Editorial

Molecular radionuclide therapy-induced salivary gland toxicity: an unappreciated threat to patients' quality of life?

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Targeted molecular radionuclide therapy (MRT) has become an increasingly prominent nuclear medicine sub- specialty. For many decades, radioiodine (^{131}I) therapy for both benign and malignant thyroid conditions was the main therapy in practice. More recently, the field has seen an explosion of research and clinical trials testing new radiopharmaceuticals, particularly those targeting pros- tate-specific membrane antigen (PSMA) [1]. Increasing understanding of the molecular mechanisms of cancer in recent years, innovative pharmaceutical development, and the availability of new radioisotopes have enabled consid- erable advances in the field of MRT that could potentially revolutionize cancer treatment in the coming years.

Molecular radionuclide therapy is designed to act like a 'silver bullet'

Alpha- or beta-particle emitting radiopharmaceuticals aim to deliver a deleterious radiation dose directly at a cellular level, while having limited or no toxic effects on healthy tissues. In many MRT treatments, the bone marrow, liver and kidneys are considered organs at risk, either based on dosimetric analysis or clinical concerns. Salivary gland toxicity, however, often remains neglected or trivialized – reported as 'self-limiting' or 'easily prevented or treated' – or simply dismissed as 'avoidable by administration of large amounts of sour liquids during therapy' [2].

Salivary gland toxicity in molecular radionuclide therapy: what is the magnitude of the problem?

Radiation-induced toxicity to the salivary glands can man- ifest in a wide range of ways, including various degrees of sialadenitis (mouth swelling, or salivary gland or cervical pain), xerostomia (dry mouth) and mucositis, difficulties in mastication and swallowing (dysphagia), taste disturbance (dys- or hypogeusia), speaking difficulties, dental decay, and oral infections, such as candidiasis. Many of these symptoms can be lifelong and thus degrade the quality of life of long-term surviving patients [3]. Determining the exact prevalence and severity of these MRT-induced sal- ivary gland morbidities remains difficult. There are many reasons for this. First, there is great variability in patients' perception thresholds for reporting salivary problems, par- ticularly when the patient is unaware of the possibility of such side effects. Second, there is no format for the routine documentation of these side effects after therapy. Third, limited awareness in the nuclear medicine community and a lack of collaborative pathways with oral medicine specialists in dealing with these side effects could also be to blame. Fourth, there is limited research and consider- able variability in the outcome measures used in clinical research regarding salivary gland hypofunction, together with a lack of consensus or nuclear medicine guidelines on assessing, preventing and treating salivary gland dys- functions after MRT. The Common Terminology Criteria for Adverse

Events is a helpful tool to monitor adverse events in cancer trials. This, however, should be com- bined with the use of validated patient-reported outcome measures to capture the burden of salivary gland toxicity in terms of severity, duration, overall impact on general health and quality of life. Finally, other confounding var- iables, such as other xerostomic medications, the ageing process, hormonal changes (such as menopause), autoim- mune conditions or previous external radiotherapy to the head and neck region, may obscure the overall effect of radiopharmaceuticals [4].

What is the incidence of salivary gland toxicity in molecular radionuclide therapy? The very limited available evidence estimates that one out of three patients develops chronic salivary gland problems and becomes symptomatic after radioiodine ^{131}I treatment for thyroid cancer [5,6], whereas dysfunction of at least one salivary gland can be identified on scinti- graphic imaging in about 50% of cases [6]. Similarly, tran- sient salivary gland dysfunction was diagnosed in about one-third of ^{177}Lu-PSMA therapy patients [7], although milder xerostomia and dysgeusia symptoms were found to be more frequent, ranging from about 20 to 60% of cases [8,9]. Initially thought to occur quite rarely [10], salivary gland pain and xerostomia were demonstrated in 43 and 62% of patients, respectively, following high- specific-activity ^{131}I-meta-iodobenzylguanidine (MIBG) therapy for pheochromocytoma and paraganglioma [11]. Severe, grade III sialadenitis and mucositis have also been noted in these patients [12]. Importantly, salivary gland dysfunction (grade I/II) has been observed in the majority of patients (94–100%) treated with alpha- particle-emitting ^{225}Ac-PSMA therapy in metastatic castration-resistant prostate cancer [13]. There is insuf- ficient evidence available on patient-reported outcome measures relative to dry mouth and quality of life, or on the long-term functional and radiobiological effect of MRT on the salivary glands. Going forward, we will see salivary gland-related adverse effects more frequently as the adoption of PSMA-based MRT increases.

Why are many radiopharmaceuticals taken up in the salivary glands?

Understanding the mechanism of uptake and trapping of radiopharmaceuticals in the salivary glands is important when considering protective measures to the glands. The uptake can either be linked to specific cellular pathways or be inadvertently nonspecific. For example, the uptake of ^{131}I in differentiated thyroid cancers relies on the expression of sodium iodide symporter (NIS). As the sali- vary glands also express NIS, they naturally take up radi- oiodine and are exposed to high beta radiation [14]. In the case of ^{131}I-radiolabelled MIBG therapy, the intense radioactivity seen in the salivary glands is not due to dis- sociated ^{131}I derived from the ^{131}I-MIBG compound, as previously thought, but rather due to a specific uptake linked to the dense sympathetic neuronal elements within the salivary glands [15]. As another example, PSMA imaging and therapies are effectively targeting the high PSMA expression on prostate cancer cells compared to the low PSMA expression in normal tissues. Despite a low PSMA expression in the salivary glands proven by immunohistochemical studies [16], diagnostic imaging has often documented a rather high uptake of PSMA- targeted radiopharmaceuticals in the salivary glands, which is likely nonspecific. It is noteworthy that salivary gland toxicities have been the main limiting factor in dose escalation studies and a cause of treatment discon- tinuation for both ^{177}Lu-PSMA and ^{225}Ac-PSMA [16,17].

Is there a way to prevent molecular radionuclide therapy-induced damage to the salivary glands?

Preventing and reducing uptake, while increasing clearance of MRT radiopharmaceuticals and restoring the damage to the salivary glands from MRT is the logical approach to reduce salivary gland toxicity. Various preclinical and early clinical research studies have been conducted on methods to protect the salivary glands during MRTs. Some studies indicate that external massage to the salivary glands could have a beneficial role by expelling radioiodine-containing saliva or increasing the circulation and clearance of radiop- harmaceuticals from the glands via the bloodstream [18]. Conversely, others have suggested that external cooling of the salivary glands would be more effective in reduc- ing radiopharmaceutical uptake

due to vasoconstriction, but this failed to prove helpful in a systemic analysis [19]. Dehydration increases the risk of toxicity, whereas ade- quate hydration supports good salivary gland function [20]. The use of different sialagogues, including lemon juice or vitamin C, has also been suggested to increase salivation. But controversy persists on whether the use of these sialagogues should be delayed for 24 h, or implemented earlier (>2–24 h) or in the first 2 h after ^{131}I admin- istration, and on whether similar sialagogue regimens should be implemented in other MRT treatments [21,22]. Parasympathetic medication and amifostine have been tested in an attempt to prevent salivary damage; however, the use and effectiveness of these agents is still a matter of debate, mainly due to the limited evidence and lack of appropriate confirmatory studies [23]. Given the possibility of some specific binding of PSMA radiopharmaceuticals in the salivary glands, inhibitors of PSMA uptake, such as 2-(phosphonomethyl)pentanedioic acid [24], folic polygluta- mate [25] or monosodium glutamate [26], are also being investigated, but there is concern that their use would limit the overall therapeutic effect of MRT. Other radio- protective substances (e.g. botulinum toxin, short-acting anticholinergic agents, local anaesthetics, histamine, vita- min E, statins), have also been tested [27] but have not been incorporated yet into the clinical routine, as robust clinical evidence is lacking.

Treating molecular radionuclide therapy- induced damage to the salivary glands

Beyond prevention, there is even less information avail- able in the nuclear medicine literature on how to man- age or alleviate patients' symptoms when xerostomia or sialadenitis occur following MRT. The appropriate use of artificial saliva or various mouthwash products, the imple- mentation of intense sialorrheic managements (e.g. the 'Cincinnati regimen') [28], salvage sialendoscopy [29], and the prompt involvement of oral medicine specialists are important aspects that need to be considered when planning MRT.

In the near future, the salvage approach might rely on the regeneration of the salivary glands. An early clinical trial of head and neck patients after radiotherapy showed that ultrasound-guided transplantation of adipose tissue- derived mesenchymal stem cells is possible and can lead to a 33% improvement in salivary flow after radiation- induced xerostomia [30].

Conclusion

Despite the prospect of a bright future for MRT, the prevention of salivary gland damage in the field of MRT remains an unmet need today. Until we have a clearer understanding of the type of effects these treatments are having on patients and the time course of the effects, it will be challenging to work out the best methods to prevent their impact on the salivary glands. Establishing suitable protocols, however, to protect the salivary glands during MRT and assure better posttherapy management for damage mitigation are urgently needed to improve the outcomes and quality of life of patients undergoing MRT today and in the near future. Increased awareness of this issue amongst the nuclear medicine community and collaboration with oral medicine specialists might be the key to understanding this long-overlooked issue.

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Conflicts of interest

There are no conflicts of interest.

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