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SPECIAL ARTICLE

Systematic review of oral cryotherapy for management of oral mucositis caused by cancer therapy

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Abstract
Purpose This systematic review analyzed the strength of the literature and defined clinical practice guidelines for the use of oral cryotherapy for the prevention and/or treatment of oral mucositis caused by cancer therapy.
Methods A systematic review on relevant oral cryotherapy studies indexed prior to 31 December 2010 was conducted by the Mucositis Study Group of the Multinational Association of Supportive Care in Cancer/International Society for Oral Oncology (MASCC/ISOO) using OVID/MEDLINE, with publications selected for review based on defined inclusion and exclusion criteria. Findings from the reviewed studies were integrated into guidelines based on the overall level of evidence for each intervention. Guidelines were classified into three types: recommendation, suggestion, or no guideline possible.
Results Twenty-two clinical studies and two meta-analyses were analyzed. Results were compared with the MASCC/ISOO guidelines published in 2007. The recommendation for the use of oral cryotherapy to prevent oral mucositis in patients receiving bolus fluorouracil (5-FU) was maintained, in agreement with the 2007 guidelines. A suggestion for use

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of oral cryotherapy to prevent oral mucositis in patients receiving high-dose melphalan as conditioning regimen with or without total body irradiation for HCST was revised from the 2007 guidelines. No guideline was possible for any other intervention, due to insufficient evidence.

Conclusions The evidence continues to support the use of oral cryotherapy for prevention of oral mucositis in patients receiving bolus 5-FU chemotherapy or high-dose melphalan. This intervention is consistent with the MASCC/ISOO guidelines published in 2007. The literature is limited by the fact that utilization of a double-blind study design is not feasible. Future studies that compare efficacy of oral cryotherapy with other mucositis agents in patients receiving chemotherapy with relatively short plasma half-lives would be useful.

Keywords Oral mucositis · Oral cryotherapy · Cancer

Introduction

Cryotherapy has been utilized in a number of clinical settings to reduce side effects of cancer therapy. The first report of this intervention for preventing 5-FU-associated mucositis was published in 1991 [1]. There have been multiple additional clinical trials performed during the subsequent years [2–23] as well as two meta-analyses [24, 25]. Mechanisms behind the intervention have not been studied in detail. However, promotion of vasoconstriction resulting in reduction in delivery of cytotoxic drugs to at-risk tissue, as described by Mahood et al. [1], generally continues to be viewed as the most likely modeling.

The following recommendations for use of oral cryotherapy for oral mucositis were reported by the MASCC Mucositis Study Group in 2007 [26]:

Standard-dose chemotherapy: prevention

The panel recommends that patients receiving bolus 5-FU chemotherapy undergo 30 min of oral cryotherapy to prevent oral mucositis.

The panel suggests the use of 20 to 30 min of oral cryotherapy to decrease mucositis in patients treated with bolus doses of edatrexate.

High-dose chemotherapy with or without total body irradiation plus hematopoietic stem cell transplantation (HSCT): prevention

The panel suggests the use of cryotherapy to prevent oral mucositis in patients who are receiving high-dose melphalan as a conditioning agent in HSCT.

Cryotherapy was recommended in the previous guidelines for the prophylaxis of oral mucositis in patients who were receiving bolus 5-FU and possibly edatrexate (an investigational agent); both drugs are characterized by relatively short half-lives (5-FU: mean half-life of elimination from plasma of approximately 16 min, depending on dose [27]; edatrexate: mean plasma half-lives for the 30- and 100-mg/m^2 dosages were α, 12.9 min; β, 1.5 h; and Υ, 11.9 h, respectively) [28]. Melphalan is another such drug with a half-life of 8 min to 2 h depending on dose, as well as individual metabolism. The 2007 guideline process delineated that studies with high-dose melphalan administered as conditioning therapy pre-stem cell transplant, although with only relatively small sample sizes, showed consistent results in favor of using cryotherapy as a cost-effective preventive intervention. For some patients, adherence to the cooling protocol may be confounded by the physically uncomfortable sensation they experience while holding ice in the mouth for 30 min or longer. In addition, some patients may develop a conditioned aversion to the use of ice chips in relation to the chemotherapy experience.

The aim of the present study was to systematically review the literature on the use of oral cryotherapy in prevention and/or treatment of oral mucositis caused by cancer therapy.

Methods

The detailed methods are described in the Methods paper by Bowen et al. [29] and the Perspectives paper by Elad et al. [30]. Briefly, a literature search for relevant papers published before 31 December 2010 was conducted using OVID/MEDLINE, with papers selected for review based on defined inclusion and exclusion criteria. In addition, the bibliographies of review papers were individually studied in order to identify potential additional publications.

The list of intervention keywords used for the literature search of this section included “cold therapies, cold therapy, cryotherapies, ice, ice chips, ice tips, oral cooling, therapies, cold, therapy, cold.”

Two experts independently reviewed each paper; data were extracted using a standardized electronic form. Studies were scored for their level of evidence based on Somerfield criteria [31], and flaws were listed according to Hadorn criteria [32]. A well-designed study was defined as a study with no major flaws per these criteria.

Findings from the reviewed studies were integrated into these guidelines based on the overall level of evidence for each intervention. Guidelines were classified into three types: recommendation, suggestion, or no guideline possible.

Results

The literature searches identified 268 papers for initial consideration, of which 235 papers were excluded after evaluating

Table 1 Publications

Cohort	Number of publications
Publications reviewed	22 original studies[a]
	2 meta-analyses
Publications deferred (e.g., letters to editor, commentaries, reviews)	11

[a] Plus one additional study analyzing same cohort as 1 of the 22 studies

the title and abstract. The remaining 33 papers were then analyzed in detail, resulting in additional 11 papers being excluded for not meeting inclusion criteria. As described in the Methods paper by Bowen et al. [29], reasons for exclusion included (1) effects of cryotherapy as an intervention not being reported, (2) animal or in vitro studies, (3) literature review, or (4) the study being published in a non-English language. The final set of 22 original reports and 2 meta-analyses was included in the final review (Table 1). A 23rd study [23] involving supplementary evaluation of data reported in 1 of the 22 publications [22] was also included. The two meta-analyses [24, 25] were analyzed separately.

All cryotherapy studies that were reviewed were directed to prevention, and all cryotherapy was administered via topical oral administration.

Outcomes of the current review in relation to the guidelines published in 2007 are listed in Table 2. In summary:

Standard-dose chemotherapy—5-FU bolus: prevention

2007 guideline: the panel recommends that patients receiving bolus 5-FU chemotherapy undergo 30 min of oral cryotherapy to prevent oral mucositis.

2011 guideline: no change in recommendation.

This recommendation was based on seven studies (six randomized clinical trials (RCT); one cohort study) (Table 2).

Table 2 Summary of study findings of topical oral ice chips for prevention of oral mucositis

Cancer type	Treatment modality	Author, year	Overall level of evidence	Guideline determination
Various solid tumors	CT[a] (5-FU bolus i.v.[b])	Baydar 2005 [2] Cascinu 1994 [3][c] Hudes 1999 [4] Mahood 1991 [1][c] Nikoletti 2005 [5] Papadeas 2007 [6] Sorensen 2008 [7]	II	Recommendation: that patients receiving bolus 5-FU chemotherapy undergo 30-min oral cryotherapy to prevent oral mucositis
Various solid tumors	CT (5-FU continuous infusion i.v.)	Rocke 1993 [8] Yokomizo 2004 [9]	III	No guideline possible
Various solid tumors	CT (edatrexate i.v.) (investigational drug)	Dreicer 1997 [10] Gandara 1997 [11] Edelman 1998 [12]	III	No guideline possible
Solid tumor (lung)	CT (etoposide, mitomycin, vinblastine i.v.)	Karagözoğlu 2005 [13]	III	No guideline possible
Hematologic cancers	HSCT[d] with or without TBI[e] (CT = melphalan)	Aisa 2005 [14] Bhatt 2010 [15] Dumontet 1994 [16] Gori 2007 [17] Lilleby 2006 [18] Mori 2006 [19] Ohbayashi 2008 [20] Sato 2006 [21] Svanberg 2007 [22] Svanberg 2010 [23]	III	Suggestion to use cryotherapy to prevent oral mucositis in patients receiving high-dose melphalan, with or without total body irradiation, as conditioning for HSCT

[a] CT = chemotherapy

[b] i.v. = intravenous

[c] Included in 2004 guideline review as basis for recommendation

[d] HSCT = hematopoietic stem cell transplant

[e] TBI = total body irradiation

Table 3 Standard-dose chemotherapy: prevention of oral mucositis meta-analyses

Name of agent	Route of administration	Cancer type and treatment modality	Author, year	Overall level of evidence	Guideline determination	Comments
Ice chips	Oral	Meta-analysis	Stokman 2006 [24]	n/a	n/a	Evaluated 2 studies included in current cryotherapy guidelines review
Ice chips	Oral	Meta-analysis	Worthington 2010 [25]	n/a	n/a	Evaluated 7 studies included in current cryotherapy guideline review

Two studies have been published since the previous guidelines update [6, 7], with both showing benefit for oral cryotherapy. One of these studies [6] was scored as level II evidence (single, well-designed RCT) and showed a significant reduction in incidence and mean grade of stomatitis in the cryotherapy group during all three cycles of chemotherapy based on both physician ($P<0.01$) as well as patient evaluation ($P<0.01$). The study by Sorensen et al. [7] similarly found a significant reduction in the incidence ($P<0.005$) and duration ($P<0.01$) of mucositis in patients treated with cryotherapy compared to normal saline mouth rinse. Interestingly, a third group administered chlorhexidine for mucositis prophylaxis showed similar protection compared to cryotherapy.

Standard-dose chemotherapy—edatrexate bolus: prevention

2007 guideline: the panel suggests the use of 20 to 30 min of oral cryotherapy to decrease mucositis in patients treated with bolus doses of edatrexate.

2011 guideline: no guideline possible.

No new studies have been published since the last guidelines update. Since edatrexate appears not to have progressed from the investigational drug stage, the panel chose not to formulate a guideline for use of oral cryotherapy for prevention of mucositis with this agent during therapy.

Standard-dose chemotherapy—5-FU continuous infusion: prevention

2007 guideline: n/a.

2011 guideline: no guideline possible.

The data based on two studies [8, 9] did not permit development of a guideline due to insufficient evidence. Rocke et al. [8] compared two lengths of cryotherapy (30 vs. 60 min) and found no additional benefit for extending cooling duration for prevention of mucositis. Yokomizo et al. [9] investigated allopurinol ice balls in 20 patients. When compared to 32 control patients, they found significant reduction in incidence and severity of mucositis with use of the intervention ($P<0.05$).

Standard-dose chemotherapy—etoposide, cisplatin, mitomycin, vinblastine: prevention

2007 guideline: n/a.

2011 guideline: no guideline possible.

The evidence based on a single RCT with flaws [13] was insufficient to formulate a guideline. Karagözoğlu et al. [13] completed a small study of 60 lung cancer patients and found that 5 min of oral cryotherapy was beneficial for reducing patient and physician reported incidence, duration, and severity of oral mucositis. Further research in this population is warranted.

High-dose melphalan with or without total body irradiation plus HSCT: prevention

2007 guideline: the panel suggests that cryotherapy be used to prevent oral mucositis in patients receiving high-dose melphalan as conditioning for HSCT.

2011 guideline: the panel suggests that cryotherapy be used to prevent oral mucositis in patients receiving high-dose melphalan, with or without total body irradiation, as conditioning for HSCT.

This suggestion is based on two case series [16, 20], four non-randomized clinical trials [14, 15, 19, 21], and three RCTs [17, 18; 22 supplemented by 23] (Table 2). The collective evidence was scored as level III. The RCTs, each with major flaws identified, found significant benefit for cryotherapy compared to no intervention or saline in two studies [18, 22] and no benefit in the study conducted by Gori et al. [17]. The remaining studies of lower evidence all reported improvement in mucositis.

These findings, based on evaluation of original studies, were reinforced by the two meta-analyses [24, 25] (Table 3).

Discussion

The members of the group systematically reviewed the literature published up to 31 December 2010 relative to use of oral cryotherapy in chemotherapy patients. Unlike

many drugs or devices utilized for the prevention of oral mucositis, oral cryotherapy is typically readily available in the clinical setting; it is safe, inexpensive, and generally well tolerated by patients.

There were few changes from the MASCC/ISOO mucositis guidelines published in 2007, in relation to the use of oral cryotherapy. It is important to note the high degree of rigor that was applied to the rating of quality of evidence. The authors, however, recognize that clinical judgment and experience may result in oral cryotherapy being utilized as a preventive intervention outside of these guidelines and suggestions. This approach may be uniquely appropriate for selected patients and therapy regimens, unlike many other mucositis interventions. Variables that warrant consideration include duration of chemotherapy administration (i.v. bolus versus administration over 24 h), half-life of the chemotherapeutic agent, adult versus pediatric population, and patient tolerance of the oral cryotherapy intervention.

A potential weakness in the study designs regarding the preventive use of oral cryotherapy is that none utilized a double-blinded, placebo-controlled methodology. However, this is justifiable in that it is not possible to design a patient-blinded study of the use of ice chips in the mouth for 30 min. Despite this limitation, consistency of the results over several selected studies and the benefits seen for days after treatment supported the continuation of the guidelines published in 2007. In addition, only two studies [17, 21] investigated oral cryotherapy in pediatric populations. There is thus limited study of this intervention in this cancer cohort.

Future studies incorporating the comparison of oral cryotherapy with other mucositis agents effective in preventing oral mucositis caused by chemotherapy with relatively short plasma half-lives would be useful. Additional studies of oral cryotherapy in pediatric oncology populations are warranted as well.

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