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Review Article

Role of Gene Therapy in Head and Neck Cancers: A Review

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***ABSTRACT*:**
Standard approach to the treatment of head and neck cancer include surgery, chemotherapy, and radiation. More recently, dramatic increases in our knowledge of the molecular and genetic basis of cancer combined with advances in technology have resulted in novel molecular therapies for this disease. In particular, gene therapy, which involves the transfer of genetic material to cells to produce a therapeutic effect, has become a promising approach. The aim of this review is to analyse the different modalities of gene therapy currently used to manage precancerous and cancerous lesions of the oral cavity.

Keywords: Squamous cell carcinoma, gene therapy, viral vectors.

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INTRODUCTION

Oral cancer (OSCC, for Oral Squamous Cell Carcinoma) is a genetic disease in which the genes that control cell growth and apoptosis are mutated, allowing cells to acquire the ability to invade and metastasize. Despite research efforts and new therapies, five-year survival has not improved over the past 4-5 decades. Patients with recurrent oral cancer that is refractory to chemotherapy or radiotherapy have a life expectancy of only months and the response rate to second- and third-line treatments is only 15%. This situation could drastically change over the next few years, thanks to the revolution in our knowledge of the disease brought about by molecular studies, which have already allowed us to differentiate between premalignant and malignant conditions. The introduction of new genes and the activation or inactivation of others may inhibit or suppress tumour growth. Gene therapy can potentially attack cancerous cells while respecting normal tissue. It may be useful to manage disease recurrence and as a co-adjuvant therapy, e.g., in resected tumour margins. Clinical application of this technique in the treatment of oral cancer and precancer requires optimization of viral vectors and improvement of transfection effectiveness.[1] As defined in the government's genetics white paper in 2003, gene therapy is ''the deliberate introduction of genetic material into patient's cells in order to treat or prevent a disease''. Early gene therapy research was directed at disorders with a single, identifiable genetic defect such as severe combined immunodeficiency disease (SCID), cystic fibrosis and haemophilia.[2] The goal of gene therapy is to introduce new genetic material into cancer cells that will selectively kill cancer cells with no toxicity to the surrounding non-malignant cells. In OSCC this is an attractive treatment for two reasons.

First, tumors are often accessible for direct injection of genetic therapeutic agents. Second, locoregional failure remains the predominant pattern of failure and cause of death among patients with recurrent disease. Recently, clinical trials of gene therapy in OSCC have been completed and many data suggest the possibility and feasibility of this approach together with more conventional modality treatment such as radiation therapy and chemotherapy. Gene therapy involves the introduction of foreign DNA into somatic cells to produce a therapeutic effect. A variety of vectors have been used to transfer genes into cells. Viral vectors remain the gene transfer vehicles of choice, with retroviral and adenoviral vectors constituting 25% of all viral vectors currently in use in clinical trials. Several strategies have been developed for cancer gene therapy including 1) Replacement of tumor suppressor gene function; 2) Blockage of dominant oncogene function; 3) Oncolytic virus therapy, which selectively kill tumor cells but not normal cells; 4) Genetic prodrug activation therapy; 5) Genetic immunomodulation. These approaches may converge and can often be used in combination to amplify potential therapeutic effects.[3]

Gene therapy approaches to oral cancer and precancer

OSCC is a good candidate for gene therapy because primary and recurrent lesions are readily accessible for injection or application of the agent.[4] Current gene therapy approach includes- Addiction gene therapy in which there is regulating tumour growth by introducing tumour suppressor genes that inactivate carcinogenic cells. Numerous studies have described p53 alteration as an early event in oral cavity carcinogenesis, and mutated p53 expression is frequently observed in non-cancerous epithelium adjacent to OCSS.[5] Moreover, the percentage of epithelial cells expressing mutated p53 is usually higher with greater severity of the epithelial disorder. For these reasons, one of the tumour suppressor genes most commonly used in gene therapy is the p53 gene, and numerous viral vectors, especially adenoviral vectors, have been developed for its application. Some authors analysed the efficacy of gene p53 to inhibit tumour growth as a function of the use or not of adenovirus vectors with replicative capacity. Results showed that efficacy was higher when the replicating vectors were used, although the reasons for this improvement are not fully understood.[6] A phase III study is currently under way on adenovirus vector Ad5CMV-p53. This is applied by intramucosal injection followed two hours later by a mouthwash. From the next day, it is administered as a mouthwash twice a day for 2-5 days. This treatment is repeated every 28 days and has shown a capacity to inhibit disease progression in precancerous lesions with no toxic effects.[7] Other tumour suppressors introduced into tumour cells by gene transfer are Rb (retinoblastoma gene) and mda-7 (melanoma differentiation-associated gene-7). Their effects on apoptosis and tumour growth appear to be similar to those of interleukin-24 (Il-24), a Th1 cytokine that triggers an anti-tumour and pro-apoptotic response in the immune system.[8] Gene transfer of gene p27 was found to inhibit the cell cycle of tumour cells, inducing apoptosis and triggering the suppression of tumour growth. It has been demonstrated that gene p27 mutations are highly related to the appearance of tongue cancer. According to these results, the therapeutic use of p27 gene may in the future prove useful for the treatment of OSCC.[9] One of the most promising gene therapy approaches is the use of viruses that replicate only tumour cells, designated oncolytic viruses. This procedure emerged from the discovery of adenoviruses lacking E1B, which did not grow in normal cells but grew in cells without p53, one of the most common characteristics of tumour cells. Adenovirus ONYX-015, which presents deletion of the E1B region, has been used to control OSCC lesions.[10]

Table 1- Gene therapy approaches in oral cancer and precancer.

GENE OR LEVEL OF ACTION	VECTOR USED/APPROACH	MECHANISM OF ACTION
Mutated or altered P53	Adenovirus ONYX-015	Increases replication in cells with altered p53 (OSCC) by using adenovirus or ONYX-015
Mutated or altered P53	Adenovirus ONYX-015	Reduction of leukoplakias
Alteration of Rb protein	OAS403	Controls expression of gene E4 and decreases *in vivo* and *in vitro* toxicity
MnSoD gene	Addiction G.T	Suppresses tumour malignity by reducing peroxide flow and therefore cell mitosis
Anti-ICAM-2	Immunotherapy	Complete regression of oral cavity tumours
MDR1, MRP1, DHFR	Suicide G.T	Reduces tumour angiogenesis, increases apoptosis, modifies immune system

***MnSOD: Manganese Superoxide Dismutase, MDR1: Multidrug resistant protein 1, MRP1: Multidrug related protein, DHFR: Dihydrofolate-reductase, GT: Gene Therapy, OAS-Oncolytic Adenovirus. ICAM- Intercellular Adhesion Molecule.*

DISCUSSION

The prognosis of patients with Squamous Cell Carcinoma of the Head and Neck is poor. The goal of gene therapy is to introduce new genetic material into cancer cells that will selectively kill cancer cells with no toxicity to the surrounding non-malignant cells. In OSCC this is an attractive treatment for two reasons. First, tumors are often accessible for direct injection of genetic therapeutic agents. Second, locoregional failure remains the predominant pattern of failure and cause of death among patients with recurrent disease. Recently, clinical trials of gene therapy in OSCC have been completed and many data suggest the possibility and feasibility of this approach together with more conventional modality treatment such as radiation therapy and chemotherapy.[12] (Table 1) As anticancer agents, viral products have an excellent profile and do not appear to enhance the toxicity of either chemotherapy or radiation making them good candidates for combined modality treatment strategies. The most frequently reported adverse events with adenoviral products are fever and chill, asthenia, injection site pain, nausea and vomiting. However, the vast majority of these adverse events are mild to moderate. Efficacy is limited to loco-regional control. In head and neck cancer, local and/or regional tumor recurrence develops in approximately one-third of patients, despite definitive treatment. Two-thirds of patients dying of this disease have no evidence of symptomatic distant metastases. Therefore, local and regional disease control is paramount in this disease, underscoring an urgent need for more effective local therapies. The promise of adenovirus mediated gene therapy has not yet translated in patient survival primarily because of the inability to deliver the therapeutic gene to a large number of cells. Further optimization of vectors will be essential for the improvement of clinical effectiveness of cancer gene therapy.[3]

CONCLUSION

Gene therapy in HNSCC remains confined to trials but seems likely to progress to clinical use in combination with conventional modalities. Cancer of a single cell type in a single organism is heterogeneous at the molecular level. The subtyping of these malignancies is still in its infancy. When more is known, more specific gene therapies will be able to be tailored accordingly.

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