**Treatment with cryotherapy for reducing cancer therapy-associated oral side effects**

**Summary**
Cooling the mouth (oral cryotherapy) to manage and prevent oral side effects (mainly mucositis) during cancer therapy has been used and studied for more than 25 years now. There are several research reports and clinical reviews on the use of ice balls, ice chips, ice cubes, crushed ice, and flavored ice to manage cancer therapy-associated oral mucositis.

**Background**
The primary oral side effect of cancer chemotherapy and radiotherapy is mucositis, which results in scarring of mucosal tissue in the mouth, causing swelling, discomfort, and pain. This leads to delays in treatment or complete cessation of treatment in many cases. It can also lead to poor drug absorption, and may result in oral infections such as the fungal infection candidiasis.

A range of treatments to address this problem have been attempted, including pain killing drugs (anesthetics, analgesics), oral coating agents to soothe the condition, anti-inflammatory drugs, antimicrobials to prevent infection and worsening of the condition, and non-drug alternatives including nutritional supplements, laser therapy, and ice therapy. Basic oral care and hygiene is considered an important part of any such treatment.

The earliest reports of cooling the mouth using ice to manage side effects of cancer chemotherapy and radiation therapy can be traced back to the early 1990s.

This report summarizes all existing information of the use of ice and related treatments to address the problem of oral mucositis in cancer patients undergoing chemotherapy and radiation therapy. The information is classified based on the source, consisting of research articles, medical reviews, clinical trial data, product information, and other non-technical literature such as magazine articles or other web-based media. Information sources are cited and included in the report with hyperlinks wherever possible. All downloaded literature has been collated.

**Research Articles**
A study in 1991 by the Cedar Rapids Oncology Project in Iowa hypothesized that blood vessel constriction due oral cryotherapy would prevent chemotherapy drugs from reaching oral mucosa and causing side effects such as mucositis. This is the first documented study to use ice chips placed in patients’ mouths before chemotherapy, in an effort to prevent oral side effects. The study used 5-fluorouracil as chemotherapy.
A research article published in 1991 mentions the use of “ice packs within the mouth” to show that it reduces blood flow to the nasal mucosa. Ice packs applied to the forehead did not affect blood flow to the nasal mucosa.

A follow-up of the above study in 1993 compared two durations of oral cryotherapy (30 minutes and 60 minutes) with 5-fluorouracil chemotherapy, and found no significant benefit of 60 minutes over 30 minutes of ice chip usage.

The use of ice balls containing Elase (ulcer-healing ointment containing fibrinolysin and DNAse) as a treatment for mucositis caused by cancer radiation therapy was reported by a Japanese research group in 1996.

In 1998, a study found that prophylactic ice chip cryotherapy was useful in preventing mucositis in edatrexate and carboplatin chemotherapy.

A study in 2005 compared the use of plain ice and flavoured ice for preventing oral mucositis due to 5-fluorouracil use. The study found that both were equally effective in reducing mucositis, but that plain ice caused fewer side effects such as nausea, sensitivity, and headache. The study recommended the investigation of unsweetened ice products such as frozen fruit juices as alternatives to plain ice.

A 2012 study found that one hour of treatment with crushed ice in healthy volunteers caused a decrease of approximately 13°C (approximately 55°F) in mouth temperature.

A study in 2013 reported the reduction of oral pain and mucositis due to radiation therapy, by the use of ice cubes placed in the mouth.
Reviews
Clinical practice guidelines issued in 2005 recommended 20-30 minutes of oral cryotherapy for patients receiving 5-fluorouracil or edatrexate. The guidelines recommend placing ice chips in the mouth starting five minutes before the chemotherapy bolus injections.


The multinational association of supportive care in cancer (MASCC) has released guidelines for the management of mucositis and associated complications. Their 2005 and 2014 guidelines recommend the use of ice for reduction of oral mucositis associated with certain types of chemotherapy.


A 2015 review in the journal of pain and symptom management lists provides an excellent overview of supportive cryotherapy. It lists the use of ice chips, crushed ice, ice balls with allopurinol (anti-inflammatory), smooth ice cube, and flavored ice as different types of ice therapy.

- https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4013268/

Cochrane systematic reviews on keeping the mouth cold during cancer treatment support the use of oral cryotherapy and provide guidelines for achieving reductions in oral mucositis caused by chemotherapy.

- https://link.springer.com/article/10.1007/s00520-012-1562-0

The use of a range of agents including cryotherapy and laser treatment for oral mucositis reduction has been summarized in this review.

- https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4808317/

Clinical Trial Records
Two current U.S. clinical trials can be found with a goal of investigating the effect of cryotherapy in chemotherapy-induced mucositis in stem cell transplantation.

Three completed U.S. clinical trials have investigated the use of ice chips in patients receiving chemotherapy and/or stem cell transplantation.

- [https://clinicaltrials.gov/ct2/show/NCT01066624?term=ice+chips&draw=1&rank=5](https://clinicaltrials.gov/ct2/show/NCT01066624?term=ice+chips&draw=1&rank=5)
- [https://clinicaltrials.gov/ct2/show/NCT01789658?term=ice+chips&draw=1&rank=7](https://clinicaltrials.gov/ct2/show/NCT01789658?term=ice+chips&draw=1&rank=7)

**Other Literature including non-technical articles**

Overviews of oral mucositis and the various treatment possibilities including oral cryotherapy can be found in these general content websites:


- This is a very brief YouTube video with the title “ice pack for inside your mouth”, showing the use of an ice cube wrapped in a paper towel.
  [https://www.youtube.com/watch?v=-7CeqSsES0k](https://www.youtube.com/watch?v=-7CeqSsES0k)
- This is a very brief YouTube video summarizing the use of cryotherapy for mucositis.
  [https://www.youtube.com/watch?v=SAuNPGDC6hg](https://www.youtube.com/watch?v=SAuNPGDC6hg)
- This is YouTube video summarizing the strategies to cope with oral mucositis caused by cancer chemotherapy, briefly mentioning ice cubes and “ice lollies”.
  [https://www.youtube.com/watch?v=V_RtDMnZ7as](https://www.youtube.com/watch?v=V_RtDMnZ7as)