interleukin (IL)-2, interferon (IFN)-α, and tumor necrosis factor (TNF)-α, were initially used [9][10][11]. Manipulation of the immune system by blocking ligands and receptors that act as regulators of T cell activation, so-called immune checkpoints (ICs), exemplified by the cytotoxic T lymphocyte associated antigen 4 (CTLA-4) and programmed cell death protein 1 (PD-1) and its ligand (PD-L1), has become an important strategy to control advanced tumors. Immunotherapy became a substantially evaluable therapy as the ICIs received Food and Drug Administration (FDA) approval in 2011 [12][13]. It was also confirmed that antibody therapy against CTLA4 or PD-1 as an immune checkpoint inhibitor (ICI) can maintain its effects for a longer period of time and has fewer side effects than conventional treatments [14]. However, in the KEYNOTE 012 trial for advanced cancer using an ICI, the overall response rate of the patients treated with the anti-PD-1 antibody was 18%, demonstrating that there are cases in which treatment alone is not curative [15]. New immunological therapies, such as antibodies that inhibit other immunosuppressive ligands, vaccine therapy and chimeric antigen receptor (CAR)-T cells, are also being investigated [4][8][16][17][18].

Oncolytic virus (OV) therapy is a treatment that aims to infect the tumor with the virus and destroy the tumor by its cytopathic effects. In addition to the cytopathic effects, OV activates systemic tumor immunity and is expected to be effective for metastatic tumors to which the virus is not directly administered [19][20][21][22][23]. In 2015, a mutant HSV-1, talimogene laherparepvec (T-vec), was approved by the United States FDA for difficult-to-resect melanoma [24][25]. Thereafter, T-vec treatment was extended to other malignancies such as HNSCC, breast cancer, pancreatic cancer and sarcoma [21][26]. OV therapy frequently causes adverse events such as fever, fatigue, nausea, malaise, and increased liver function, which are associated with viral infections. Severe adverse events, including hypotension, tachycardia, cellulitis, dyspnea, and pleural effusion, have also been reported [27]. However, the lack of severe late-onset and permanent dysfunction observed as a sequela of surgery and chemoradiotherapy (CRT) suggests that OV therapy can be used in combination with radiotherapy and chemotherapy. Indeed, the therapeutic effects of T-vec and an ICI on melanoma were

doubled compared with the administration of these alone [28][29], suggesting that ICIs can be concomitant agents with OV. Although OV can be administered by intratumoral or intravenous injection, HNSCC develops at a site near the surface, which has the advantage of being treated by direct administration of the virus to the tumor.

2. Current OV Therapy for HNSCC

Viruses currently employed in clinical studies for HNSCC include DNA viruses, such as herpes simplex virus type 1 (HSV-1), vaccinia virus and adenovirus, and RNA viruses such as reovirus, measles virus and vesicular stomatitis virus (VSV) [19][21][26] (Table 1). In these viruses, virulence genes were deleted to reduce their pathogenicity, the virus was altered to selectively infect tumors and a foreign gene, such as a cytokine gene, was added to increase tumor immunity. As RNA viruses, virus strains that are originally low in pathogenicity, tumor-selective, and highly oncolytic are used. The mechanisms of tumor-selectivity of OVs are different in each OV, but RAS expression in tumor cells and the IFN system may play important roles in HSV-1 and reovirus. Other mechanisms are also involved, such as selective replication of thymidine kinase (TK) gene-deleted vaccinia virus in cancer cells and p53 mutation and/or loss of p14arf dependence of an E1B-55kDa gene-deleted adenovirus [23]. The choice of virus for HNSCC depends on whether the administration is systemic or local. In particular, HSV-1 cannot be administered intravenously because it is rapidly neutralized by the existing antibody against HSV-1.

Table 1. Clinical trials of oncolytic virotherapy for HNSCC.

Virus Type	Virus Name	Clinical Phase	Number of Patients	Route of Administration	Co-Therapy	Type of Cancer	Ref
HSV-1 (JS1 strain)	T-Vec	I/II	17	i.t.	RT+cisplatin	HNSCC, stage III/IV	[30]
		Ib	36	i.t.	pembrolizumab	HNSCC, recurrent, metastatic	[31]
HSV-1 (HF strain)	HF10	I	17	i.t.	—	breast cancer, HNSCC, pancreatic cancer, recurrent and non-resectable	[32]
Vaccinia virus (Lister strain)	GL-ONCI	I	19	i.v.	RT+cisplatin	HNSCC, locoregionally advanced	[33]
	MVA-EL	I	16	intradermal	—	nasopharyngeal carcinoma, EB positive	[34]
Adenovirus type 5	ONYX-015	II	37	i.t.	—	HNSCC, recurrent	[35]

	AdGV.EGR.TNF.11D	I	14	i.t.	RT+5FU +hydroxyurea	HNSCC, irradiated, unresectable, recurrent	[36]
Reovirus type 3 (Dearing strain)	REOLYSIN	I/II	31	i.v.	carboplatin, paclitaxel	solid tumors including HNSCC, heavily pretreated	[37]

RT, radiotherapy; i.t., intratumoral; i.v., intravenous.

Herpesviridae: HSV-1 is a typical DNA virus that has been investigated as an oncolytic virus and replicates in the nucleus. The majority of adults are infected and usually have antibodies to neutralize free viruses. The genome size is approximately 150 kb, which is sufficient to insert foreign genes [38]. T-Vec is a recombinant human HSV-1 lacking γ34.5 and viral ICP47 genes, which accelerates the expression of US11 gene, and encodes granulocyte-macrophage colony stimulating factor (GM-CSF) [39]. In the treatment of advanced melanoma, the combination of T-Vec with the ICI ipilimumab or pembrolizumab resulted in an objective response rate of 18% for ipilimumab alone versus 39% for the combination. In Phase Ib clinical studies, when patients with advanced melanoma were treated with T-Vec and pembrolizumab, the objective response (OR) and complete response (CR) were 62% and 33%, respectively, which confirmed that T-Vec was more effective when used in combination with an ICI, being a typical example of successful combinational immunotherapy [28][29]. For HNSCC, T-vec injection into metastatic lymph nodes before surgery and CRT promoted the highly degenerative changes on metastatic lymph nodes [30]. Recently, a multicenter phase 1b/3 trial for 36 patients with recurrent or metastatic HNSCC refractory to platinum-based chemotherapy was performed to determine the effects of a combination of T-Vec and pembrolizumab. One dose limiting toxicity (DLT) of T-vec-related fatal arterial hemorrhage was reported. Other than this DLT, there were no treatment-related fatal adverse events. A confirmed partial response (PR) was observed in 5 (13.9%) patients. Ten (27.8%) patients were unevaluable due to early death. The median progression-free survival (PFS) and overall survival (OS) were 3 months (95%CI, 2.0–5.8) and 5.8 months (95% CI, 2.9–11.4), respectively. The efficacy of the combination was similar to that of pembrolizumab monotherapy in historical HNSCC studies [31]. HF10 has a deletion in the UL56 gene and has cell fusion ability. It was previously administered for solid tumors, including pancreatic cancer and HNSCC, and was slightly effective [32][40]. In nine pancreatic cancer patients who completed the treatment, tumor responses were three PR, four stable disease (SD) and two progressive disease (PD) [40]. In preclinical studies, G47D-mIL12, a G47DHSV-1 expressing murine IL-12, was combined with antibodies against ICs (CTLA-4, PD-1 and PD-L1), overcoming the highly immunosuppressive TME of murine glioblastoma and eradicating the mouse tumors [41]. Inhibition of the TGF-β signaling pathway was reported to be beneficial for OV treatment with HSV-1 [42]. The combined use of EGFR-CAR-transduced NK-92 cells with oncolytic HSV-1 had superior antitumor effects on brain metastases of breast cancer compared with the administration of each alone [43].

Poxviridae: As no antibody against vaccinia virus is present in most adults, it can be administered intravenously to infect both primary and distant metastatic lesions. In a phase I clinical study, the safety of GL-ONCI, formally named GLV-1h68, was examined in 19 patients who had locally advanced HNSCC without distant metastases by intravenously viral administration. GL-ONCI was constructed by inserting three expression cassettes encoding Renilla luciferase-Aequorea green fluorescent protein fusion, galactosidase, and b-glucuronidase into F14.5, J2R encoding thymidine kinase and A56R encoding hemagglutinin loci of the genome, respectively [44]. A systemic rash developed as an adverse event. At 30 months of follow-up, the 2-year PFS and OS were 64.1% and 69.2%, respectively [33]. In a phase Ib study, patients with platinum-resistant /refractory recurrent ovarian cancer received repeated intraperitoneal injection of GL-ONCI. Disease control (PR+CR > 15 months) was observed in 55% of the patients [45]. As a preclinical study, vvDD with a double-deletion of the genes encoding TK and the vaccinia growth factor (VGF) was constructed, and its antitumor effects were examined in murine colon and ovarian cancer models in vitro and in vivo. vvDD attracted effector T cells, and induced PD-L1 expression in both cancer and immune cells [46]. Furthermore, vvDD-DAI, which overexpresses the intracellular pattern recognition receptor, the DNA-dependent activator of IFN-regulatory factors (DAI), was prepared in order to increase IFN production and innate and passive immunity. Compared with vvDD alone, administration of vvDD-DAI increased tumor-infiltrating $CD8^+$ T cells into the tumor, translating into better efficacy against melanoma in mice [47]. Myxomavirus (MYXV) that belongs to *Poxviridae* family was also altered by deleting the M0111L gene encoding the Bcl-2 homolog from wild-type MYXV, and the lack of Bcl-2 homolog sensitized brain tumor cells to virus-induced cell death and the survival of

tumor-bearing mice was prolonged in an immunocompetent model of glioblastoma [48]. Epstein–Barr virus (EBV) is associated with several malignancies, including nasopharyngeal carcinoma. A therapeutic vaccine, MVA-EL, was produced using the modified vaccinia Ankara vector to encode a functional inactive fusion protein of full-length LMP2 and the C-terminal half of EBNA1 [34]. In phase I trials, patients with nasopharyngeal carcinoma received intradermal MVA-EL vaccination. After vaccination, immunity increased to at least one antigen in 8/14 patients (7/14, EBNA1; 6/14, LMP2), including recognition of epitopes [49].

Adenoviridae: Although adenovirus is a small DNA virus with a genome size of 26–45 kb, foreign genes can be integrated and a variety of mutant viruses have been constructed [50]. An E1B-55kDa gene-deleted adenovirus, ONYX-015, was developed for treatment of tumors lacking p53 function [35]. In a phase II clinical trials, 37 patients with recurrent HNSCC received intratumoral and peritumoral ONYX-015 injection, and highly selective tissue destruction was observed; significant tumor regression (>50%) was noted in 21% of evaluable patients [35]. A E1 substituted replication-incompetent recombinant adenovirus encoding the p53 gene Ad-p53 was injected intratumorally or intraoperatively in combination with surgery and CRT to treat patients with stage III-IV hypopharyngeal cancer and lymph node metastasis. The OS and disease-free survival (DFS) were significantly extended in the surgery+CRT+rAd-p53 group compared with those in the surgery+CRT group [51]. AdGV.EGR.TNF.11D is a non-replicating adenovirus that expresses human TNF-α under the control of the radiation-inducible promoter (EGR-1). AdGV.EGR.TNF.11D was administered intratumorally and combined with 5-FU and hydroxyurea for the treatment of recurrent HNSCC patients receiving re-irradiation. The response rate was 83.3% and the average survival time was 9.6 months [36]. As a preclinical study, LOAd703 armed with costimulatory CD40L and 4-1BBL was constructed. Infection of LOAd703 was associated with dendritic cell (DC) maturation/expansion, which in turn increased the activation/expansion of NK and tumor-specific T cells, leading to oncolytic activity against pancreatic cancer cells [52]. Delta-24-RGD adenovirus, also called DNX-2401, is a virus in which an RGD peptide motif was introduced into adenovirus fibers to promote interaction with tumor integrins and 24 base pairs were deleted in the E1A gene to restrict replication in tumor cells with abnormalities in the p16/RB/E2F pathway. This was injected to patients with recurrent malignant glioma and resulted in good responses with long-term survival [53]. Bispecific T cell-engagers (BiTEs) represent a new-class of immunotherapeutic molecules consisting of two-single-chain variable fragments (scFv) connected by a flexible linker. One scFv binds to the T lymphocyte marker CD3, whereas the second scFv is directed against one tumor antigen expressed on the surface of tumor cells. By co-engaging T cell effectors and cancer cells, BiTEs can mediate immune-mediated tumor cell lysis [54][55][56][57]. An oncolytic adenovirus, ICOVIR-15K expressing a BiTE antibody targeting EGFR was previously constructed [55]. The virus secretes BiTEs, which bind specifically to $CD3^+$ and EGFR+ cells. After the transfer of mononuclear cells to tumor-bearing mice with EGFR-expressing tumor, administration of ICOVIR-15K into the tumor resulted in persistent accumulation of cytotoxic T cell (CTL) and increased antitumor effects. In CAR-T cell therapy, HER2-specific CAR-T cells alone cannot cure solid tumors in the immunosuppressive microenvironment of tumors [18]. The presence of adenovirus-encoded IL-12p70 can prevent the disappearance of HER2- and CAR-expressing T cells at the tumor site. Therefore, adenovirus expressing IL-12p70 and encoding the PD-L1 blocking antibody, CAd12-PDL1, was constructed [18]. When HNSCC xenografts in mice were treated with HER2 and CAR2.CAR-T cells in combination with CAd12-PDL1, the survival rate of the mice was approximately 25 days with either approach, while it was extended to over 100 days by the combined therapy with the control of distant metastasis.

Reoviridae: Reovirus is a double-stranded RNA virus that can grow in RAS-expressing cells. It can be delivered to tumors by intravenous administration and kill tumor cells with few side effects. In a phase I/II study, a total of advanced 31 patients, including 14 with HNSCC, were treated with reovirus type 3 Dearing (RT3D) in combination with taxanes. One (3.8%) patient had CR and 6 (23.1%) had PR, suggesting activity in cancer of the head and neck [37]. A phase II study of reovirus in combination with paclitaxel or carboplatin was conducted for pancreatic adenocarcinoma and melanoma. In the case of pancreatic cancer, the addition of reovirus was not superior to carboplatin/paclitaxel [58]. As a preclinical study in mice, the combination of reovirus with anti-PD-1 antibody enhanced the therapeutic efficacy against subcutaneous melanoma in mice. This showed that checkpoint inhibition increased both NK cell-mediated tumor cell killing and CD8+ T cell antitumor immune responses while reducing Treg activity [59].

Paramyxoviridae: Measles virus is a minus single-stranded RNA virus. Due to its systemic dissemination properties, intravenous administration can be used as a delivery route. MV-NIS is a detoxified measles virus Edmonton strain that expresses the sodium/iodide symporter (NIS) [60]. CD46 acts as a cell-side receptor during the entry of measles virus and the oncolytic efficacy of MV-NIS is highly correlated with the density of CD46 receptors on target cells. Numerous ions in addition to iodide are transported efficiently by the NIS protein, which enables NIS expression imaging with readily available radioisotopes, such as iodine-123, iodine-125, or technetium-99m, which can be detected by radiation (PET) or

single-photon emission computed tomography combined with computed tomography (SPECT/CT) [61]. NIS expression on the surface of infected cells facilitates uptake of radioisotopes, and when used in combination with an isotope, the antitumor effects of MV-NIS are increased in HNSCC cells [62].

Rhabdoviridae: VSV is a negative-strand RNA virus with low preexisting immunity in humans. VSV has high oncolytic potency and causes strong induction of the innate immune response. VSV encoding the interferon beta transgene (VSV-IFNβ) has increased specificity for tumor cells versus normal healthy tissue. The use of the IFN-β transgene provides tumor specificity by protecting cells whose IFN response is normal and only enables replication in cells with a defective IFN pathway. [63]. In a preclinical study, intratumoral or intravenous administration of VSV-IFNβ resulted in growth delay of SCC and improved survival compared with controls [64], and the anti-tumor function for VSV-IFNβ significantly increased when combined with ICIs in CT26 colon cancer and B16-F10 melanoma mouse models [65].

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