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PSMA-Targeted Radionuclide Therapy and salivary gland toxicity: why does it matter?

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The promise of PSMA-targeted radionuclide therapy is being demonstrated by a growing number of reports detailing institutional experience with various agents and prospective clinical trials are in progress to further establish the safety and efficacy of this approach in advanced, castrate-resistant prostate cancer. Although extremely promising, PSMA-ligand therapy remains a non-curative treatment and, therefore, the prolongation in survival and amelioration of disease-related symptoms must be balanced against the direct toxicities of the treatment and their impact on quality of life. Of these, xerostomia is amongst the most common and debilitating of these, particularly for ^{225}Ac-PSMA. The nature of this dysfunction is incompletely understood and strategies for its prevention and treatment are still under evaluation.

The salivary glands are divided into major (parotid, submandibular and sublingual glands) and accessory/minor groups. The amount of saliva secreted by the salivary glands is approximately 1L/day (70% arising from the major salivary glands). The salivary pH ranges from 6.5 to 7. Saliva has complex functions that act together to inhibit oral bacterial overgrowth and to protect dentition. Although salivary compounds have been fully characterized, saliva still remains impossible to synthetize. Radiotherapy-induced xerostomia is multifactorial. The primary cause of irreversible hyposalivation is loss or impairment of acinar cells and their progressive replacement by connective tissue and fibrosis. The mechanisms involved are both the loss of functional glandular stem/progenitor cells and the impairment of microvasculature and parasympathetic innervation. Below the threshold of 50 Gy, severe dysfunction to gland tissue is rare, and radiation damage is generally transient and reversible. In irradiated patients, the saliva becomes more viscous and more acidic; which compromises the antibacterial action of saliva. Salivary hypofunction is the objective decline in salivary flow, while xerostomia is the subjective perception of dry mouth by the patient. Hyposalivation and its corollary xerostomia are common (68–91%) in long-term irradiated patients with head and neck cancer. Hyposalivation exacerbates tooth decay and periodontal disease. Irradiated patients complain about problems of mastication, swallowing, sleep, and speech, xerostomia inducing a burning sensation of the mouth, and dysgeusia. All taken together, these symptoms severely impair the quality of life of patients. The morbidity of irradiation related to salivary gland dysfunction can be scored with specific grading systems developed by the Radiation Therapy Oncology Group (RTOG).

Similar side effects may be obtained by targeted internal radiotherapy with small molecules targeting the prostate specific membrane antigen (PSMA), which are being used for therapy of metastasized prostate cancer. Although immunohistochemistry shows a rather heterogeneous PSMA staining with only low to moderate staining intensity the uptake of

radiolabeled small molecule based PSMA ligands is high, suggesting both specific and non-specific tracer accumulation, with the mechanism of the latter remaining unclear. The frequency and the extent of the resulting symptoms are dependent on the absorbed dose and the isotope used. In contrast to small molecules radiolabelled anti-PSMA, antibodies show only a low uptake in the salivary glands (*1*) supporting the hypothesis that the accumulation of small molecule inhibitors of PSMA is at least partially non-specific.

A first iteration of PSMA-directed radionuclide therapy of advanced, castrate resistant prostate cancer used ^{131}I. This study involved 28 patients and was in the pre-abiraterone and pre-enzalutamide era. Seven of these 28 patients treated with one administration of ^{131}I-labelled MIP1095 reported a slight to moderate xerostomia, and, in one patient, mucositis was detected. These side-effects recovered after 3 to 4 weeks (*2*). Multiple administration (up to three fractions) were considered in a further 34 patients. In this analysis, xerostomias higher than grade 1 occurred more frequently in patients receiving a higher number of fractions. Again, most patients reported recovery from xerostomia after a few weeks. However, the duration of the symptoms was longer after the second or third therapy in most cases (*3*). Data for xerostomia after therapy with ^{177}Lu-labelled PSMA-617 are available from different groups. In an analysis of 30 patients treated with 3 cycles of 6 GBq, most of the patients reported no relevant dysfunction of salivary glands (*4*). Substitution of saliva (spray/gel) was prescribed for 2 patients who developed xerostomia after the third cycle. After the first and second cycles only transient xerostomia was occasionally observed. Similar data were obtained from a multicenter analysis of 145 patients with mild to moderate xerostomia reported for only 11 (8%) patients (*5*). In conclusion, at therapeutically relevant activities, ^{177}Lu-labelled PSMA rarely leads to symptoms. In contrast, although leading to excellent therapeutic effects even with complete remissions in a considerable number of cases ^{225}Ac may lead to a destruction of the salivary glands (*6*). This seems to be a function of the activity

administered to the patient. Treatment activities of 50kBq/kg were without toxicity but induced insufficient anti-tumor response in patients with high tumor burden. However, an increase in administered activity led to severe xerostomia becoming the dose-limiting toxicity if treatment activity exceeded 100kBq/kg per cycle (*6*). From a dosimetry standpoint, there is a wide inter-patient variability both in tumor and healthy tissues, including the salivary glands. The range of absorbed dose delivered to the salivary glands per administered activity ^{177}Lu-DKFZ-PSMA-617 varied from 0.8 to 2.5 Gy/GBq (*4, 7, 8*). Regardless of the methodology implemented, all approaches relied on planar imaging and used OLINDA sphere module to evaluate the absorbed dose delivered to salivary or parotid glands. In a recent article, Kratochwil *et al.* reported dosimetric estimates for ^{225}Ac-PSMA-617 based on the extrapolation of the pharmacokinetics obtained with ^{177}Lu-PSMA-617 reported in their previous article (*6*). The substitution of a beta emitter (such as ^{177}Lu) by an alpha emitter (225Ac) has dramatic dosimetric implications with huge absorbed dose gradients.

Preventive strategies have not been successful in mitigating these side-effects of salivary gland function (local cooling, lemon juice and vitamin C, displacement strategy using PMPA) (*9, 10*). Accordingly, other than developing ligands with lower salivary gland uptake, prospects for preventing salivary gland radiotoxicity appear limited, except by reducing administered activity, which may compromise therapeutic efficacy. However, it may be that higher administered activities are achievable with the first cycle of treatment when tumor burden and PSMA-binding affinity are highest and provide the protective benefit of tumor-sink effect on salivary uptake. Alternatively, radioprotectors, such as amifostine, could be considered but may also reduce radiosensitivity in tumor sites.

Accepting that some degree of salivary gland dysfunction is likely, therapeutic interventions to reduce its impact on quality of life become relevant. The first-line treatment for radiotherapy-induced salivary gland dysfunction in head and neck cancer patients is use of

sialagogues, namely pilocarpine and cevimeline, with proven efficacy in all stages of hyposalivation. However, as muscarinic receptor agonists, their use is limited by poorly tolerated side-effects. On the other hand, salivary substitutes and mouthwash have no proven effect on hyposalivation but can temporarily relieve xerostomia symptoms. It is likely that these approaches will be similarly effective in the setting of PSMA-related salivary gland toxicity.

Future prospects for salivary gland preservation may include several approaches such as intraglandular injection of botulinum toxin or several compounds (e.g., vitamin E, MnBuOE) or sialendoscopy which has shown clinical improvement in patients with radioiodide-induced sialadenitis. The most promising approach to addressing the problem of radiation-induced hyposalivation appears likely to be therapies that lead to regeneration of salivary tissue, including intraglandular gene therapy (e.g., Aquaporin-1, Sonic hedgehog), down-regulation of key regulators of DNA damage-induced apoptosis (antisense therapy) and stem cell therapy.

At present ^{177}Lu- and ^{225}Ac-labelled PSMA ligands are done predominantly after failure of all guideline-conforming therapies and therefore treated patients usually have a limited life-expectancy, which offsets the duration of possible side effects. Nevertheless, accumulating evidence suggests that stratification of risk of salivary gland toxicity balanced against the likelihood of therapeutic benefit is needed to select the appropriate patients for treatment, the optimal isotope and the appropriate administered activity. Introduction of alpha therapy earlier in the course of the disease should be done in the setting of prospective studies, because this may need a reduction of administered activity. However, a reduction of administered activity may limit therapeutic efficacy, which is a strong argument for a controlled systematic assessment of the therapeutic window.

Attempts to prevent xerostomia have been largely unsuccessful and therefore more work is required to optimize administered activity in order to balance the risk of salivary toxicity with therapeutic effectiveness. Improved prospective radiation dosimetry models will need to be developed. Efforts to further improve our understanding of the mechanisms of non-specific uptake of PSMA ligands in the salivary glands may lead to new preventive strategies while improved treatments of salivary gland dysfunction, if these can be identified, are also important. We await the results of ongoing gene therapy trials with interest.

Compliance with ethical standards

NA

Conflicts of interest

The authors have nothing to disclose.

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