

Date: June 20, 2013

Title: Using oral cryotherapy to prevent oral mucositis in patients receiving chemotherapy

Clinical Question:

- P (*Population/Problem*) Among patients of all ages receiving chemotherapy
I (*Intervention*) does oral cryotherapy*
C (*Comparison*) compared to no intervention
O (*Outcome*) reduce the severity of, or prevent, chemotherapy-induced oral mucositis?

[Definitions for terms marked with * may be found in the Supporting Information section.](#)

Target Population for the Recommendation:

Inclusion: Oncology or bone marrow transplant patients being treated with bolus 5-FU, melphalan, or BEAC (high dose carmustine, etoposide, cytarabine, and cyclophosphamide) chemotherapy regimens

Exclusion: Patients with malignancies of the head or neck; patients who are unable to eat or drink; patients who are developmentally or physically unable to perform the intervention

Recommendation:

It is strongly recommended that patients being treated with bolus 5-FU, melphalan, or BEAC chemotherapy regimens receive oral cryotherapy during the infusion to prevent, or reduce the severity of, oral mucositis (Worthington et al., 2011 [1a]; Nikoletti, Hyde, Shaw, Myers, & Kristjanson, 2005 [2a]; Svanberg, Ohrn, & Birgegard, 2010 [2a]; Katranci, Ovayolu, Ovayolu, & Sevinc, 2012 [2b]).

Notes: There is not enough evidence to make a recommendation for or against the use of oral cryotherapy in patients being treated with methotrexate (Worthington et al., 2011 [1a]). There was no evidence found related to the use of oral cryotherapy with other chemotherapy drugs.

Discussion/Synthesis of Evidence related to the recommendations:

Oral cryotherapy has been shown to be effective in preventing and/or reducing the severity of oral mucositis when used with patients receiving certain chemotherapy regimens. Its use has been studied in patients being treated with bolus 5-FU, melphalan, and other myeloablative chemotherapy regimens, most commonly BEAC. In patients receiving bolus 5-FU, cryotherapy initiated five minutes prior to the start of the infusion and maintained for a total of thirty minutes was shown to significantly reduce the incidence and severity of mucositis ($p=0.008$) (Worthington et al., 2011 [1a]). A crossover trial conducted by Nikoletti et al., 2005 [2a] went a step further and studied the effects of plain ice versus flavored ice compared to saline mouth rinses for patients being treated with bolus 5-FU. The results of this study showed that both plain ice and flavored ice were effective in reducing the severity of oral mucositis. Also, patients who used saline mouth rinses were significantly more likely to develop mucositis than those who used either form of cryotherapy (Nikoletti et al., 2005 [2a]).

Oral cryotherapy was also found to be effective in preventing mucositis in patients being treated with melphalan (Worthington et al., 2011 [1a]; Svanberg et al., 2010 [2a]). The severity of mucositis was significantly lower in the patients who received cryotherapy during, and for up to six hours after the administration of melphalan, than in those who used saline mouth rinses (Worthington et al., 2011 [1a]). A randomized controlled trial found cryotherapy to be effective in preventing mucositis associated with melphalan when used in a much shorter time frame ($p < 0.05$); cryotherapy was initiated at the start of the infusion and stopped with the completion of the infusion (Svanberg et al., 2010 [2a]). In addition to melphalan, this trial also showed that cryotherapy was effective ($p < 0.05$) in reducing the severity of mucositis in patients receiving BEAC chemotherapy regimen prior to bone marrow transplant (Svanberg et al., 2010 [2a]). Secondary outcomes of the trial included decreased length of stay, reduced need for total parenteral

nutrition, and better nutritional status among patients who received cryotherapy during chemotherapy administration (Svanberg et al., 2010 [2a]).

Oral cryotherapy is a cost-effective and easily implemented nursing intervention that is well-tolerated by patients (Svanberg et al., 2010 [2a]; Katranci et al., 2012 [2b]). The most common adverse effects reported were headache and nausea (Nikoletti et al., 2005[2a]).

Reference List:

- Katranci, N., Ovayolu, N., Ovayolu, O., & Sevinc, A. (2012). Evaluation of the effect of cryotherapy in preventing oral mucositis associated with chemotherapy- a randomized controlled trial. *European Journal of Oncology Nursing*, 16, 339-344. [2b]
- Nikoletti, S., Hyde, S., Shaw, T., Myers, H., & Kristjanson, L. (2005). Comparison of plain ice and flavoured ice for preventing oral mucositis associated with the use of 5 fluorouracil. *Journal of Clinical Nursing*, 14, 750-753. [2a]
- Sonis, S., Eilers, J., Epstein, J., LeVegue, F., Liggett, W., Mullahga, M...Wittes, J. (1999). Validation of a new scoring system for the assessment of clinical trial research of oral mucositis induced by radiation or chemotherapy. *Cancer*, 85, 2103-2113. [3a]
- Svanberg, A., Ohrn, K., & Birgegard, G. (2010). Oral cryotherapy reduces mucositis and improves nutrition- a randomized controlled trial. *Journal of Clinical Nursing*, 19, 2146-2151. [2a]
- Worthington, H.V., Clarkson, J.E., Bryan, G., Furness, S., Glenny, A.M., Littlewood, A,...Khalid, T. (2011). Interventions for preventing oral mucositis for patients with cancer receiving treatment (Review). The Cochrane Collaboration. [1a]

IMPLEMENTATION

Applicability Issues:

Patients should be given small ice cubes that can be easily moved around in the mouth without causing irritation. Ice should be replenished as it melts, and patients should be instructed to move the ice in an attempt to keep the entire oral cavity cold (Katranci et al., 2012 [2b]). The use of flavored ice may be useful in promoting compliance in pediatric patients.

For bolus 5-FU, oral cryotherapy should be initiated five minutes prior to the start of the infusion and maintained for a total of thirty minutes (Worthington et al., 2011 [1a]). For melphalan and BEAC chemotherapy regimens, oral cryotherapy should begin at the start of the infusion and be maintained for the duration of the infusion (Svanberg et al., 2010 [2a]).

Relevant CCHMC Tools for Implementation:

None found

Outcome or Process Measures:

Mucositis should be assessed and measured daily using a tool that has been found to be valid and reliable. Although widely used, there is no evidence to support the validity or reliability of the World Health Organization mucositis assessment scale. The Oral Mucositis Assessment Scale (OMAS) was created as a research tool and has been shown to be valid and reliable (Sonis, et al., 1999 [3a]). For inpatients, mucositis should be assessed daily for at least 28 days after treatment. Outpatients should have mucositis assessments weekly, ideally at 7, 14, 21, and 28 days after treatment (Worthington et al., 2011 [1a]).

SUPPORTING INFORMATION

Background/Purpose of BES Development:

Oral mucositis is a common complication of cancer treatment. With symptoms ranging from mild pain to severe ulceration of the oral mucosa, oral mucositis can have serious adverse effects on patient quality of life (Worthington et al., 2011 [1a]). Mucositis can lead to poor nutrition, and may require the use of total parenteral nutrition if mouth sores are severe enough to prevent the patient from eating and drinking (Svanberg et al., 2010 [2a]). Oral ulcers place

immunocompromised patients at an increased risk for septicemia (Worthington et al., 2011 [1a]). Mucositis can cause significant pain, often requiring the use of narcotics or patient-controlled analgesia. Mucositis has also been associated with increased length of hospital stays and delays in cancer treatment (Worthington et al., 2011 [1a]). Despite the significant morbidity associated with mucositis, and the wide variety of prophylactic agents available, there is little consistency among institutions, and many commonly used interventions are not evidence-based (Worthington et al., 2011 [1a]).

Definitions:

Oral cryotherapy: the use of ice to cool the oral cavity

Search Strategy:

Databases: MedLine, CINAHL, Scopus, The Cochrane Library

Search Terms: mucositis, stomatitis, cryotherapy, chemotherapy

Limits, Filters, Search Dates: English language, humans, 1990-present

Date Last Search Done: 3.12.13

Relevant CCHMC Evidence-Based Documents:

None found

Group/Team Members: *(Name, Credentials, Specialty/Area of Expertise)*

Team Leader/Author: Stephanie L. Feist, RN BSN, Cancer and Blood Diseases Institute

Support/Consultant: Barbara K. Giambra, PhD(c), MS, RN, CPNP, Evidence-Based Practice Mentor- Research, Center for Professional Excellence, Research and Evidence-Based Practice

Ad Hoc/Content Reviewers: DeAnna Hawkins, RN, MSN NEA-BC, Cara Johnson RNIII, BSN, CPON®

Conflicts of Interest were declared for each team member:

- No financial or intellectual conflicts of interest were found.
- No external funding was received for development of this BEST.
- The following conflicts of interest were disclosed:

Note: Full tables of the [LEGEND evidence evaluation system](#) are available in separate documents:

- [Table of Evidence Levels of Individual Studies by Domain, Study Design, & Quality](#) (abbreviated table below)
- [Grading a Body of Evidence to Answer a Clinical Question](#)
- [Judging the Strength of a Recommendation](#) (dimensions table below)

Table of Evidence Levels (see note above):

Quality level	Definition
1a† or 1b†	Systematic review, meta-analysis, or meta-synthesis of multiple studies
2a or 2b	Best study design for domain
3a or 3b	Fair study design for domain
4a or 4b	Weak study design for domain
5a or 5b	General review, expert opinion, case report, consensus report, or guideline
5	Local Consensus

†a = good quality study; b = lesser quality study

Table of Language and Definitions for Recommendation Strength (see note above):

Language for Strength	Definition
It is strongly recommended that... It is strongly recommended that... not...	When the dimensions for judging the strength of the evidence are applied, there is high support that benefits clearly outweigh risks and burdens. (or <i>visa-versa</i> for negative recommendations)
It is recommended that... It is recommended that... not...	When the dimensions for judging the strength of the evidence are applied, there is moderate support that benefits are closely balanced with risks and burdens.
There is insufficient evidence and a lack of consensus to make a recommendation...	
<i>Given the dimensions below and that more answers to the left of the scales indicate support for a stronger recommendation, the recommendation statement above reflects the strength of the recommendation as judged by the development group. (Note that for negative recommendations, the left/right logic may be reversed for one or more dimensions.)</i>	
Rationale for judgment and selection of each dimension:	
1. Grade of the Body of Evidence	<input checked="" type="checkbox"/> High <input type="checkbox"/> Moderate <input type="checkbox"/> Low
<i>Rationale:</i> Worthington et al., 2011 [1a]; Nikoletti et al., 2005 [2a]; Svanberg et al., 2010 [2a]; Katranci et al., 2012 [2b]	
2. Safety/Harm (Side Effects and Risks)	<input checked="" type="checkbox"/> Minimal <input type="checkbox"/> Moderate <input type="checkbox"/> Serious
<i>Rationale:</i> Overall, oral cryotherapy was well-tolerated by patients. Patients with dentures that had to be removed during the intervention experienced some discomfort (Katranci et al., 2012 [2b]). Nausea, mouth sensitivity, and headache were the most common adverse effects, although it should be noted that nausea may be the result of the chemotherapy rather than the cryotherapy (Nikoletti et al., 2005 [2a]).	
3. Health benefit to patient	<input checked="" type="checkbox"/> Significant <input type="checkbox"/> Moderate <input type="checkbox"/> Minimal
<i>Rationale:</i> Oral cryotherapy during certain chemotherapy regimens has been shown to reduce the severity of, or prevent, oral mucositis (Worthington et al., 2011 [1a]). This can improve patient quality of life by reducing pain and improving nutrition (Svanberg et al., 2010 [2a]).	
4. Burden on patient to adhere to recommendation	<input checked="" type="checkbox"/> Low <input type="checkbox"/> Unable to determine <input type="checkbox"/> High
<i>Rationale:</i> Most patients reported being able to perform the intervention without difficulty for the duration of the infusion (Svanberg et al., 2010 [2a]).	
5. Cost-effectiveness to healthcare system	<input checked="" type="checkbox"/> Cost-effective <input type="checkbox"/> Inconclusive <input type="checkbox"/> Not cost-effective
<i>Rationale:</i> In addition to reducing the severity of mucositis, oral cryotherapy was shown to reduce the length of hospital stay, decrease the need for total parenteral nutrition, and improve the nutritional status of patients (Svanberg et al., 2010 [2a]).	
6. Directness of the evidence for this target population	<input checked="" type="checkbox"/> Directly relates <input type="checkbox"/> Some concern of directness <input type="checkbox"/> Indirectly relates
<i>Rationale:</i>	
7. Impact on morbidity/mortality or quality of life	<input checked="" type="checkbox"/> High <input type="checkbox"/> Medium <input type="checkbox"/> Low
<i>Rationale:</i> Chemotherapy can cause oral mucositis, which adversely affects patient quality of life by causing severe pain, interfering with eating and drinking, and placing the patient at an increased risk for infection (Worthington et al., 2011 [1a]). Oral cryotherapy has been shown to effectively reduce the severity of, or prevent, chemotherapy-induced oral mucositis (Worthington et al., 2011 [1a]).	

Copies of this Best Evidence Statement (BEST) and related tools (if applicable, e.g., screening tools, algorithms, etc.) are available online and may be distributed by any organization for the global purpose of improving child health outcomes.

Website address: <http://www.cincinnatichildrens.org/service/i/anderson-center/evidence-based-care/bests/>

Examples of approved uses of the BEST include the following:

- Copies may be provided to anyone involved in the organization's process for developing and implementing evidence based care;
- Hyperlinks to the CCHMC website may be placed on the organization's website;
- The BEST may be adopted or adapted for use within the organization, provided that CCHMC receives appropriate attribution on all written or electronic documents; and
- Copies may be provided to patients and the clinicians who manage their care.

Notification of CCHMC at EBDMinfo@cchmc.org for any BEST adopted, adapted, implemented, or hyperlinked by the organization is appreciated.

Please cite as: Feist, S., Cincinnati Children's Hospital Medical Center: Best Evidence Statement Using oral cryotherapy to prevent oral mucositis in patients receiving chemotherapy, <http://www.cincinnatichildrens.org/svc/alpha/h/health-policy/best.htm>, BEST 171, pages 1-5, 6/20/13.

This Best Evidence Statement has been reviewed against quality criteria by two independent reviewers from the CCHMC Evidence Collaboration. Conflict of interest declaration forms are filed with the CCHMC EBDM group.

Once the BEST has been in place for five years, the development team reconvenes to explore the continued validity of the recommendation. This phase can be initiated at any point that evidence indicates a critical change is needed. CCHMC EBDM staff perform a quarterly search for new evidence in an horizon scanning process. If new evidence arises related to this BEST, authors are contacted to evaluate and revise, if necessary.

For more information about CCHMC Best Evidence Statements and the development process, contact the Evidence Collaboration at EBDMinfo@cchmc.org.

Note

This Best Evidence Statement addresses only key points of care for the target population; it is not intended to be a comprehensive practice guideline. These recommendations result from review of literature and practices current at the time of their formulation. This Best Evidence Statement does not preclude using care modalities proven efficacious in studies published subsequent to the current revision of this document. This document is not intended to impose standards of care preventing selective variances from the recommendations to meet the specific and unique requirements of individual patients. Adherence to this Statement is voluntary. The clinician in light of the individual circumstances presented by the patient must make the ultimate judgment regarding the priority of any specific procedure.