

Xerostomia in patients undergoing anticancer therapy

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Abstract

Xerostomia, commonly referred to as dry mouth syndrome, is the result of a decrease or absence of salivary flow, producing mucosal thirst. It is usually caused by systemic autoimmune diseases, including diabetes, neurological disorders and Sjögren's Syndrome, however dry mouth itself is associated with a variety of mood disorders and anxiety disorders and their treatment; and, several medicines are reported to cause xerostomia in at least 10% of users. Therapeutic options include agents that act as saliva and mimic and provide temporary relief of xerostomia, however they do not promote the production of salivary and are therefore considered a cure for alternative restorations.

Medications such as chemotherapy, pain medication, anti-depressants, diuretics (water pills) can cause xerostomia. When caused by damage to the salivary gland, it can be a lifelong problem and requires patience in treatment. Radiation also causes dry mouth when salivary glands are exposed to radiation. This article summarizes xerostomia in patients undergoing anticancer therapy.

Keywords: Xerostomia, saliva, chemotherapy, radiation damage, salivary glands, saliva substitutes

Introduction

Saliva can indicate the present condition of the human body and is a very important health indicator.¹ Interestingly, patients who complain of xerostomia often do not show any signs of intent hyposalivation and their symptoms are likely to return to a change in and/or a change in size in saliva formation.² Xerostomia, commonly referred to as dry mouth syndrome, is a result of decreased weight or poor circulation.³ Patients with xerostomia include symptoms such as mucosal dryness, mouth discomfort and taste change,^{4,5} broken and crooked lips, and dry nasal passages.⁶ These symptoms can lead to simple activities such as swallowing, talking and sleeping being difficult and painful.^{4,5,7,8} If left untreated, xerostomia can significantly reduce the oral pH, thus increasing the cellular composition and caries.^{4,9} In fact, 3 out of 10 adults suffer from gum disease and tooth decay due to xerostomia.¹⁰ Xerostomia is also a leading cause of oral candidiasis, a common oral disease⁵ and has been reported to be more common in women than in men,¹¹ and is more common in the elderly,^{12,5,6,9,13} where approximately one in five reported the condition.⁵

While not associated with various diseases as a component, xerostomia is often considered to be a common side effect in many drugs, for example, drug use is the most common cause of xerostomia^{12,5,9} due to some effects on salivary hypofunction in the mouth.^{1,6,14,15} Xerostomia is said to be more common in people taking large doses of drugs^{5,16,17} and / or taking high doses of the drug.^{1,14} In opposition to pharmacological studies, it has actually been shown that it is a better predictor of dry mouth than age or sex.^{12,18} However, at present we were unable to predict the differences between drugs depending on how xerogenic they were.

It is common for you to sometimes have a dry mouth if you are physically or emotionally paralyzed, but a dry mouth may be a sign of a serious illness or condition. If you have a rare dry mouth (known as xerostomia) it is important to consult your dentist. Dry mouth is defined as the result of a decrease in the amount of saliva in the mouth. Dry mouth is also known as xerostomia. Xerostomia can make it difficult to talk, eat, and digest food and lead to poor nutrition. Xerostomia remains an unresolved grievance especially for the people of the economic region in spite seeking medical or dental consultation.¹⁹

Dry mouth is a common side effect of cancer treatment, which is found most frequently among patients undergoing targeted radiotherapy especially in the head and neck. This condition can last for several months, or it can be permanent if the salivary glands are damaged during radiotherapy. Dry mouth is also common among patients taking certain

chemotherapy regimens known to increase saliva intake and cause dry mouth. Even the available evidence is limited, with patients on certain drugs known to include salivary gland hypofunction. Another treatment option includes dose reduction of drugs or by substituting drugs with less xerogenic drugs.²⁰

Radiotherapy (RT) plays a major role in the treatment of Head and Neck Chemotherapy, whether as a single-dose modality or in combination with chemotherapy, surgery, or both.^{21,22,23} Higher delivery methods, such as Intensity Modulated Radiation Therapy, excise large salivary glands more often because of the proximity of primary tumors and lymph nodes^{24,25} with several secondary outcomes representing a challenge in multidisciplinary groups.²⁶

Xerostomia is the most common and most prominent adverse effects during and after Head and Neck Chemotherapy radiotherapy due to damage to the salivary gland.^{25,27} Approximately 70% of patients receiving Head and Neck Chemotherapy radiotherapy develop hyposalivation with significant changes in volume, consistency and pH of open saliva disease.²⁵ Due to the large and sensitive changes in saliva, patients are at increased risk for oral and dental diseases with significant deterioration in quality of life.^{25,27} Xerostomia can continue for as long as 6 months to several years after Radiotherapy. The severity of the damage was determined by the salivary function before treatment, the location of the salivary tissue exposed the total radiation exposure and the individual response.^{28,29}

Several treatments with different protocols such as cytoprotectants (amifostine), Intensity Modulated Radiation Therapy, cholinergic stimulants, submandibular gland transmission, intraoral stent and stem cell therapies have been administered against xerostomia. Apart from this, there is little improvement in the ability to prevent this limitation. The purpose of this study was to review current information regarding xerostomia in patients undergoing anticancer therapy in order to discuss the real-world view of reducing the incidence and severity of the problem.

Several medications can cause dry mouth, such as those used to control allergy, cold symptoms, or hypertension, as well as other ways to relieve pain. Talk to your doctor or pharmacist, or check the details that come with your medication to see if dry mouth can be a good result. Other medical treatments, such as head and neck radiation, can affect salivary gust and reduce or decrease the normal flow of saliva. There are personal habits, such as

breathing in the mouth, drinking alcohol, or using tobacco products, which can dry your mouth.³⁰

Dry mouth is usually caused by a decrease in the amount of salivary flow or a change in the biochemical composition. Patients with dry mouth often have difficulty chewing, swallowing, or talking. Let us not forget that drugs with the most powerful xerostomizing effect are the most widely used and frequently used (the treatment of iron disorders and cardiovascular diseases).³¹

Chemotherapy drugs can change the type of saliva and the amounts produced. Radiation in the head and neck can damage the salivary gland, causing a marked decrease in saliva production.³²

Anticancer drugs which cause xerostomia

Depending on the mode of its action they can be categorized into the following groups

ANTI CANCER DRUGS
(1) antimetabolites
(2) alkylating agents
(3) natural products including mitotic inhibitors, antibiotics and enzymes
(4) random synthetics
(5) hormones

Alkylating agents
Oxazaphosphorines : Cyclophosphamide, Ifosfamide
Nitrogen mustards: Busulfan, Chlorambucil, Melphalan
Hydrazine: Temozolomide
Platinum-based agents: Cisplatin, Carboplatin, Oxaliplatin

Topoisomerase inhibitors:
Topoisomerase I inhibitors :Irinotecan ,Topotecan

Topoisomerase II inhibitors : Etoposide , Teniposide	Anthracyclines Doxorubicin Daunorubicin Idarubicin
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Mitotic inhibitors:	
Vinca alkaloids, Vincristine Vinblastine	Taxanes Docetaxel Paclitaxel

Antimetabolites :
Antifolates, Methotrexate, Pemetrexed
Pyrimidine antagonists, Cytarabine, 5-Fluorouracil (5-FU), Gemcitabine, Capecitabine
Purine analogs: 6-Mercaptopurine (6-MP), Azathioprine (prodrug for 6-MP)
Purine antagonists: Fludarabine
Ribonucleotide reductase inhibitors, Hydroxyurea (hydroxycarbamide)

Others
Antibiotics: Bleomycin, Actinomycin D, Mitomycin,
Enzymes: L-asparaginase
Proteasome inhibitors: Bortezomib
Tyrosine kinase inhibitors: Imatinib, Erlotinib

*Adapted from reference (1)

Side effects

Oral complications of cancer treatment come in a variety of forms and difficulties, depending on the person and the cancer treatment. The degree and type of treatment toxicity is highly correlated with the level of complete patient protection before and during chemotherapy, the procedure itself, the frequency and volume of treatment, the method of administration, and the type of tumor. In many patients, these medications can cause a number of oral problems

including mucositis, pain, infection, hemorrhage, xerostomia, and neurologic and nutritional problems.

Patients with undiagnosed and metastatic cancer can benefit weaning (palliative) chemotherapy. With current guidelines, the first treatment is chemotherapy agent-turned-agent, e.g. cisplatin or carboplatin compound with a third-generation drug cytotoxic, gemcitabine, taxane (paclitaxel, docetaxel), or vinorelbine. Random Meta Analysis clinical trials comparing cisplatin and carboplatin suggest that the clinical effect of cisplatin is slightly higher than that carboplatin-based chemotherapy unless associated with an increase in toxic side effects.³³ Poor performance and high toxicity of chemotherapy has caused great confidence for many years in surgery or other methods, as a small positive effect on survival rates were seen.³⁴

Complications are a new medical problem that occurs during or after a disease, procedure, or treatment and that makes it difficult to recover. Complications can be side effects of a disease or treatment, or they can have other causes. Oral problems affect the oral health of patients. Cancer patients have a higher risk of oral complications for a number of reasons: Chemical and radiation therapy can slow or stop the growth of new cells. Chemical and radiation therapy stimulates the healthy balance of bacteria in the mouth. These changes can lead to mouth ulcers, infections, and tooth decay and make the mouth condition worse.

Possible side effects of radiation

Radiation therapy can cause skin reactions such as sunburn, mouth problems, trouble in swallowing, nausea, vomiting and fatigue. These usually cool down later in the treatment.

The most common side effect in the radiation of head and neck region is a reduction in saliva known as xerostomia which can lead to dry mouth. Radiation can also cause sore throat, sores in the mouth and throat, stiffness, difficulty swallowing, short-term taste loss, bone pain and osteoporosis. Radiation can make dental problems worse, too. Most doctors recommend having your teeth checked by a dentist before starting radiation therapy to the head or neck area. In some cases, the dentist may also recommend removing certain teeth before treatment to reduce the chance of infections later.

In the largest salivary glands, radiation is only given to the face and neck and cancer. This reduces the risk of long-term side effects. But in rare cases, both sides of your face and neck may need radiation therapy. This can damage other saliva glands, resulting in permanent dry

mouth. This often causes problems with eating and swallowing and can lead to tooth decay. Gastrointestinal injury can be reduced if a drug called amifostine (Ethyol®) is given before each radiation treatment. This drug can be hard to tolerate, so it is not helpful for everyone.

Radiation therapy can also damage the thyroid gland, which may appear up to months or even years later. A blood test to check for thyroid function will be done during follow-up (after the treatment is completed). Some patients may need to take pills to replace the thyroid hormone at some point. Although the means of development are great reduced rt3-related toxicity, many patients are still experienced side effects of rt.³⁵

It is important to discuss the side effects of radiation treatment with your doctor before starting treatment, and make sure everything is done to try to minimize these issues as much as possible. If you have side effects, there are ways to reduce many of them, so be sure to discuss any problems with your cancer care team.

Principles for Management of xerostomia patients undergoing anticancer therapy

An important goal of xerostomia treatment: the promotion of secretion that possess the potential of providing the benefits of natural saliva. Oral dry patients will remain chronic patients, so the development of continuous preparation is long-term management.

The management of Xerostomia and Salivary Gland Hypofunction can be divided into seven basic goals:

- Drinking Water
- Promotion of salivary flow
- The replacement of saliva or its substitution
- Reduce the loss of soft tissue
- Protect caries and improve re-collection
- Protect against soft tissue injury and disease
- Improve comfort

Saliva replacement:

In some cases, when it is difficult to use salivary glands or the salivary gland injury is irreversible, the only option may be a saliva substitute.

There are two treatments in case of metabolic dysfunction which are forms of alternative therapy. The endo native approach includes pharmacological, mechanical stimulation, genetic solutions. The supernatural approach precedes drinking water, moisture preparations and salivary replacement.³⁶

Saliva substitution may contain substances of the natural environment (salivary macromolecules such as mucins, lysozyme, lactoferrin) that provide high biocompatibility. However, these compositions are mainly designed for the replacement of rheological modifiers^{37,38} (xanthan and garlic gum, carboxymethyl cellulose (CMC), glycerol), electrolytes, preservatives, and sweeteners. Many authors^{39,40} analyze the literature data in clinical and laboratory experiments. The results of the study indicate that in patients with xerostomia (especially after radiotherapy), commercially available tender preparations appear to significantly reduce the symptoms of dry mouth. Mostly, however, these are oral lubricants, which replace the need for regular watering, softening the mucous membranes and reducing mouth discomfort. In general, softening the oral mucous membrane reduces symptoms, although the effects are temporary.⁴¹ New types of drying spaces, usually in the form of twins or orally, attempt to mimic some of the properties of human saliva and contain antimicrobial substances and have a specific spitting and rebuilding properties. Unfortunately, the data on the proper use of these settings is confusing. Literature data have a certain risk of bias,⁴² studies were performed on a small group of patients and contained less information. Generally, according to previous results,^{43,44} mucin-based substitution has been shown to be better than carboxymethylcellulose-based preparations due to the folding and softening properties. However, there is no data on complex new arrays that may have similar physicochemical, rheological and lubricating properties such as saliva, containing lubricants, and sites of immunomodulatory and remineralization.

Management of xerostomia in patients undergoing anticancer therapy

Oral problems are more common in patients with cancer, especially those who deliver chemotherapy. Reducing side effects is an important part of cancer care and treatment. This is palliative care or supportive care. Dry mouth cannot be prevented, but other treatments may help. The following guidelines should be followed to combat and reduce the symptoms of dry mouth.

(1) Medicines that prevent or reduce the negative effects of radiation therapy, such as amifostine (Ethyol).

- (2) Replacement of Saliva and oral muscles with hyetellose, hyprollose, or carmellose.
- (3) Medicines that stimulate the salivary gland, such as pilocarpine (Salagen) or cevimeline (Evoxac).
- (4) Other ways to stimulate salivary glands, such as sucking on sugar-free sweets or chewing sugar-free gum.
- (5) Acupuncture, one study suggests may help with dry mouth.

Dental problems can be prevented:

- Visit your dentist before starting radiation or chemotherapy to check for oral and dental health. Plan this as soon as possible. If you need dental removal, it should be done at least 3 weeks before treatment to keep your mouth healed.
- Brush your teeth after each meal and at bedtime with a gentle brush and fluoride tooth. Soak the brush with warm water to make the bristles soft even.
- Floss gently once a day.
- Clean your mouth 4 to 6 times a day, especially after meals, with salt and baking powder. Try a solution of half a teaspoon of salt and half a teaspoon of baking soda in 1 cup of warm water.
- When radiation therapy is started, use fluoride rinses and gels. These are an important part of maintaining your oral health during cancer treatment.
- Drink a few glasses of water throughout the day, and use saliva to form your mouth.
- Avoid oral primers and other dental products containing alcohol. Products for people with dry mouth are available without a prescription.

Use a light cleaner, especially at night.

- Some dentists may also offer toothpaste or rinses to treat infections in the mouth. Consider the following tips for treating dry mouth:

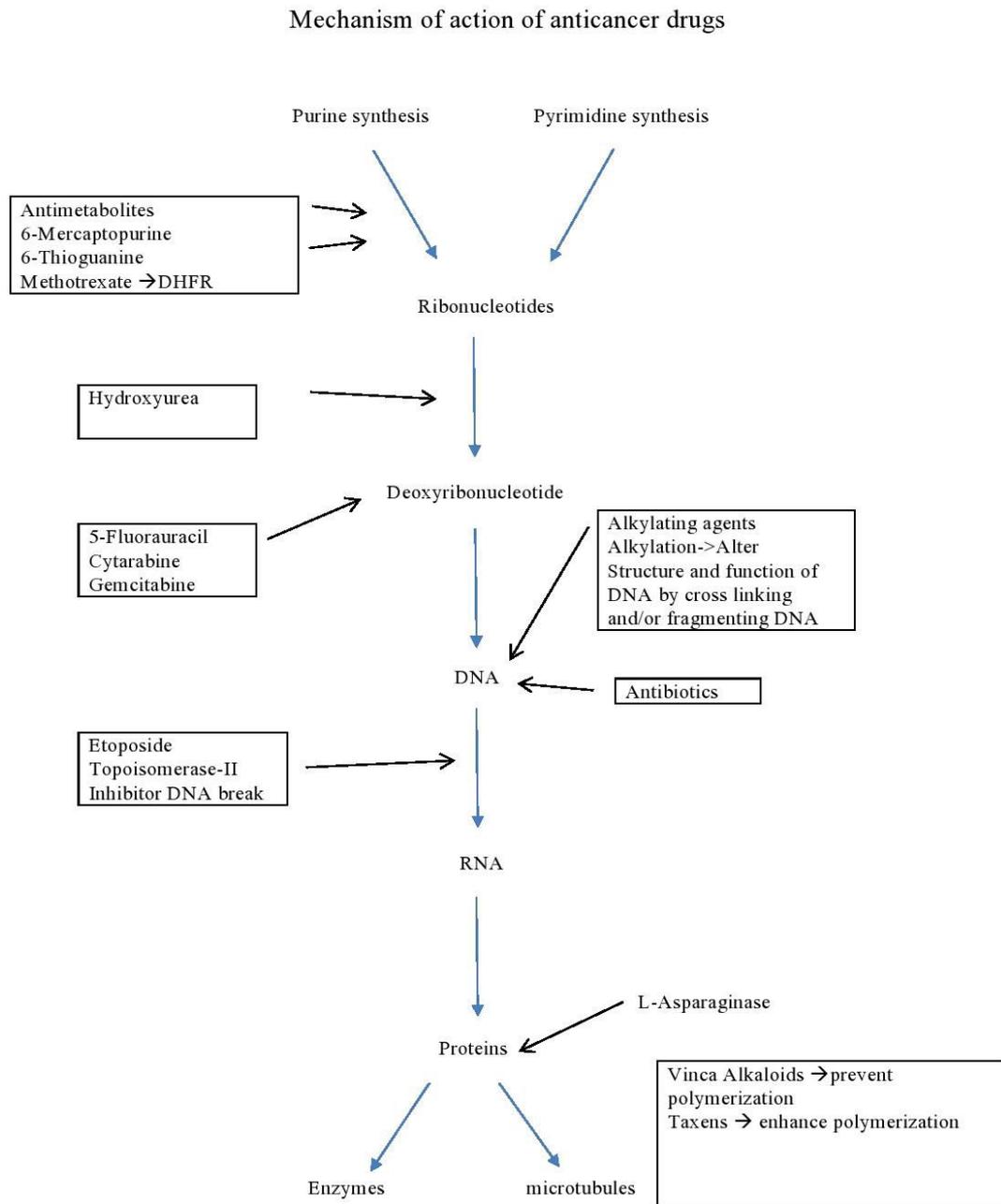
Drink at least eight cups of water a day. Carrying a bottle of water can help you drink enough.

- Avoid alcohol, drinks with caffeine (such as coffee, tea, and sugar), and acid soaps.
- Eat soft or hot food for room.
- Moisten dry foods with broth, sauces, butter, or milk.
- Avoid dry, packaged or solid foods.
- Avoid acid or spicy foods that may burn your mouth.
- Do not smoke or chew tobacco.
- Avoid sticky, sugary foods and drinks.

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Legends:

Fig 1: Mechanism of action of anticancer drugs (adapted from Ref. no. 36)



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