Japanese Dental Science Review (2016) xxx, xxx–xxx

Contents lists available at ScienceDirect

Japanese Dental Science Review

journal homepage: www.elsevier.com/locate/jdsr

Review Article

Presage of oncolytic virotherapy for oral cancer with herpes simplex virus

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Received 17 May 2016; received in revised form 2 October 2016; accepted 8 October 2016

KEYWORDS
Herpes simplex virus;
Oncolytic virotherapy;
Oral cancer

Summary A virus is a pathogenic organism that causes a number of infectious diseases in humans. The oral cavity is the site at which viruses enter and are excreted from the human body. Herpes simplex virus type 1 (HSV-1) produces the primary infectious disease, gingivostomatitis, and recurrent disease, labial herpes. HSV-1 is one of the most extensively investigated viruses used for cancer therapy. In principle, HSV-1 infects epithelial cells and neuronal cells and exhibits cytotoxicity due to its cytopathic effects on these cells. If the replication of the virus occurs in tumor cells, but not normal cells, the virus may be used as an antitumor agent. Therefore, HSV-1 genes have been modified by genetic engineering, and *in vitro* and *in vivo* studies with the oncolytic virus have demonstrated its efficiency against head and neck cancer including oral cancer. The oncolytic abilities of other viruses such as adenovirus and reovirus have also been demonstrated. In clinical trials, HSV-1 is the top runner and is now available for the treatment of patients with advanced melanoma. Thus, melanoma in the oral cavity is the target of oncolytic HSV-1. Oncolytic virotherapy is a hopeful and realistic modality for the treatment of oral cancer.

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http://dx.doi.org/10.1016/j.jdsr.2016.10.001

Please cite this article in press as: Yura Y. Presage of oncolytic virotherapy for oral cancer with herpes simplex virus. Japanese Dental Science Review (2016), http://dx.doi.org/10.1016/j.jdsr.2016.10.001

1. Introduction

Head and neck cancer accounts for 6% of all malignancies worldwide. Oral cancer is included in head and neck cancer, is the fifteenth most common malignancy globally, and accounts for approximately 1% of all malignancies in Japan. Most cases of oral cancer are squamous cell carcinoma (SCC). Surgery, radiation, chemotherapy and the combination of these modalities are common therapeutic methods to treat patients. The therapeutic effects of chemoradiotherapy using cisplatin markedly improved 5-year overall survival over radiotherapy alone; however, survival rates in advanced cases are still low [1,2]. A recent aspect is the introduction of molecular target therapy using an antibody against the epidermal growth factor receptor (EGFR), cetuximab. The treatment of locoregional advanced head and neck cancer with concomitant high-dose radiotherapy plus cetuximab has improved locoregional control and reduced mortality [3], although cisplatin-based chemoradiotherapy remains the standard of care until equivalence with radiotherapy plus cetuximab is reproducibly demonstrated [4].

Immunotherapy with biological response modifiers (BRMs) including OK-432 (picibanil) and BCG has been used to enhance antitumor immunity and biological responses have been reported; however, their effects on tumor immunity have been non-specific [5]. Tumor antigen-specific vaccinations have since been perceived as a potentially effective approach to improve outcomes by mobilizing antitumor immunity and reversing immune escape in cancer patients. Phase 1 studies using survivin-derived peptides and p53 peptide vaccines for patients with head and neck cancer were found to be safe and achieved moderate clinical outcomes [6,7]. On the other hand, efforts to restore latent antitumor immunity have focused on antibody-based interventions targeting cytotoxic T lymphocyte antigen 4 (CTLA-4) and programmed cell death protein 1 (PD-1) on T cells and its principal ligand (PD-L1) on tumor cells. The immune checkpoint inhibitor to either PD-1 or PD-L1 has produced significant antitumor activity with markedly less toxicity than the CTLA-4 inhibitor. In clinical trials on these immune checkpoint inhibitors, positive responses were observed in patients with melanoma, renal cancer, lung cancer, bladder cancer, and head and neck cancer [8,9].

Another recent advance in cancer treatments is the use of viruses that destroy tumors, *i.e.*, oncolytic viruses. Since some viruses exhibit oncolytic abilities, attempts to use viruses as antitumor agents were made in the 1950s [10]. In Japan, the mumps virus was used and clinical effects were observed in 37 out of 90 terminal cancer patients; however, further clinical studies were not performed [11]. On the other hand, a virus is the most reliable vector to transfer human genes into deficient individuals. In 1990, a clinical trial on gene therapy was initiated to transfer the adenosine deaminase (ADA) gene into the T cells of two children with severe combined immunodeficiency using a retrovirus to deliver the gene [12]. Gene therapy was also applied to the treatment of cancer. For example, the wild-type tumor suppressor gene p53 carrying a retrovirus or adenovirus was introduced into lung cancer patients in whom the p53 gene was mutated in order to restore the function of wild-type p53 [13,14]. Repeated intratumoral injections of adenovirus (Ad-p53) were tolerated well, resulted in the transgene expression of wild-type p53, and appeared to mediate antitumor activity in a subset of patients with advanced lung cancer. Viruses for gene therapy are generally replication-restricted in order to prevent the endless spread of viral infection in the body. A virus infects appropriate target cells, introduces genes into the cells, and its replication is then terminated. Target cells that acquire a tumor suppression gene are destroyed by the action of the gene, whereas cells devoid of the infection survive, and its effect on cancer is gradually lost, resulting in the failure of this therapy. This is a limitation of replication-restricted viruses. As a next step, replication-competent viruses were reconsidered as a tool to destroy a larger number of tumor cells by inoculated viruses and progeny viruses (Fig. 1). This concept was proposed by Martuza, a doctor of neurosurgery [15]. Mar-

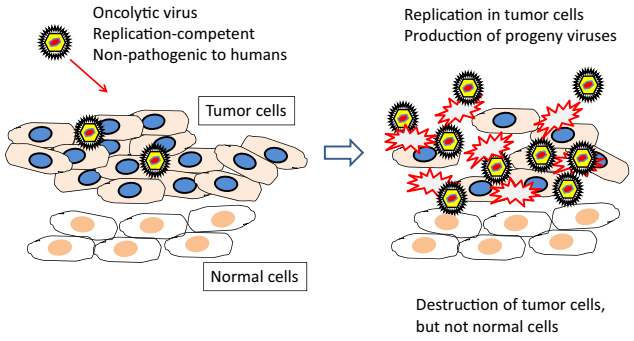

Figure 1 Schematic representation of selective killing effects of oncolytic viruses on tumor cells.

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