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Radioactive iodine: An unappreciated threat to salivary gland function

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Abstract

Thyroid cancer is an endocrine malignancy whose prevalence is increasing in the United States. Nearly 57,000 new cases of thyroid cancer are estimated to be diagnosed in 2017. The standard of care for differentiated thyroid cancer is thyroidectomy followed by ablation of thyroid remnants with high-dose radioactive iodine (^{131}I). Apart from thyroid glands, ^{131}I accumulates in cells of salivary glands and compromises its function. Xerostomia is, therefore, a frequent and often persistent complaint of patients. Despite adoption of standard preventive measures, parenchymal damage and chronic salivary dysfunction are observed in a substantial number of patients. Saliva is important for oral homeostasis, and its reduction increases the risk of oral morbidity. As differentiated thyroid cancer patients have an excellent survival rate, preservation of salivary gland function carries added significance. A focus on treatments that preserve or restore long-term salivary flow can significantly improve the quality of life of thyroid cancer survivors.

Keywords

radioiodine; salivary hypofunction; thyroid cancer; xerostomia

1 INTRODUCTION

Thyroid cancer is the most common primary endocrine malignancy, whose prevalence worldwide has steadily increased. It is estimated that the disease will afflict 56,870 Americans in 2017, with women accounting for ~75% of cases (Siegel, Miller, & Jemal, 2017). Over 90% of thyroid cancers are differentiated papillary or follicular thyroid carcinomas, and they have an excellent prognosis due to the non-aggressive nature of the disease and effectiveness of ^{131}I therapy. Standard treatment of differentiated thyroid cancer is a near-total or total thyroidectomy followed by high-dose ^{131}I treatment for ablation of tumor remnants. Incorporation of ^{131}I has effectively reduced disease recurrence and

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CONFLICT OF INTEREST

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mortality, and the 10-year overall survival rate exceeds 80% with patients reaching a normal residual life expectancy (Links et al., 2005).

Uptake of ^{131}I is near-specific to thyroid tissue, but its off-target accumulation in cells of the salivary glands is responsible for the observed side effects. Active accumulation of ^{131}I in follicular cells of the thyroid glands occurs through the sodium/iodine symporter. This transport system is present also on the basolateral membranes of striated ducts of salivary glands and is attributed to radioiodine accumulation in ductal cells (La Perle et al., 2013). However, similar to active uptake of ^{99m}Tc-pertechnetate by ATP-dependent $Na^+/K^+/Cl^-$-cotransport system, substitution of chloride results in ^{131}I accumulation in acinar cells of the salivary glands (Helman, Turner, Fox, & Baum, 1987).

2 RADIOIODINE AND XER OSTOMIA

Sialadenitis is a common salivary gland complication of ^{131}I therapy (Van Nostrand, 2011). Painful swelling of the salivary glands and an accompanying decrease in salivary flow are characteristics of the condition (Mandel & Mandel, 2003). Approximately 24% of the administered ^{131}I dose is secreted in saliva, and the host inflammatory response to radiation damage causes constriction of salivary ducts with salivary retention and symptoms of obstruction. Acute sialadenitis often resolves within days, but loss of fluid producing acinar cells and inflammatory scarring of salivary ducts often lead to recurrent exacerbations that portend chronic sialadenitis and xerostomia. The prevalence of chronic symptomatic salivary dysfunction (16–54%) and abnormal salivary gland scintigraphic findings (37%–72%) vary among studies (Clement et al., 2015), but because of the recognition of long-term side effects, the American Thyroid Association has issued guidelines in conservative use of ^{131}I in low-risk thyroid cancer patients (Kim, Yousman, Wong, Cheng, & McAninch, 2016). Xerostomia following ^{131}I treatment was shown to be dose related with a dose–response relationship between activity (>100 mCi; 3.7 GBq) and symptoms of salivary morbidity (Dingle, Mishoe, Nguyen, Overton, & Gillespie, 2013). An important determinant of severity of salivary toxicity was cumulative radioiodine dose. Patients exposed to cumulative activity >150 mCi (5.55 GBq) were more likely to suffer from xerostomia and associated complications (Jeong, Kim, Lee, Ahn, & Lee, 2013; Dingle et al., 2013). In a recent prospective study of patients that received cumulative ^{131}I of 100–150 mCi (3.7 to 5.5 GBq), a reduction in stimulated saliva was noted in 34% of patients at the 5 month follow-up visit, and a high dose was associated with ≥50% drop in saliva in 10% of patients (Klein Hesselink et al., 2016). More importantly, an assessment of long-term salivary function at 5 years found that 16.4% patients complained of persistent xerostomia, and 47.4% patients had abnormal scintigraphy findings involving at least one major salivary gland (Jeong et al., 2013). Based on alterations in quantitative scintigraphy, a number of studies have suggested parenchymal damage as an underlying reason for salivary dysfunction (Caglar, Tuncel, & Alpar, 2002; Wu et al., 2015). Current management of xerostomia rests on symptomatic relief through the use of sialogogues and emollients, but in light of the normal residual life expectancy of patients, a definitive treatment for a long-lasting reprieve from dry mouth will greatly improve life for cancer survivors.

3 TREATMENT OF S ALIVARY GLAND DYSFUNCTION

High success rates of thyroid treatment were found to correlate well with high doses of radioiodine therapy (Song et al., 2015). Sparing of contralateral glands or stem cell-rich regions of salivary glands can be achieved using intensity-modulated radiotherapy in treatment of head and neck cancers (Murdoch-Kinch, Kim, Vineberg, Ship, & Eisbruch, 2008; van Luijk et al., 2015), but systemic administration of ^{131}I indiscriminately affects all salivary glands. In an effort to reduce salivary gland damage during ^{131}I administration, a common clinical strategy is to stimulate salivary flow with sialogogues such as sour candies or lemon juice, or parasympathetic agonists such as pilocarpine to reduce ^{131}I transit time through the glands. However, with no clear effect of a reduction in salivary morbidity, there is little evidence to support their use (Alexander, Bader, Schaefer, Finke, & Kirsch, 1998; Nakada et al., 2005). In fact, contrary to expectations, absorbed radiation dose to the glands was higher with lemon-induced salivary gland stimulation, than without, because of a corresponding increase in blood flow to the glands (Jentzen et al., 2010, 2014).

Amifostine is a cytoprotective agent that showed initial success at attenuating salivary gland toxicity of ^{131}I therapy in preclinical and early clinical investigations (Bohuslavizki et al., 1998; Kutta et al., 2005). However, with unclear evidence of radioprotection in randomized controlled clinical trials (Kim et al., 2008; Ma, Xie, Chen, Wang, & Zuo, 2009; Ma, Xie, Jiang, Wang, & Zuo, 2010), additional studies are warranted to confirm or refute its benefits. Usefulness of salivary endoscopy (sialendoscopy) in relieving obstructive symptoms and improving salivary flow in ^{131}I-induced sialadenitis was demonstrated in previous studies (Nahlieli & Nazarian, 2006; Strychowsky, Sommer, Gupta, Cohen, & Nahlieli, 2012). Duct dilation and removal of mucus plugs and debris had a favorable effect on salivary flow for up to 6 months (Bhayani et al., 2015); however, the procedure was of little value in alleviating xerostomia in patients with recalcitrant sialadenitis (Kim, Choi, Hong, Hyun, & Lim, 2016). In essence, sialendoscopy is a promising intervention for treatment of early, but not late, ^{131}I-associated sialadenitis.

Repurposing therapies that have demonstrated promise in ameliorating external beam radiation-induced salivary hypofunction in animal models provide hope of a substantive treatment that combats ^{131}I-induced salivary dysfunction. Retroductal delivery to salivary glands offers the opportunity to selectively target the organ for gene or protein therapy. Suppressing loss of salivary function by (i) increasing functional parenchyma through expression of growth factors such as keratinocyte growth factor (Lombaert et al., 2008; Zheng et al., 2011), (ii) overriding cell death with activation of prosurvival mechanisms through expression of sonic hedgehog protein (Hai et al., 2016) or knockdown of PKC delta (Arany, Benoit, Dewhurst, & Ovitt, 2013), or (iii) improving DNA repair capabilities of cells with tousled-like kinase 1 (TLK1) expression (Timiri Shanmugam et al., 2013) may provide long-term solutions to salivary morbidity. On the other hand, reversal of impaired salivary flow can be realized through aquaporin gene therapy. Aquaporin, a water-channel protein, was shown to effectively increase fluid output from dysfunctional salivary glands in preclinical studies and in a phase I/II human clinical trial on patients with radiotherapy-induced salivary function (Baum et al., 2006, 2012).

There is a small, but consistently higher, incidence of secondary primary malignancy in patients treated with ^{131}I (Lang, Wong, Wong, Cowling, & Wan, 2012; Ko, Kao, Lin, Huang, & Yen, 2015), and the use of viral vectors that carry a risk of insertional mutagenesis should be weighed. In this regard, episomal viral vectors, non-viral gene transfer, or alternately, direct protein transfer, are safer options. Taking into account the short half-life of ^{131}I, a radio-protective gene or protein therapy may be better-suited to tide-over the exposure period. Direct protein transfer of cell-permeable TLK1 better preserved salivary function against external beam radiation (Sunavala-Dossabhoy et al., 2012), and its usefulness against radioiodine damage is worth investigating.

4 CONCLUSION

The β-emitting iodine isotope ^{131}I has long been regarded as a magic pill in the treatment of thyrotoxicosis and thyroid cancer. Lower doses of ^{131}I are used to suppress an overactive thyroid, whereas high doses are reserved for destroying thyroid remnants after cancer surgery. As salivary side effects correlate with cumulative ^{131}I activity, dentists managing oral health of benign and malignant thyroid disease patients have a unique opportunity to intervene with measures that help keep oral complications to a minimum.

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