An Evidence-based Guideline on using Cryotherapy for
Chemotherapy-induced Oral Mucositis in Adult Cancer Patients

Submitted by

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Oral mucositis is a common adverse side-effect caused by cancer treatments and can lead to mucosa toxicity. Patients with oral mucositis may experience extreme pain and may not be able to eat, drink and talk and, as a result, their quality of life is impaired. Thirty to eighty five percent of patients undergoing chemotherapy would develop oral mucositis. Preventing or reducing incidence of oral mucositis and its severity can help reduce patients’ sufferings. One of the methods to achieve this objective is the oral cryotherapy, which is a prophylactic intervention. However, there is no evidence-based guideline to instruct nurses on providing oral cryotherapy to cancer patients.

The aims of this study are 1) to establish an evidence-based guideline on applying cryotherapy to reduce the incidence and severity of chemotherapy-induced oral mucositis, 2) to develop a standard nursing care and assess its transferability and feasibility, and 3) to develop a communication plan and evaluation plan for this guideline in an oncology
department for the targeted local hospitals in Hong Kong.

A systematic search of four electronic journal databases identified seven articles corresponding to 6 randomized controlled trials (RCTs) on using oral cryotherapy for adult cancer patients. Five RCTs with high to weak quality reported supporting evidence for the beneficial effect of oral cryotherapy on chemotherapy-induced oral mucositis, whereas 1 RCT with moderate quality failed to identify supportive evidence for the use of oral cryotherapy. However, potential confounding factors were identified to be presented in that insignificant RCT. Hence, there was sufficient evidence to show that oral cryotherapy can significantly reduce chemotherapy-induced oral mucositis in adult cancer patients.

An evidence based guideline for using cryotherapy on chemotherapy-induced oral mucositis in adult cancer patients was established. The transferability and feasibility of the proposed oral cryotherapy guideline were assessed. As identified, the clinical situation and patient characteristics in the local settings are similar to those who reported in the reviewed studies. Staff readiness, skills and resources are also readily available in the target clinical settings. Findings from the reviewed studies of oral cryotherapy can be transferred to the local target settings and are feasible to be implemented. It is also estimated that the innovated guidelines for cryotherapy can save HK$3,210,745 per year for the target setting.

Stakeholders for the innovated guideline in the local setting were identified. And a communication plan was developed. A pilot study lasting for 10 weeks will be conducted to
test the feasibility of the staff training session and the implementation of the oral cryotherapy guideline. Modification of innovated guidelines will be made after evaluating the data collected from the pilot study. Eventually, the final version of the evidence-based guideline will be established. A six months evaluation plan will be used to evaluate the implementation of the new guideline. The policy for adopting the oral cryotherapy will be determined with the outcome measures, including the incidence of chemotherapy-induced oral mucositis, mean of the oral mucositis score, staff satisfaction level, and the cost and benefit ratio of the innovated guideline.
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at The University of Hong Kong.

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Declaration

I declare that this dissertation represents my own work, except where due acknowledgement is made, and that it has not been previously included in a thesis, dissertation or report submitted to this University or to any other institution for a degree, diploma or other qualifications.

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Poon Sze Wan
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Chapter 1: Introduction

1.1 Background

Oral mucositis is a painful inflammation and ulceration of oral mucosal membranes (Black & Hawks, 2005). It is a common adverse side-effect caused by cancer treatments, particularly rapid intravenous chemotherapy or high-dose chemotherapy, and it can subsequently lead to mucosa toxicity. In 2007, 24,342 people in Hong Kong were newly diagnosed with cancer. Among various types of cancers, lung cancer and colorectal cancer are most prevalent and chemotherapy is the common cancer treatment (Hospital Authority, 2009).

Patients who receive every cycle of chemotherapy are at risk of developing oral mucositis. Studies reported that 30% of patients undergoing chemotherapy developed oral mucositis (Etling et al., 2003; Nottage et al., 2003). The incidence rate of oral mucositis is particularly high in some of the chemotherapy regimens. For example, the rates of developing oral mucositis were 83% and 74% for 5-fluorouracil (5-FU) and high dose chemotherapy infusion in autologous blood stem cell transplantation respectively (Meropol et al., 2003; Lilleby et al., 2006). Patients always complain that oral mucositis is an extremely painful experience. They are not able to eat, drink, and talk. Recently, Cheng et al. (2010) reported that severe oral mucositis can impair quality of life. Moreover, oral mucositis can lead to a lot of negative consequences which require additional medical treatments. Due to all these
negative consequences, prophylactic intervention for preventing and/or reducing the severity of oral mucositis is needed. It not only improves patients’ quality of life and maintains effective cancer treatment but also reduces the medical expense of the health care system.

1.2 Affirming the Need

In an oncology ward of a public hospital in Hong Kong, many patients suffered from oral mucositis, which is a side-effect of chemotherapy. The prevalence of chemotherapy-induced oral mucositis is high in the local setting. More than 50% of patients who underwent chemotherapy suffered from oral mucositis. This problem is particularly serious for those who previously received several cycles of chemotherapy treatment.

In current practice, there is no standard nursing care for oral mucositis. Consequently, nursing care varies according to nurses’ individual practice. Some colleagues prefer to give nursing advice to their patients once they discover the patient has developed oral mucositis, some may just report it to the physicians. In the latter case, physicians usually prescribe oral gargling to reduce patients’ discomfort. Oral gargling is a pharmacological measure and the common garglings are thymol gargle, aspirin gargle, and chlorhexidine gargle. Nurses can administrate oral gargle only after doctor’s prescription and this treatment can only be used once the oral mucositis has developed. That is, the target patients have already suffered from mucositis. In order to reduce patient’s risk of developing oral mucositis, prophylactic
treatment or early intervention for oral mucositis is essential. Since nurses always stay with patients during hospitalization, nurses can provide prompt treatment according to patients’ condition. In addition, nurses are responsible for administrating chemotherapy. If prophylactic intervention is provided according to the chemotherapy schedule, nurses are the most suitable personnel to provide it.

Once oral mucositis has developed, the condition cannot be resolved immediately. The duration of oral mucositis is around 12 days (Gori et al., 2007; Karagozoglu & Ulusoy, 2005). Majority of patients require chemotherapy treatment in every two weeks such as the administration of FOLFOX and FOLFIRI in the ward. Once patients have recovered from the previous cycle of chemotherapy-induced oral mucositis, a new cycle of oral mucositis usually develops. Therefore, prophylactic treatment that prevents and/or reduces the severity of chemotherapy-induced mucositis is essential. If prophylactic treatment is not provided to the patient, he/she may continuously suffer from chemotherapy-induced oral mucositis.

For patients who develop oral mucositis, their quality of life is greatly affected. Patients complain about the extreme pain even though they are using oral gargling. Extreme pain can result in the use of opioid and analgesia as pain relief but this may increase the risk of constipation, nausea and vomiting (Svanberg, Gunner & Ohrn, 2007; Lilleby et al., 2006). Difficulty in swallowing food usually makes patients reluctant to eat and that leads to a reduction of oral food intake. Loss of fat, altered energy usage and metabolism will result in
malnutrition. Malnutrition can subsequently decrease response and tolerance to chemotherapy. Moreover, weight loss can alter patient’s chemotherapy scheme. One of ten patients who suffer from severe oral mucositis and weight loss requires a reduction of chemotherapy dose. The effectiveness of the cancer treatment will then be jeopardized. It can also reduce the control of both tumor growth and metastasis. Besides, the lesion of mucositis can increase the risk of bleeding and infection. This may lead to systemic infection, which is fatal among cancer patients receiving chemotherapy (Svanberg et al., 2007; Svanberg, Gunner & Ohrn, 2010).

Cryotherapy is a cost-effective prophylactic measure for chemotherapy-induced oral mucositis. Various studies have supported that cryotherapy has a positive effect on reducing the development, severity and pain score of oral mucositis. The mechanism of oral mucositis reduction by cryotherapy is that oral cooling causes oral local vasoconstriction and also reduces blood flow to oral cavity. The quantity of cytotoxic drug delivers to oral mucosa will then be decreased. Thus, it reduces local irritation and subsequently reduces oral mucositis (Svanberg et al., 2007; Svanberg et al., 2010; Papadeas, Naxakis, Riga & Kalofonos, 2007; Karagozoglu et al., 2004; Lilleby et al., 2006). Also, Karagozoglu et al. (2005) reported that cryotherapy increases oral pH and thus saliva becomes more alkaline (i.e. pH 7.0 – 7.5). This prevents dryness of the mouth and can reduce the risk of oral mucositis.

Cryotherapy is well tolerated by participants. Although some participants may
experience some side-effects (e.g. headache, mouth numbness, sore throat, and gum pain),
these adverse symptoms will disappear after the completion of cryotherapy (Papadeas et al., 2007). In addition, Cryotherapy is also an inexpensive, easily available, and non-pharmacological intervention. Moreover, it is schedule-dependent. Nurses can apply cryotherapy as nursing intervention according to the chemotherapy administration schedule. Furthermore, oral cryotherapy does not interrupt the dosage of chemotherapy or decreases the efficacy of chemotherapy (Papadeas et al., 2007). In other words, cancer treatment is barely affected by cryotherapy. Therefore, cryotherapy may be a useful nursing intervention for preventing oral mucositis in local clinical wards of public hospitals.

Among the seven studies reviewed in this research project, most of them reported that oral cryotherapy can significantly reduce the incidence and severity of chemotherapy-induced oral mucositis (Svanberg et al., 2007; Svanberg et al., 2010; Papadeas et al., 2007; Karagozoglu et al., 2004; Lilleby et al., 2006; Sorensen, Skovsgaard, Bork, Damstrup, & Ingeberg, 2008). However, one study reported that oral cryotherapy fails to significantly alleviate oral mucositis (Gori et al., 2007). The effectiveness of oral cryotherapy on the prevention of chemotherapy-induced oral mucositis remains inconclusive.

Because cryotherapy is newly adopted in the nursing practice in local public hospitals, standard nursing care protocol of oral cryotherapy has yet been available. A systematic review to assess current evidences on the efficacy of cryotherapy in reducing
chemotherapy-induced oral mucositis in comparison to normal oral care is thus needed.

1.3 Objectives and Significance

The objectives of this study are:

1. To investigate the effectiveness of cryotherapy in reducing the incidence and severity of chemotherapy-induced oral mucositis;

2. To establish a standard and evidence-based guideline for using cryotherapy as a prophylactic measure for chemotherapy-induced oral mucositis;

3. To assess the transferability and feasibility of using oral cryotherapy prophylactic measure in the oncology ward settings in Hong Kong;

4. To design an implementation plan for evaluating the effectiveness of oral cryotherapy after its implementation in clinical setting

Ultimately, the outcome of this dissertation will lead to the establishment of an evidence-based nursing guideline benefiting patients, nurses and the hospitals. From the patients’ perspective, oral cryotherapy not only reduces the incidence and severity of oral mucositis but also reduces oral pain. Less opioid will then be used for oral pain relief. Consequently, total parental nutrition (TPN) and duration of hospitalization will be reduced because of the maintenance of oral intake (Papadeas et al., 2007; Svanberg et al., 2007; Svanberg et al., 2010). Patients who suffer less from mucositis will have improved quality of
From nurses’ perspective, an evidence-based guideline can standardize nursing practices and provide the best nursing care according to existing evidences. And from hospitals’ perspective, expenses relating to chemotherapy-induced mucositis can be greatly reduced (e.g. costs associated with the use of TPN and cost of hospitalization). Etling (2003) estimated that oral mucositis can increase the cost of hospitalization for each chemotherapy cycle by more than US$3,500, causing a huge financial burden to the medical system. Ultimately, an effective prophylactic intervention of oral mucositis can reduce the local medical expenses.
2.1 Search and Appraisal Strategies

2.1.1 Inclusion and Exclusion Criteria

In the present study, all data were extracted from published research articles, which reported studies investigating the effect of oral cryotherapy on chemotherapy-induced oral mucositis in adult cancer patients. The inclusion and exclusion criteria for selecting the relevant studies are listed below:

Inclusion criteria:

1. Randomized controlled trials (RCTs).
2. Cancer patients aged 18 years or above.
3. Studies relating to oral cryotherapy and chemotherapy-induced oral mucositis.
4. Primary studies.

Adult cancer patients were targeted because this patient group covered the largest population of cancer patients. Also, they are the targeted clients of local hospitals. Chemotherapy is the most common cancer treatment provided in the local setting. Chemotherapy-induced oral mucositis is one of the most common complaints and can result with serious consequences. Cryotherapy is a non-pharmacological measure which is newly introduced to the local clinical setting. Primary studies relating to oral cryotherapy and chemotherapy-induced oral mucositis were focused.
Exclusion criteria:

1. Studies targeting on pediatric patients.

2. Ice using in oral cryotherapy was made of additive solution such as juice.

3. Ice contained pharmacological component(s).

4. Non-empirical research papers (e.g. editorials/ comments/ letters/ news).

5. Studies using qualitative study design.

In order to prevent any effects from additive in ice, only those studies using ice made of pure water or normal saline were included. Furthermore, ice that contains any pharmacological component would require prescription from a physician and that would lead to a reduction in the active intervention role of nurses. Last but not least, it is difficult to quantify the outcomes of intervention published in editorials, comments, letter, news or those from qualitative studies. Therefore, these types of studies were excluded in the present study.

2.1.2. Identification of Studies

We searched four electronic journal databases: CINAHL (EBSCOhost), Cochrane library, PubMed and British Nursing Index for eligible studies. Key search terms were “oral mucositis/ stomatitis / oral infection/ oral inflammation/ infection of oral mucosal membrane”; “cryotherapy/ ice cubes/ ice water/ cold mouthwash/ oral cooling/ ice therapy”; “chemotherapy/ antineoplastic therapy”; and “intervention / measure/ nursing care/ guideline/
method”. There was no restriction for the years of publication. However, the language of the publication was restricted to Chinese and English. For all potential studies, their titles and abstracts were screened. Studies were then excluded if they met any exclusion criteria, and included according to the inclusion criteria. Only studies with full-text research articles available were retained. This was to ensure that the content of the selected studies met the criteria. Reference lists of the selected studies were also screened to search for additional relevant studies. Details of the search strategy are summarized as a table in Appendix 1.

2.1.3. Data Extraction

Data of the selected studies were presented in a table of evidence according to guidelines of the Scottish Intercollegiate Guidelines Network (SIGN). Every table of evidence included patient characteristics, intervention group, control group, mucositis grading system, outcome measure, and effect size. The outcome measures included the incidence of oral mucositis, duration of oral mucositis, oral mucositis score, usage of intravenous narcotic, usage of TPN, and pH value. The table of evidence is provided in Appendix 2.

2.1.4 Appraisal Strategies

Appraisal checklist of SIGN (SIGN, 2004) was used to criticize and appraise the quality of all identified and selected studies. It is a reliable and valid checklist which was developed
for systematic analysis of scientific papers. The quality of each study was determined according to the methodology. In the appraisal checklist, code “++” indicates that the employed methodology was very unlikely to suffer from bias, which may affect the study’s conclusion; “+” indicates that the employed methodology was unlikely to suffer from bias, which may affect the study’s conclusion; “-” indicates that the employed methodology may have suffered from bias and it may affect the study’s conclusion. Level of evidence in each study was determined according to the SIGN (SIGN, 2008). RCTs, meta-analyses, and systematic review of RCTs belongs to level 1. All of the selected studies in the present study were RCTs, so all the selected studies belong to level 1. Appraisal checklist for each identified and selected study are provided in Appendix 3.

2.2 Results

2.2.1 Search Results

After using keywords to search for the relevant publications and limiting to those reporting RCTs, 63 abstracts were retrieved. Full text articles of 60 RCTs were retrieved. 18 RCTs relating to oral cryotherapy and chemotherapy-induced oral mucositis were rejected according to the exclusion criteria (e.g. pediatric patients were the target group). Twenty-three of the searched studies were irrelevant to the objectives of this dissertation. Among the potential studies, 3 studies did not have full text available, so it was not able to
review the content of studies and examine whether they met the selection criteria. Finally, seven primary studies remained. After reading the full text articles of these 7 studies, two papers were based on the same RCT (Svanberg et al., 2007; Svanberg et al., 2010). Since these 2 papers focused on different outcome measures, they were both included in the present study. The reference lists of selected studies were read but no additional relevant paper was discovered. Finally, 7 primary studies based on 6 RCTs were selected and included in this dissertation for review. Detailed results of the journal database search are summarized in the Appendix 1.

2.2.2 Study Characteristics

All the seven selected papers involved 6 RCTs. Table of evidence is showed in Appendix 2. The extracted patient characteristics included patients’ age, sex and smoking status. The mean or median age of participants among the studies ranged from 37.7 to 60 years old or above. Majority of participants were middle-aged and received chemotherapy as cancer treatment. Data of smoking status were only available in 3 RCTs. Of which, 68 to 87% participants were non-smokers. Three RCTs reported a female-to-male ratio close to 1 (0.73 – 0.97); 2 RCTs recruited considerably more females (female-to-male ratios of 1.93 and 2.33); 1 RCT recruited considerably more males (female-to-male ratio = 0.30). Because smoking status and gender have not been identified as confounding factors affecting the efficacy of
cryotherapy, missing of the smoking status data and variation in the gender ratios in these RCTs would not alter the conclusion of the present study.

In the intervention arms, all RCTs required their patients to suck ice cubes or rinse their mouths with ice water to continuously keep their mouths cool before, during and after chemotherapy infusion. In the control arms, 2 RCTs required participants to rinse their mouth with room temperature normal saline. But 4 RCTs did not specify their control measure. Despite mucositis grading systems varied among these RCTs, all of the mucositis grading systems provide compatible data on oral condition. This is because all the mucositis grading systems were formulated on the basis of a reliable and valid grading system, such as the World Health Organization (WHO) oral mucositis system. Incidence of oral mucositis and oral mucositis score were the major outcome measures in all these 6 RCTs. In addition, other outcome measures were reported for some of the RCTs, including duration of mucositis, use of intravenous narcotic drugs, use of TPN, and oral pH value. The effect sizes for the various outcome measures were reported in all these 6 RCTs.

Participants’ characteristics in these 6 RCTs were similar to the corresponding patient group in the local clinical setting. For example, middle-aged people in Hong Kong also have a high risk of developing cancer. The results of the 6 selected RCTs can be generalized to Hong Kong clinical settings.
2.2.3 Methodological Quality of Studies

By using the SIGN appraisal checklist to assess the methodological quality of the 7 selected studies (Appendix 3), two papers from the same RCT were classified as high quality (Svanberg et al., 2007; Svanberg et al., 2010), four studies were classified as moderate (Sorensen et al., 2008; Papadeas et al., 2007; Lilleby et al., 2006; Gori et al., 2007), and one was classified as weak (Karagozoglu et al., 2005). In Karagozoglu et al.’s study (2005), the similarities and differences between the intervention arm and control arm was not addressed. Therefore, it was unable to determine whether the observed differences in the clinical outcomes were caused by the intervention or just associated with the differences between the study arms. In addition, the procedures of the randomized allocation of participants in the intervention arms were not provided in detail. Confounding factors may be presented and result in a high risk of bias. Also, the effect sizes of the outcome measures were not clearly mentioned. Thus, Karagozoglu et al.’s study (2005) was classified with weak quality.

For all the 7 selected articles, details about the intervention arms and the aim/objective/focus question were clearly stated in the introduction section. All the 6 RCTs included random assignments for allocating their participants into the intervention or control arm. The randomization method was described in 2 RCTs (Svanberg et al., 2007; Svanberg et al., 2010; Gori et al., 2007). The RCT reported by Svanberg et al. (2010) used stratified randomization in block of six, and Gori et al. (2007) used a randomization list. In Papadeas et
al.’s study (2007), participants who were born in even days were assigned to the intervention arm, whereas those who were born in odd days were included in the control arm. Although Papadeas et al. (2007) reported their randomization methods in details (e.g. using date of birth for randomization), this method was not a true randomization. Therefore, this study should not reach a high level of quality. For 2 of the RCTs, randomization methods were not explained clearly in the articles. Therefore, their level of evidence cannot be graded as high (Lilleby et al., 2006; Sorensen et al., 2008).

Concealment was not mentioned in all these 7 selected studies. Regarding the issue of “blinding”, it was practically not possible to “blind” participants in the intervention arm because they had to suck ice cubes. Participants would aware the different between the two intervention arms. In the same token, it was not possible to “blind” nurses who administrated the oral cryotherapy to patients. Nevertheless, “blinding” to evaluators assessing the oral mucositis assessment was possible. In 1 RCT, otorhinolaryngologists who were responsible for evaluating participants’ oral condition in the intervention arms were “blinded”.

In all the 7 selected studies, patient characteristics were not significantly different between the intervention arm and the control arm before the treatments were given, except Karagozoglu et al.’s study (2005). In Gori et al.’s study (2007), one item in patient characteristics was reported to be different. In particular, the numbers of participants received related and unrelated stem cell transplantation were statistically significantly different
between the two study arms. However, univariate analysis showed that such difference was not significantly associated with the severity of oral mucositis. Therefore, the difference in the numbers of participants received related and unrelated stem cell transplantation did not affect their conclusion.

The dropout rate of participants was low in all the 7 selected studies. The dropout rates were <20% in the intervention arm and <5% in the control arm. Such low dropout rates should not significantly affect the study quality. Regarding the outcome measurement, all oral mucositis grading systems were based on reliable and valid oral mucositis grading scales.

Moreover, in Svanberg et al.’s study (2010), it was clearly stated that participants were underwent intention-to-treat analysis. However, it is not clear for all other studies. Svanberg et al.’s study (2010) fulfilled more than eight criteria in the SIGN appraisal checklist with “adequate addressed or above”. Thus, Svanberg et al.’s study (2010) reporting in two articles was rated as high quality.

One high quality RCTs (i.e., Svanberg et al. (2010)), 3 moderate quality RCTs and 1 weak quality RCT (i.e., a total of 5 RCTs) indicates that oral cryotherapy can reduce chemotherapy-induced oral mucositis significantly, whereas only one moderate quality RCT does not support the beneficial effect of oral cryotherapy on oral mucositis. There are sufficient evidence showing that oral cryotherapy can significantly reduce chemotherapy-induced oral mucositis. Thus, all these studies are included for “Summary and
2.3 Summary and Synthesis

2.3.1 Summary

Among the 5 selected RCTs supporting oral cryotherapy, 4 RCTs reported a statistically significant reduction of the incidence of grade 3 – 4 oral mucositis (Svanberg et al., 2010; Sorensen et al., 2008; Lilleby et al., 2006; Karagozoglu et al., 2005). The incidence of oral mucositis reduced by 22% - 60% in the intervention arm comparing to control arm. Svanberg et al. (2010) reported intervention in allogeneic group and Gori et al. (2007) reported that less percentage of participants had severe oral mucositis in the intervention arms when compared to control group, although the difference was not statistical significant (p=0.46).

Papadeas et al. (2007), Svanberg et al. (2007) and Lilleby et al. (2006) reported a significant reduction of oral mucositis score when using the oral cryotherapy (p<0.05). Particularly, it was reported that at least 0.5 mucositis score can be reduced in a four-graded oral mucositis grading system. One study reported that, when oral cryotherapy was continuously used as a prophylactic measure, both physician- and patient-judged mucositis scores decreased significantly (p<0.01) even in the next two cycles of chemotherapy (Papadeas et al., 2007). This can imply that participants in the intervention arm experienced less oral pain. Karagozoglu et al. (2005) did not provide a p-value, and Gori et al. (2007)
reported no statistically significance in reducing mucositis score. However, in both RTCs, lower mucositis scores were observed in the intervention arms, suggesting a probable beneficial effect of cryotherapy on chemotherapy-induced oral mucositis.

Four days-shorted oral mucositis duration were reported in the intervention arm (p<0.05) in two RCTs (Sorensen et al., 2008; Karagozoglu et al., 2005). If participants developed oral mucositis, their oral mucositis might heal faster in intervention arm. However, Gori et al. (2007) reported the durations of oral mucositis for the intervention arm and control arm were the same.

Furthermore, 2 RCTs reported that participants in the intervention arm required fewer days of intravenous narcotic usage (p=0.04) (Svanberg et al., 2007; Lilleby et al., 2006). Moreover, Lilleby et al. (2006) reported that cryotherapy significantly reduced the use of TPN. One study reported that oral pH increased in the intervention arm (Karagozoglu et al., 2005).

In addition, the compliance with oral cryotherapy was high. Less than 20% dropout rate was reported in the oral cryotherapy arm in all of the 7 selected studies. 87% complete compliance was obtained in Sorensen et al.’s study (2008). In all the studies, participants complained that oral cryotherapy cause numbness of teeth and oral cavity, headache, and taste disturbance. However, these side effects disappeared immediately when the oral cryotherapy was completed (Sorensen et al., 2008; Papadeas et al., 2007; Karagozoglu et al.,
2005).

2.3.2 Synthesis

All 6 selected RCTs (i.e., a total of 7 articles) measured the incidence of oral mucositis, oral mucositis score, and/or duration of oral mucositis as the study outcomes. Crushed ice was used in the oral cryotherapy in the intervention arms in all RCTs. Five RCTs of high to weak quality reported oral cryotherapy would significantly benefit oral mucositis, but one RCT of moderate quality failed to identify a significant beneficial effect on oral mucositis. A possible reason may be the presence of confounding factor(s), such as the folinic acid and total body irradiation (TBI) treatments, as suggested by Gori et al. (2007).

In Gori et al.’s study (2007), patients who had undergone folinic acid and TBI treatments were recruited into both the intervention group and control group. However, in all the RCTs supporting the beneficial effect on oral cryotherapy did not include subjects receiving folinic acid and TBI treatments. Although cases receiving folinic acid and TBI treatments were well balanced in the study arms in Gori et al.’s study (2007), incidence of severe oral mucositis was significantly lower in participants receiving folinic acid (p=0.016). Folinic acid was an antioxidant and it may have masked the effect of oral cryotherapy on chemotherapy-induced oral mucositis. Gori et al. (2007) also reported statistically significant difference (p=0.007) between participants with and without TBI. Participants with TBI were
at higher risk of developing oral mucositis. It is because participants’ oral mucosal membranes can be directly irritated and damaged by radiation during TBI treatment. Thus, it can imply that oral cryotherapy does not have beneficial effect on oral mucositis in patients receiving both chemotherapy and TBI treatment. Since folinic acid treatment may reduce oral mucositis, it may be possible to combine oral cryotherapy and folinic acid treatment to reduce chemotherapy-induced oral mucositis.

Also, no matter what types of outcome measures were included in the assessment (e.g. such as incidence of oral mucositis, oral mucositis score or the duration of oral mucositis), the ultimate goal of all the reported outcome measures was the severity of chemotherapy-induced oral mucositis. In the 7 selected studies, all of the outcome measures can used to measure the significant beneficial effect of oral cryotherapy on oral mucositis. Hence, incidence of oral mucositis, oral mucositis score and duration of oral mucositis can be used as outcome measures in oral cryotherapy guideline.

Various chemotherapy schemes were used among the 6 selected RCTs. Two RCTs with high/moderate quality involved chemotherapy containing Melphalan (Svanberg et al., 2007; Svanberg et al., 2010; Lilleby et al., 2006); 2 RCTs with moderate quality focused on 5-flurouracil (5FU) (Papadeas et al., 2007; Sorensen et al., 2008); and Karagozoglu et al.’s study (2005) used combined course chemotherapy. Five RCTs reported a significant beneficial effect of oral cryotherapy on oral mucositis. It is worth noting that Gori et al.’s
study (2007), which did not support the use of oral cryotherapy, was based on Methotrexate (MTX). 5FU and Melphalan are chemotherapy drugs with short half-life (i.e. around 30 minutes) (Rocke et al., 1993), whereas the half-life of MTX is long (i.e. 1 to 6 hours). It is possible that oral cryotherapy is more effective when the chemotherapy drugs of shorter half-life are used. Chemotherapy drugs of longer half-life may increase the exposure of oral toxicity, resulting in a less obvious beneficial effect of oral cryotherapy.

Ice cubes or ice chips were used in oral cryotherapy among five selected studies: 2 studies used crushed ice and 2 studies used the ice together with ice-cold water in the intervention arm. Intervention that uses either ice cube or crushed ice or ice-cold water may have beneficial effect on oral mucositis. Ice cube or crushed ice or ice-cold water would not affect the efficacy of oral cryotherapy. Keeping oral cavity cool is crucial. Hence, ice cube, which is easy to make or store, can be an effective material for oral cryotherapy.

Time for the implementation of oral cryotherapy is important. If oral cryotherapy is not administered at an appropriate time point, its efficacy may diminish. In all 6 selected RCTs (i.e., the 7 selected articles), cryotherapy was administrated before the infusion, during and after the chemotherapy. One exception is the study of moderate quality in which it did not report the beneficial effect of cryotherapy administrated during and after chemotherapy infusion, all other supporting studies administrated cryotherapy before, during and after. Therefore, there is sufficient evidence supporting that such time schedule for cryotherapy
administration is effective.

For the duration of performing cryotherapy, four studies with high to moderate quality suggested that, in order to obtain its effectiveness, the duration of performing oral cryotherapy before chemotherapy should be 5 minutes to 30 minutes. And the duration after chemotherapy stopped and continued cryotherapy should range from 30 minutes to the end of chemotherapy session (Svanberg et al., 2007; Svanberg et al., 2010; Sorensen et al., 2008; Papadeas et al., 2007; Lilleby et al., 2006). Majority of papers suggested the duration of cryotherapy should be 5 minutes before and 30 minutes after chemotherapy. Hence, these durations of cryotherapy can be effective.

Varied oral mucositis grading systems were used among the reviewed studies. Since all the mucositis grading scales were either proven to be reliable and valid or modified from widely used mucositis grading scale, it would not alter the conclusion of the selected RCTs.

Lastly, all selected RCTs had an ongoing assessment for oral mucositis during hospitalization. This assessment is essential for nurses and physicians to monitor the development and severity of oral mucositis. So it is necessary for nurses to assess oral condition on a daily basis while patients were receiving in-patients chemotherapy treatment. Moreover, Sorensen et al. (2008) suggested that assessment of oral mucositis should be carried out at day 14 and day 28 after the chemotherapy. This schedule is important for monitoring the oral condition of patients who receive outpatient day-chemotherapy session.
Based on the seven analyzed RCTs, oral cryotherapy can effectively reduce chemotherapy-induced oral mucositis. Patients who are undergoing short half-life chemotherapy such as 5-fluorouracil and melphalan are the target group. The suggested schedule for the administration of the oral cryotherapy should be 5 minutes before, during and 30 minutes after chemotherapy. Crushed ice is preferable in oral cryotherapy and patients are required to keep their oral cavity consistently cool. The use of Oral mucositis grading of WHO is recommended in local clinical setting since this grading system is valid and reliable and has been widely used in clinical setting. Healthcare providers such as nurses and patients will be responsible for evaluating oral mucositis. Evaluations performed by nurses are essential. Nurses’ perception, cooperation and satisfaction towards innovated guideline are crucial. If they perceive the innovated guideline is user-friendly and can benefit patients to relieve oral mucositis, their compliance towards the guideline may enhance. The assessment will perform on a daily during hospitalization and at day 14 and day 28 after the oral cryotherapy was used in chemotherapy session.
Chapter 3: Translation and Application

3.1 Implementation Potential

3.1.1 Target Audience and Setting

The proposed innovation is oral cryotherapy for reducing the incidence and severity of chemotherapy-induced oral mucositis. The target audience is adult cancer patients (i.e. aged between 18 to 65 years) who are undergoing intravenous chemotherapy treatment. The integrated review conducted in Chapter 2 has demonstrated that there is sufficient evidence showing oral cryotherapy is more effective in chemotherapy with short half-life. Thus, patients who are receiving short half-life intravenous chemotherapy are targeted.

The proposed innovation will be used in a clinical oncology department in a public hospital in Hong Kong. The department has six oncology wards, including four in-patients admission wards, one day-chemotherapy ward, and a specialist out-patient clinic. In order to develop an evidence-based guideline for implementing the new innovation into the target setting, the implementation potential including the transferability, feasibility and cost/ benefit ratio of the innovation are assessed (Polit & Beck, 2008).

3.1.2 Transferability of the Findings

In order to transfer the evidence-based innovation into clinical situation, characteristics of target audience between the target setting and the reviewed studies should be compared. This is to assess the “fitness” of the innovation in the proposed setting. In the reviewed
studies, they focused on participants aged 18 years or above. The mean or median age of the participants among the reviewed studies ranged from 37.7 to 60 years. In the target setting, all participants are aged 18 years or above and majority of them are middle-aged, which are similar to the reviewed studies.

Participants in the reviewed studies were receiving chemotherapy. Although both chemotherapy and radiotherapy are the available cancer treatments in the target setting, only patients who are undergoing chemotherapy alone will be targeted. No matter how severe the patients are suffered from oral mucositis, oral cryotherapy can be used and can benefit her. As in the reviewed studies some of the participants have already suffered from oral mucositis and some with health oral condition, it is similar to the target setting in which some participants have health oral condition and some have oral mucositis. For patients who are undergoing intravenous chemotherapy more than 3 hours, they are not recommended to use oral cryotherapy because it is impossible for them to continuously suck ice cubes for more than 3 hours.

Although there are no official statistics regarding the number of the target patients in the target setting, there are around 2500 new cases received chemotherapy in 2010. Both Etling et al. (2003) and Nottage et al. (2003) estimated that 30% patients undergoing chemotherapy would develop oral mucositis. Therefore, it is estimated that 750 cases would develop oral mucositis. Hence, around 330 new cases would be benefited from the innovation in each
year.

The philosophy of care of the use of oral cryotherapy is to improve patients’ quality of life. In previous studies, it showed that oral cryotherapy can reduce the severity of chemotherapy-induced oral mucositis. The new innovation can also improve the quality of nursing care in cancer patients. The hospital accreditation of the local public hospitals is to maintain and improve the quality for healthcare services (Hospital Authority, 2010). Also, the mission and value of local setting states that nurses should provide patient orientated quality care. Thus, the philosophy of care in the innovations and the local setting is similar.

Both the duration of implementing and time for evaluating the effect of the new innovation are a determining factor for the approval of the implementation of oral cryotherapy in the target setting. A total of 11 months should be required for implementing the innovation, including 2 weeks for setting up the innovation programme, 2 weeks for preparing equipment and training staffs, 2 months for conducting a pilot test, 2 months for discussing the findings from the pilot test and refining the guideline, and 6 months for implementing the oral cryotherapy and evaluating the entire innovation programme. In total, 11 months will be used for implementing the cryotherapy. The characteristics of patients and philosophy of care in the target setting are similar to those in the reviewed studies. Therefore, it is possible to translate the innovation into the local setting.
3.1.3 Feasibility

After recognizing the innovation has satisfactory transferability from the reviewed studies into the local clinical setting, feasibility is another factor to be considered. Nurses are responsible for administrating oral cryotherapy according to the chemotherapy schedule. Nurses will assess patients’ oral condition before administrating oral cryotherapy. They have the right to offer oral cryotherapy according to patients’ oral condition. If cryotherapy is regarding as undesirable, nurses can stop administrating it at any time.

In general, when a new innovation is implemented into a clinical setting, friction may occur. The level of friction can affect the feasibility of implementation. Among the nursing staffs in the target setting, the degree of friction induced by the innovation may be low. Some nursing staffs may be reluctant to adopt the new practice, some may consider it is troublesome in performing the new innovation. And some may not the confidence to perform the oral cryotherapy. Since no extra skill has to be learnt for administering the oral cryotherapy, the friction should be low among staffs.

The use of oral cryotherapy may increase the workload of the staffs in the local setting. For every instance, nurses are required to use five minutes to prepare and instruct patients to use cryotherapy. Specifically, they are required to make sterile ice, discard expired ice, and monitor freezers temperature. Moreover, healthcare assistants have to use twenty minutes to perform standard cleaning procedures on ice racks. However, majority of nursing staff would
agree that oral mucositis is a problem in the local setting. Ignoring this problem may cause even more workload because oral mucositis may result in increased admission rate or longer length of hospitalization. So the increased workload of using oral cryotherapy is comparatively more reasonable, acceptable and feasible than that in the current practice. Consensus among staff for the new innovation is high.

Friction from administrative level on using the oral cryotherapy is low. The oncology department in the target local hospital has solid experiences in adopting new evidence based innovations. For example, a home based chemotherapy infusion scheme, and different types of dressing practice and material on various radiotherapy-induced wounds have previously been implemented in the target department. Administrators in the target setting encourage evidence-based practice. The practice not only improves healthcare quality, it also helps maintain a high standard and updated nursing care to patients. Moreover, it can promote the reputation of the target setting among public local hospitals.

Furthermore, chemotherapy-induced oral mucositis has a high prevalence rate even with the use of a variety of mouthwashes in current practice. In the reviewed studies, sufficient evidences have found to support the beneficial effect of oral cryotherapy on chemotherapy-induced oral mucositis and oral cryotherapy is also found to cause limited adverse effects. The target setting should support new oral cryotherapy as new innovation to reduce the severity of chemotherapy-induced oral mucositis. Consensus from administrative
level can be obtained.

Resources availability can affect the feasibility of the implementation. For this oral cryotherapy, the required resources include manpower and equipment. In the manpower aspect, there are more than 60 registered nurses in the oncology department of the target local public hospital. Assessing oral condition is a basic nursing skill and it should have been included in the training in all nursing schools. In current practice, nurses in the target setting are required to assess patients’ oral condition daily. They are familiar with the use of the WHO oral mucositis grading system to assess oral condition. No additional skill should be required for nurses to perform the new innovation. Thus, more than 60 nurses are readily available and it should be sufficient for the implementation of the innovation in target setting. In other words, no additional manpower has to be added for the implementation of the oral cryotherapy. Nevertheless, a brief one hour training session will be provided to all nursing staffs. The training session will provide proper documentation of oral mucositis, reinforce the proper use of mucositis grading system, and explain the standard use of oral cryotherapy.

For a smooth implementation of an innovation, it is essential to have sufficient skilled staff available. In addition, it is also necessary to have adequate hardware equipment to cooperate with the manpower. Ice is crucial in oral cryotherapy. Freezer and water are the main components to make ice and keep it cool in cryotherapy. Currently, there are two freezers available in each ward. They are used only for keeping the cold pad cool for fever
patients. Thus, it is not necessary to buy additional freezers for the new innovation. Moreover, although it is not necessary to keep ice sterilized, sterile water will be used for making the ice. This is to minimize the risk of contamination. Bottles of sterilized water can be obtained from the pharmacy in the target hospital. In addition, twenty additional ice racks are required for making ice. More ice can make to meet patients’ needs. And some extra ice racks will be kept as back up stocks in the target setting.

Proper evaluation is crucial for assessing the effectiveness of the innovation. If the evaluation found the innovation is not effective in target setting, it is difficult to maintain this new practice among the staffs. The WHO oral mucositis grading scale will be used to evaluate the outcome of the innovation. Satisfaction level from healthcare providers and feedbacks from patients will also be used to evaluate the innovation program.

As nurses can make their decision on whether to carry out the innovation, frictions on using cryotherapy should be low. Also, consensus among nursing staff and administrators are expected to be high and the required resources and the evaluation tools of innovation are readily available in the target setting. Oral cryotherapy should be feasible to implement in the oncology department of the target public hospital.
3.1.4 Cost-Benefit Ratio

There are potential benefits for applying the new innovation, but the potential risk associated with it should not be underestimated. The potential risk which patients may be exposed to during the oral cryotherapy includes headache, numbness of teeth and gum, sore mouth, pain of hard palate, erythema, coldness, suffocation, and deterioration of oral mucositis (Papadeas et al., 2007; Lilleby et al., 2006). However, based on the reviewed studies, the risk of developing this adverse side-effect is low and they will be immediately resolved when oral cryotherapy is completed.

The most significant benefit of the oral cryotherapy is that it may reduce the prevalence and incidence of chemotherapy-induced oral mucositis. Reduced incidence rate of oral mucositis can reduce the risk of pain, infection, and improve patients’ quality of life. If the oral cryotherapy is not implemented, the prevalence of oral mucositis may remain high in the target setting. Severe oral mucositis will decrease patients’ tolerance of chemotherapy. Hence, the effectiveness of cancer treatment will be impaired. On the other hand, maintaining current practice may increase hospitalization and may also increase the medical expenses (Svanberg et al., 2007; Svanberg et al., 2010; Etling, 2003).

Comparing the potential risks of oral cryotherapy, potential benefit from it and the risk of maintaining current practice, adverse effect from oral cryotherapy is lower than maintaining the current practice. Patients, staff and administrative levels can benefit from it.
The new innovation should be adopted in the target setting.

One of the essential factors for determining the feasibility of implementing a new innovation is cost (Polit & Beck, 2008). According to the target local hospitals’ annual report in 2010, the cost of hospitalization for each patient is HK$3,590 per day (Hospital Authority, 2011). In 2010, there were 2,500 new cases received chemotherapy and 750 of them developed chemotherapy-induced oral mucositis. Around 24% of participants who suffer from severe oral mucositis can benefit from oral cryotherapy (Sorensen et al., 2007). It is estimated that 180 cases per year would not develop severe oral mucositis. Lilleby et al. (2006) reported that patients who have not received oral cryotherapy will need five more hospitalization days than patients who have received oral cryotherapy. The total cost of oral mucositis in the current practice are (HK$3,590 X 180 X 5) = HK$ 3,231,000 per year. It is not only a huge medical expense to the hospital, it also causes deteriorate healthcare professionals’ morale because of the high readmission for oral mucositis.

The cost for the new innovation includes the cost of the set up and the maintenance costs of the innovation. Both the set up cost and the maintenance cost of innovation are summarized in Appendix 4 and Appendix 5 respectively. Six nurses will be the core group responsible for implementing the innovation. They include one Advanced Practice Nurse (APN) as the nurse in-charge for the innovation and five senior registered nurses as the coordinators of the innovation. Sixty nurses in the oncology department in the target local
hospital will responsible for running the innovation. Before the commencement of the innovation, the nurse in-charge and the five nurse coordinator will have an hour meeting for the training session. All nurses will be officially released to attend the one hour training session for the innovation. The total number of hours for staff training session is 72 hours. Hence, the total cost for staff training for setting up the innovation is HK$14,710. The material of setting up the innovation includes 20 additional ice racks, photocopies of notes and stationeries. Thus, the material cost is HK$2,400. As a result, the total setup cost for the innovation is estimated as HK$17,110.

If the oral cryotherapy is approved as a standard nursing care in the oncology department of the target local hospital, yearly-based maintenance cost for the innovation will be considered. Since new staffs will be recruited every year, training session of the innovation for them will be given. Refreshment for the current staff of the innovation will be given every year in order to sustain standard nursing care. Around 70 hours will be needed for refreshment and for new staff training. Total maintenance cost for staff training is around HK$14,000 per year. When running the innovation for long term, freezers should have a regular maintenance cost and the wear off of the ice racks. Hardware materials cost estimate is HK$8,100 per year. Supplementary materials cost, such as photocopy of notes, guideline, protocol and stationeries, is estimated to be HK$1,300 per year. Hence, the total maintenance cost for the innovation is estimated to be HK$23,400 per year. However, some of the hidden
cost is difficult to estimate. This hidden cost includes meetings for modifying guideline, meetings with administrators and physicians, and briefing session. They are not included in the maintenance cost at the moment.

After calculating the medical expense for maintaining the current practice in caring chemotherapy-induced oral mucositis and expense on setting up and maintaining the new innovation for the first and second year, it is found that the new innovation can save HK$ (3,231,000 X 2 – 17,110 – 23,400) = HK$6,421,490 in the first and second year. It is also estimated that new innovation can save HK$3,210,745 per year afterwards in the target setting. Since the innovation have more potential benefits than risk and can save a huge amount of medical expense for the oncology department in the target hospital every year, the new innovation should be adopted.

3.2 Evidence-Based Practice Guideline/ Protocol

In the evidence-based guideline for the use of oral cryotherapy for chemotherapy-induced oral mucositis in adult cancer patients, the level of evidence among all reviewed studies were graded based on the Scottish Intercollegiate Guidelines Network (SIGN, 2008). And the grades of all recommendations in evidence-based guideline from the reviewed studies were graded based on the SIGN (2008). The quality of two reviewed RCTs were classified as high, i.e. 1++ (Svanberg et al., 2007; Svanberg et al., 2010), four were
classified as moderate, i.e. 1+ (Sorensen et al., 2008; Papadeas et al., 2007; Lilleby et al., 2006; Gori et al., 2007), and one was classified as weak, i.e. 1- (Karagozoglu et al., 2005).

An evidence-based guideline for the use of cryotherapy for chemotherapy-induced oral mucositis in adult cancer patients is attached in Appendix 6.
Chapter 4: Implementation Plan

4.1 Communication Plan

4.1.1 Stakeholders

Before implementing a new innovation into a clinical setting, communication with stakeholders is crucial. Proper communication can gain co-operation and support from stakeholders and thus reduces friction from them (Polit & Beck, 2008). Identification of the stakeholders is the first step.

For implementing the evidence-based guideline for the use of oral cryotherapy in adult cancer patients in the department of clinical oncology, the key stakeholders include the Chief of Service (COS), the Department Operational Manager (DOM) and four consultants of the department of clinical oncology in the hospital. They are the person in-charge of the department and are responsible for discussing the new guidelines implementation. They have the authority to approve new changes and alter resources allocation to facilitate the setup of the new innovation and sustenance in the department. COS will make the final decision for the implementation of the new guideline.

All the 60 frontline nurses are also the key stakeholders. They are responsible for administrating the oral cryotherapy according to the new guideline. They will assess patients’ oral condition daily and have the autonomy to offer oral cryotherapy based on patients’ oral condition. Five ward managers and fifteen APNs are the stakeholders as well. They will work
with the selected senior registered nurses in the innovation programme to monitor the progress of the innovation implementation. They have experiences and skills to handle and tackle potential problems and they can provide advices for the modifications of the guideline when necessary. Selected APN and senior registered nurses will provide training and make use of allocated resources during the implementation of the innovation.

Moreover, other stakeholders include 20 medical officers. Medical officers provide medical treatment when there is a deterioration of patients’ oral condition or incidence of adverse effect caused by the oral cryotherapy.

### 4.1.2 Communication Process and Implementation Strategies

After identifying the stakeholders of the innovation in the target setting, a collaborative communication plan would be established. The innovation proposer will firstly approach the senior frontline nurses. As senior frontline nurse have unique experience for providing nursing care for cancer patients, they are the appropriate persons to administer the new guideline. The opinions from the frontline senior nurses towards the existing problem are important. The proposer will discuss and chat with the frontline senior nurses about the existing problem of the high prevalence of chemotherapy-induced oral mucositis, and their opinions on the new evidence-based guideline will be collected during an informal meal discussion. Comments and their intention to improve the situation of the high prevalence and
severe oral mucositis among patients who received chemotherapy will be obtained. Frontline staff may oppose the new innovation due to the fear of increasing daily workload. However, the proportion of the opposing staff would not be high due to the general positive attitude towards innovative guideline to be obtained from most frontline nurses before proposing the guideline. Opposing staff and some of the supportive senior RNs will be approached in a group. Meeting will be held to obtain their opinions and to find out their concerns for reducing the friction. During the meeting, evidence from the reviewed studies will be reported, pointing out that maintaining the current practice may increase workload due to the increase admission rate, and explaining no additional skill is required for the innovation. Getting consensus from the frontline staffs can facilitate the implementation of the new guideline. Modifications on the new guideline will be made according to their comments.

After the modification, an evidence-based guideline will be proposed to APNs who have the same intention as the innovation proposer towards oral mucositis, as shown during the chat in mealtime. With the support of those supportive APNs, others APNs and ward managers will be met with the proposer and supportive APNs during the regular weekly ward meeting. Significance of the existing problem, the problems in using the current practice to deal with chemotherapy-induced oral mucositis and the need of change for the current practice with sufficient reason and evidence to support innovated guideline will be presented in the ward meeting. Also, benefits that would be gained in terms of cost, patients’ benefit
and staff satisfaction when using the new evidence-based guideline will be illustrated.

After obtaining the support from APNs and ward managers, the DOM and COS will be approached. A formal presentation will be presented by an APN and the innovation proposer will provide a written proposal for the evidence-based guideline for better understanding. In the presentation, the significance, transferability, feasibility and the cost-benefit ratio of the innovation will be presented in order to obtain approval and support from the administrative level.

With the approval and support from the administrative level, an innovation team will be established in the first and second week. Innovation team includes one APN as an in-charge nurse, who will also the chairperson of the innovation team, and five senior nurses as coordinators. The innovation team will establish a communication plan to communicate with the stakeholders for implementing the innovation, carrying out a pilot test, modifying the guideline, and evaluating the effectiveness of the innovation. Information of the innovation program includes the significance of oral cryotherapy, the evidence-based guideline, and timeframe of implementing the oral cryotherapy, the training program, and the schedule of the program. The timeline for communication, pilot test and evaluation is attached in Appendix 7. All these information will be delivered to the nurses via internal email, daily handover time, posting updated information on staff notice board. This is to disseminate most update information to the staffs. Educational poster about the oral cryotherapy will also be
posted to encourage and remind staff using the oral cryotherapy.

In the third and fourth week, an hour training session will be provided to all nurses by the innovation team members. All staffs will be officially released to attend the training session. In the training session, clear explanation of the guideline will be given in the training session. Trainers will acknowledge the use of the new evidence-based guideline, proper documentation of oral mucositis, explain the standard of using the oral cryotherapy, and proper ice making procedure to all nurses. No additional skill or difficult procedure is needed for the new innovation. These factors can minimize the friction from staffs toward the innovation. Equipment for the innovation such as ice racks will also be prepared within these weeks.

During the implementation of the innovation, a coordinator will be available in each ward for solving any enquiry from staff. They will demonstrate the proper use of the new guideline of oral cryotherapy. At least one innovation team member works in each duty shift. Thus, immediate clarification and acknowledgement of skills can be made when the frontline nurses come across uncertainty and difficulty when using the new innovation. Support will be given to all frontline nurses at once. Also, the evidence-based guideline will be available in each ward. All staff can access to it easily.

In the sustained stage, innovation team will be responsible for monitoring the progress of the innovation. They will ensure all the equipment is functioning and available. A pilot test
will be conducted to test the feasibility of the innovation in the clinical setting. Comments and feedbacks will be obtained by the use from meal chatting, notice board and ward weekly meeting throughout the innovation period. Evaluation, modification and improvement of the guideline will be made. Updated detail or clarification will be made at once and will notice the frontline staff during daily handover time.

4.2 Pilot Test

Pilot test is a trial run of the innovation with a small population to test for the feasibility and acceptability before the implementation apply to a large population. It is used for testing whether the methods and the procedures of innovated program are clear and sufficient, whether the chosen instruments assess the innovation outcome properly, the effectiveness of the training material, and identify possible potential problems that may encounter during the implementation of the new innovation (Polit & Beck, 2008; Sidani & Braden, 2011). Pilot test in this innovation includes staff training sessions and the implementation of using the evidence-based guideline. The pilot test will be conducted by the innovation team members. The estimated time for the pilot test is approximately two and half months.

4.2.1 Enrollment Strategies

The target participants in the pilot test will be as same as the inclusion and exclusion
criteria used in the proposed innovation. Adult cancer patients, aged 18 to 65 years old, who are undergoing intravenous chemotherapy only in the clinical oncology department and is the first time for patients receiving oral cryotherapy will regard as eligible participate in the pilot test. If patients have received previous oral cryotherapy during the pilot test, it may affect the effectiveness of the innovation in pilot study. Patients with swallowing difficulty and receiving continuous intravenous chemotherapy for more than three hours will be excluded, since it is impossible for patients to use oral cryotherapy for more than three hours. Thus, they will be excluded. Convenience sampling will be used as the sampling method. Sample size for the pilot study is taken as 30 patients. Location for the pilot test will be conducted in two in-patient oncology wards in the target hospital. Since these two in-patients wards are responsible for admitting large proportion of continuous intravenous chemotherapy patients, it is more convenient to obtain sufficient sample and better observation of oral mucositis changes during hospitalization.

4.2.2 Staff Training

Pilot test will be conducted from the third to the twelfth week. Staff training session and proposed guideline will be tested in the pilot test to test the feasibility and the adequacy. Nurses will attend staff training session before implementing the evidence-based guideline. All recruited patients will be screened by the innovation team to ensure the eligibility for the
pilot study. Nurses would follow the proposed guideline and provide nursing care to the target patients. Before the start of the oral cryotherapy, nurse will assess patient’s oral condition to determine whether they are adequate for the oral cryotherapy. Patients’ oral condition will be assessed after the completion of the oral cryotherapy and daily assessment will be conducted during hospitalization. All incidences of oral mucositis, stage of oral mucositis, start and duration of oral cryotherapy will be accurately documented.

4.2.3 Data Collection

Incidence of oral mucositis and the score of oral mucositis are the patient outcomes. They will be collected together with patient characteristics including age and gender, medical diagnosis, smoking status, types of chemotherapy treatments, assessment of oral mucositis grading before and after the oral cryotherapy in the first day of the cryotherapy, daily oral mucositis score during hospitalization, duration of oral mucositis, duration of oral cryotherapy, side-effects of the use of the oral cryotherapy, and duration of hospitalization in data collection sheet (Appendix 8). If undesired effects occurred after the use of the new innovation (e.g. choking, suffocation, severe deterioration of oral mucositis), every incident should be reported to the in-charge nurse of the innovation team. Once patient require termination of oral cryotherapy, duration of oral cryotherapy, reasons for the termination of the oral cryotherapy, and the subsequent nursing and medical treatment provided will be
documented. When the decisions among the innovation team members are different or current nursing practice infringe the use of the guideline, they will be documented and further evaluated. All data will be computerized for evaluation.

Regarding the healthcare outcome in pilot test, nurses are required to fill in a self-reported questionnaire towards the training session for collecting the healthcare outcome. The questionnaire can help measure the satisfaction level among the staffs towards the training session. In addition, the cost using for the innovation will be marked and kept in a logbook for further evaluation.

### 4.2.4 Evaluation after Pilot Testing

Evaluation of the pilot test data will be performed between the 13\textsuperscript{th} and the 20\textsuperscript{th} week. Throughout the implementation of the guideline, innovation team will meet on a weekly basis. After the completion of the pilot test, innovation team will discuss and evaluate all data collected from the documentation, observation and feedback from patients, ward managers and frontline nurses. Feedbacks from the patients can be used to assess patients’ acceptance towards the innovation. An evaluation meeting will be held and nurses, APNs and ward managers will be invited to join in the meeting voluntarily. In the meeting, they will clarify the unclear points, and recognizes any difficulties after using the new guideline. Agreement among the innovation team members and frontline nurses should be achieved
before proceeding to the new version of the guideline. This is to ensure the validity and reliability of the training session and the guideline.

Moreover, opinions and compliance of the nurses for using the new guideline will be asked through comments sharing. Innovation team will also share the successful cases and the encountered difficulties in pilot test. Modification, improvement and enhancement of the guideline will be made after analyzing the data and discussion. Cost of the innovation in pilot test will be evaluated. This helps to identify any unexpected or unidentified cost during the implementation of the innovated guideline. A new and refined guideline will establish before at the end of evaluation pilot test period (i.e. around week seventeenth to week twentieth).

### 4.3 Evaluation Plan

Evaluation can assess the effectiveness of innovation; identifying the beneficence and possible adverse effects after using the innovation, and the worthiness of using the innovation in the target clinical setting. It can also help assess whether the innovation reach its objectives as specified at the planning stage (Polit & Beck, 2008). It is crucial to identify possible outcomes before innovation. Possible outcomes in this innovation are in patient aspect, healthcare provider aspect and system aspect. So, by comparing the different outcomes before and after the implementation of the innovation, we can formally evaluate the effectiveness of the innovation.
4.3.1 Outcomes

For patients’ outcomes, the primary patients’ outcome is the incidence of patients developing chemotherapy-induced oral. And the aim of innovation is to reduce the number of patients suffering from oral mucositis. Therefore, the effectiveness of oral cryotherapy can be determined by measuring the proportion of patients suffering from oral mucositis which can reflect from the oral mucositis grading. Patients who are graded as 0 in oral mucositis are regarded as not suffering from oral mucositis.

Patients’ mucositis score is the secondary primary outcome. Measuring mucositis score can reflect the severity of oral mucositis which patients suffer from. A higher mucositis score reflects the more severe mucositis the patients suffer from. Although it is not possible to prevent patient from developing oral mucositis, the use of oral cryotherapy can help to keep patients’ mucositis score low. This can help the patient to maintain a better functioning. The innovation can be considered as effective.

All oral mucositis grading will be measured by the frontline nurses according to WHO oral mucositis grading system (0 = No symptoms; 1 = Sore mouth, no ulcer; 2 = Sore mouth with ulcers, but able to eat normally; 3 = Able to eat liquid only; 4 = Unable to eat and drink). Data will be documented and collected by using the data collection sheet (Appendix 8). The data collection sheet can facilitate nurses to document patients’ progress and facilitate innovation team to collect data for evaluation.
In regards to the healthcare provider outcome, staff satisfaction level towards new innovation will be measured. Two areas of the staff satisfaction level will be measured: satisfactory level towards the training session and satisfactory level towards the evidence-based guideline. Staff are required to complete a self-reported questionnaire score rate 1 – 4 (4 = most satisfaction and 1 = most dissatisfaction) in the areas such as appropriateness of the provided material, clarity of the guideline, competence of using the new guideline and adequacy of the given support (Appendix 9). Since the outcomes are focused on the satisfaction level towards the training session and the use of new guideline. All medical officers are asked to complete a self-reported satisfaction questionnaire after the implementation of oral cryotherapy. For frontline nurses, they are asked to complete and return the self-reported satisfaction level questionnaire after attending the training session and completing the innovation. These can help assess the acceptance of the nurses. This helps to identify areas that need more support and to facilitate nurses to use the new innovation in future.

Cost effectiveness of using innovation is considered as the system outcome. The cost of using oral cryotherapy and the benefit brought form it are expected to be lower than the cost for treating oral mucositis when oral cryotherapy is not used. Cost of using oral cryotherapy includes manpower cost, cost of setting up the innovation and maintenance cost for the innovation each year.
4.3.2 Nature and Number of clients to be involved

Patients will be recruited from 21st to 45th weeks in which this phase lasts approximately six months. Patients should receive care from the clinical oncology department of the target hospital. Patients who aged 18 to 65 years old and are receiving intravenous chemotherapy only in the clinical oncology department of the target hospital will be considered as eligible to participate in the innovation. They will be recruited and evaluated. It is difficult to provide oral cryotherapy according to the innovated guideline when patients are not receiving chemotherapy in the clinical oncology department. Patients with swallowing difficulty and receiving continuous intravenous infused chemotherapy for more than three hours will be excluded because patients with swallowing difficulties are at a high risk of developing complication (e.g. suffocation when sucking ice cubes). Also, it is not feasible to require patients to suck ice cubes for more than three hours. Compliance cannot be achieved even when oral cryotherapy is provided. Therefore, these patients will be excluded in the innovation.

Convenience sampling is used for recruiting the target patients. All target patients will be followed up from the date of admission till the date of discharge. If clients require outpatient clinic follow-up at two to four weeks after the cryotherapy, their oral mucositis score will be followed on that dates.

In order to test whether the incidence rate of chemotherapy-induced oral mucositis is
less than 50% after the implementation of the oral cryotherapy, z-test for one proportion by Russ Lenth will be used (Lenth, 2006-9). An online computer software will be used to calculate sample size. With 80% power to detect the incidence rate of chemotherapy-induced oral mucositis and the incidence of oral mucositis in clinical setting are 50%, null value will be 0.5 and actual value is 0.4. 200 eligible patients would be required for the implementation of the oral cryotherapy.

4.3.3 Timing and Frequency of the measurements

The timing and the frequency for measuring the outcomes will be different based on the types of the outcomes. Patients’ outcome is the assessment of patients’ oral condition. Nurses will assess patients’ oral mucositis five minutes before the chemotherapy and after the completion of oral cryotherapy on the first day of the implementation of the oral cryotherapy. Measuring oral mucositis before the oral cryotherapy can act as a baseline of oral condition. Measurement taken after oral cryotherapy can assess any deterioration of oral mucositis after the use of cryotherapy.

Moreover, nurses will have a daily assessment on patients’ oral mucositis during hospitalization as usual. If oral cryotherapy is required, oral condition will be assessed before the oral cryotherapy is given. Daily assessment of patients’ oral condition is a basic nursing care for monitoring the progress of oral mucositis. And it is important for nurses to assess it
before the administration of oral cryotherapy, because nurses have the autonomy to withhold cryotherapy when patients’ oral condition is not fit. On day 14 and day 28, medical officers will have a routine assessment on patients’ oral condition to assess the side effect caused by the chemotherapy during a regular follow-up for cancer treatment. Data on patients’ oral mucositis will be assessed by the medical officers and documented in the data collection sheet. These data can facilitate innovation team to evaluate the progress of patients’ oral condition after using cryotherapy for two weeks and four weeks.

Regarding the healthcare providers’ outcome, nurses are required to fill in a self-reported satisfaction questionnaire immediately after attending the staff training session. This helps assess the effectiveness of the training session. Informal monthly meeting will be held by the innovation team with the healthcare providers for obtaining their comments and satisfaction level towards the use of the guideline. After the implementation of the innovated guideline is completed from week thirty-third and week fortieth, healthcare providers will fill in self-reported satisfaction questionnaire towards entire innovation program. For system outcomes, there will be a monthly evaluation on the cost of implementing the innovation and resources allocation. Total cost expenditure of the innovation program will be evaluated at the end of entire innovation program.
4.3.4 Analysis of Outcomes

All collected data will be analyzed and evaluated in the evaluation. All patient characteristics, medical diagnosis and chemotherapy schemes will be summarized by descriptive statistics.

The incidence rate of the chemotherapy-induced oral mucositis under the current practice is 50%. Z-test for testing one proportion will be used to analysis whether the incidence rate of oral mucositis can be less than 50% among patients after the implementation of the new guideline.

For the severity of oral mucositis measured by the oral mucositis score, patients’ mucositis score below 2 preserves better function as the higher oral mucositis score represents a more severe oral mucositis. One sample t-test will be used to test whether the mean oral mucositis score of patients can become below 2 after the implementation of the oral cryotherapy.

For the cost, all expenditure used for innovated program will be recorded in a logbook and enter into a computer by a clerical staff. All cost will be evaluated at the end of innovated program.
4.3.5 Basis of Adopting the Innovation

Innovation should be determined as effective before it can be adopt in a clinical setting. To determine whether an innovation is effective depends on whether its outcome can meet certain criteria and the stated objectives. Previous clinical data and evidences from previous reviewed studies can be the criteria for the consideration of the innovation effectiveness. If innovation’s outcomes can achieve similar result as the previous reviewed studies in the similar clinical setting, innovation can be considered as effective and the innovation should be adopted.

One of the objectives in implementing the oral cryotherapy is to reduce the incidence rate and severity of chemotherapy-induced oral mucositis. If there is a decrease in the incidence and severity of mucositis, innovation will be determined as effective. Since the incidence of oral mucositis in the target setting is more than 50%, innovation will be determined as effective when the incidence rate of oral mucositis is reduced to less than 50% for patients’ primary outcome. From the evidence of the reviewed studies, mean mucositis score in oral cryotherapy group was 0.22 to 1.98. According to the WHO oral mucositis grading system, patients with mucositis score 2 are able to eat normally even with sore mouth and ulcer, their functioning are not poorly affected. Therefore, if the mean oral mucositis score in patients’ secondary outcome is below 2, the innovation will be considered as beneficial for the patients and will be determined as effective.
Regarding the healthcare providers’ outcome, more than 80% staff are expected to return their self-reported satisfaction level questionnaire and over 50% frontline staff are expected to report their satisfaction towards the use of the new guideline and attending the training session. If nurses are not satisfied with the use of guideline, the acceptance of new guideline will be low. It will be hard to maintain the compliance of nurses to implement the oral cryotherapy according to the guideline. For the system outcome, the cost of treating chemotherapy-induced oral mucositis and the cost for innovation should be less than HK$3,000,000 comparing to the cost of treating chemotherapy-induced oral mucositis without using the oral cryotherapy.
## Appendices

### Appendix 1

### Search Strategy Table

<table>
<thead>
<tr>
<th>Search items</th>
<th>Database</th>
<th>CINAHL</th>
<th>Cochrane library</th>
<th>PubMed</th>
<th>British Nursing index</th>
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<tr>
<td>Svanberg et al., 2010</td>
<td>RCT, stratified randomization, block of six randomization</td>
<td>I++</td>
<td>Mean age: 52.1yrs F: 42.3% M: 57.7% Autologous: 79.5% Allogeneic: 20.5% Non-smoker: 87.2%</td>
<td>Cryotherapy (n=39 (31 autologous; 8 allogeneic/URD)) Suck on ice chips/ rinse with ice cold water 5 mins before, during, until end of chemotherapy</td>
<td>Not specify (n=39 (31 autologous; 8 allogeneic/URD))</td>
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</tbody>
</table>

RCT = randomized controlled trials; F = female; M = male; mins = minutes; OM = oral mucositis; TPN = total parental nutrition; n.s.s. = no statistically significant
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<th>Outcome measures</th>
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<td>1++</td>
<td>Mean age: 52.1 yrs F: 42.3% M: 57.7% Autologous: 79.5% Allogeneic: 20.5% Non-smoker: 87.2%</td>
<td>Cryotherapy (n=39 (31 autologous; 8 allogeneic/URD)) Suck on ice chips/rinse with ice cold water during, until the end of chemotherapy</td>
<td>Standard oral care (n=39 (31 autologous; 8 allogeneic/URD)) use soft toothbrush, gentle toothpaste at ward</td>
<td>Modified oral mucositis assessment score (Grade 0-4)</td>
<td>1) Lower mucositis score after days 10 or 16</td>
<td>1) Autologous: 1.6 in EXP group vs 4.3 in CTR group (p=0.042); Allogeneic: 3.7 in EXP group vs 11.6 CTR group (p=0.021)</td>
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<td>2) Lower values of CRP after days 11 or 20</td>
<td>2) Autologous: 66.1 in EXP group vs 111.3 in CTR group (p=0.039); Allogeneic: 42.9 in EXP group vs 113.8 CTR group (p=0.019)</td>
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<td>3) Days iv opioids</td>
<td>3) 0.77 in EXP group vs 2.44 in CTR group (p=0.045)</td>
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<td>4) Dose iv opioids, mg</td>
<td>4) 60 in EXP group vs 355 in CTR group (p=0.07)</td>
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<td>5) Total dose of opioids, mg</td>
<td>5) 202 in EXP group vs 695 in CTR group (p=0.08)</td>
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RCT = Randomized controlled trials; F = female; M = male
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<th>Patients characteristics</th>
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<th>Control</th>
<th>Mucositis grading system</th>
<th>Outcome measures</th>
<th>Effect Size</th>
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<tbody>
<tr>
<td>Sorensen et al., 2008</td>
<td>RCT</td>
<td>1+</td>
<td>Mean age: 62 yrs F: 45% M: 55% Non-smoker: 71%</td>
<td>Cryotherapy (Arm C) (n=67) Crushed ice placed in mouth, 10 mins before, during, 35 mins after every chemotherapy infusion</td>
<td>NS (Arm B) (n=66) 10 ml added taste NS rinse in mouth 1 mins for 3times/day (D1-D21)</td>
<td>CTC grading of OM (Grade 0-4)</td>
<td>1) Incidence of grade 3–4 OM 2) Median duration of OM</td>
<td>1) 10% in Arm C vs 32% in Arm B (p&lt;0.005); 12% in Arm A vs 32% in Arm B (p&lt;0.01) 2) 1 day in Arm C vs 5 days in Arm B (p=0.003); 3 days in Arm A vs 5 days in Arm B (p=0.035)</td>
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<td>Papadeas et al., 2007</td>
<td>RCT, Randomized by date of birth</td>
<td>1+</td>
<td>Median age: 61-62.6 yrs F: 65.8% M: 34.2% Gum condition: 80.3% with good –fair Non-smoker: 68.4%</td>
<td>Cryotherapy (n=36) Crushed ice cubes swish in mouth. 5 mins before, during, 30 mins after IV administration of 5FU</td>
<td>Not specify (n=40)</td>
<td>Not specify (Grade 0-4)</td>
<td>1) Mean physician-judged stomatitis score 2) Mean patient-judged stomatitis score</td>
<td>1) 1st cycle: 0.22 in EXP group vs 0.7 in CTR group (p&lt;0.001); 2nd cycle: 0.47 in EXP group vs 0.9 in CTR group (p&lt;0.01); 3rd cycle: 0.77 in EXP group vs 1.5 in CTR group (p&lt;0.001) 2) 1st cycle: 0.25 in EXP group vs 0.7 in CTR group (p&lt;0.01); 2nd cycle: 0.5 in EXP group vs 1.2 in CTR group (p&lt;0.001); 3rd cycle: 1.2 in EXP group vs 1.7 in CTR group (p&lt;0.005)</td>
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</table>

RCT = Randomized controlled trials; F = female; M = male; mins = minutes; 5FU = 5-fluorouracil; OM = oral mucositis; Arm A = Chlorhexidine; Arm B = normal saline; Arm C = oral cryotherapy; CTC = Common Toxicity Criteria
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<th>Study type</th>
<th>Evidence level</th>
<th>Patients characteristics</th>
<th>Intervention</th>
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<th>Mucositis grading system</th>
<th>Outcome measures</th>
<th>Effect Size</th>
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<tr>
<td>Lilleby et al., 2006</td>
<td>Randomized study Stratified by age</td>
<td>1+</td>
<td>Median age: 57-59 yrs F: 70% M: 30%</td>
<td>Cryotherapy (n=21) Put 1 oz crushed ice 30 mins before, 6 hrs during, after 30 mins melphalan infusion</td>
<td>Rinse 1 oz room temp. NS (n=19), spit out every 30 mins</td>
<td>NCI common toxicity criteria (Grade 0-4)</td>
<td>1) Incidence of grade 3-4 mucositis 2) Mean mucositis score 3) Days of TPN used 4) Days of IV narcotic used 5) Days of hospitalization</td>
<td>1) 14% in EXP group vs 74% in CTR group (p=0.0005) 2) 0.41 in EXP group vs 1.06 in CTR group (p=0.0005) 3) 2 in EXP group vs 5.5 in CTR group (p=0.04) 4) 0 in EXP group vs 5.5 in CTR group (p=0.04) 5) 9 in EXP group vs 14 in CTR group (p=0.11)</td>
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</table>

F = female; M = male; mins = minutes; NS = normal saline; OM = oral mucositis; TPN = total parental nutrition; NCI = National Cancer Institute; IV = intravenous; oz=ounce
<table>
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<tr>
<th>Bibliographic citation</th>
<th>Study type</th>
<th>Evidence level</th>
<th>Patients characteristics</th>
<th>Intervention</th>
<th>Control</th>
<th>Mucositis grading system</th>
<th>Outcome measures</th>
<th>Effect Size</th>
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<tbody>
<tr>
<td>Karagozoglu et al., 2005</td>
<td>Randomized controlled study</td>
<td>1-</td>
<td>&gt; 60 years old: 66.7% F: 23.3% M: 76.7%</td>
<td>Cryotherapy (n=30) Smoothed cubes placed in mouth 5 mins before, during and till end of IV infusion chemotherapy</td>
<td>Not specify (n=30)</td>
<td>Patient- and physician- Judged Mucositis Grading (Grade 0-4)</td>
<td>1) Incidence of Patient-judged OM Grade 1-3 2) Incidence of Physician-judged OM Grade 1-3 3) Mean mucositis score 4) Mean duration of mucositis 5) Mean oral pH value in EXP group</td>
<td>1) 36.7% in EXP group vs 90% in CTR group (p&lt;0.05) 2) 10% in EXP group vs 50% in CTR group (p&lt;0.05) 3) 0.23 in EXP group vs 0.83 in CTR group (p-value not specify) 4) 7.09 days in EXP group vs 12.03 days in CTR group (p&lt;0.05) 5) Before: pH 6.07 and after: pH 7.07 in EXP group (p&lt;0.05)</td>
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F = female; M = male; mins = minutes; IV = intravenous; OM = oral mucositis;
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<th>Bibliographic citation</th>
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<th>Evidence level</th>
<th>Patients characteristics</th>
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<th>Mucositis grading system</th>
<th>Outcome measures</th>
<th>Effect Size</th>
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<tr>
<td>Gori et al., 2007</td>
<td>Randomized control study, randomization list</td>
<td>1+</td>
<td>Median age: 37.75 yrs old F: 49.2% M: 50.8% Received TBI: 29.5%</td>
<td>Cryotherapy (n=62) Keep mineral water ice/commercial ice cubes in oral cavity during and after 55 mins of MTX infusion</td>
<td>Not specify (n=60)</td>
<td>WHO scale (Grade 0-4)</td>
<td>1) Incidence of grade 3-4 oral mucositis</td>
<td>1) 46.7% in EXP group vs 53.3% in CTR group (p=0.46)</td>
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<td>2) Incidence of grade 2-4 mucositis</td>
<td>2) 80% in EXP group vs 80% in CTR group (p=0.92)</td>
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<td>3) Mucositis duration in grade 3-4 mucositis</td>
<td>3) 6 days in EXP group vs 6 days in CTR group (p=1)</td>
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<td>4) Mucositis duration in grade 2-4 mucositis</td>
<td>4) 10 days in EXP group vs 11 days in CTR group (p=1)</td>
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<td>5) Maximum mean mucositis score</td>
<td>5) 1.98 in EXP group vs 2.13 in CTR group (p=0.56)</td>
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F = female; M = male; mins = minutes; IV = intravenous; MTX = Methotrexate; TBI = total body irradiation; WHO = World Health Organization
### Methodology Checklist 2: Controlled Trials

#### Study identification

Include author, title, year of publication, journal title, pages.


#### SECTION 1: INTERNAL VALIDITY

**In a well conducted RCT study...**

**In this study this criterion is:**

<p>| | | |</p>
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<tbody>
<tr>
<td><strong>1.1</strong></td>
<td>The study addresses an appropriate and clearly focused question.</td>
<td>Adequately addressed</td>
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<tr>
<td><strong>1.2</strong></td>
<td>The assignment of subjects to treatment groups is randomized</td>
<td>Adequately addressed</td>
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<tr>
<td><strong>1.3</strong></td>
<td>An adequate concealment method is used</td>
<td>Not addressed</td>
</tr>
<tr>
<td><strong>1.4</strong></td>
<td>Subjects and investigators are kept ‘blind’ about treatment allocation</td>
<td>Adequately addressed</td>
</tr>
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<td><strong>1.5</strong></td>
<td>The treatment and control groups are similar at the start of the trial</td>
<td>Adequately addressed</td>
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<tr>
<td><strong>1.6</strong></td>
<td>The only difference between groups is the treatment under investigation</td>
<td>Adequately addressed</td>
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<tr>
<td><strong>1.7</strong></td>
<td>All relevant outcomes are measured in a standard, valid and reliable way</td>
<td>Adequately addressed</td>
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<td><strong>1.8</strong></td>
<td>What percentage of the individuals or clusters recruited into each treatment arm of the study dropped out before the study was completed?</td>
<td>1 participant dropped out in intervention, dropped out rate = 2.6% in intervention group 0% dropped out in control group</td>
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<tr>
<td><strong>1.9</strong></td>
<td>All the subjects are analysed in the groups to which they were randomly allocated (often referred to as intention to treat analysis)</td>
<td>Well covered</td>
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<tr>
<td>1.10</td>
<td>Where the study is carried out at more than one site, results are comparable for all sites</td>
<td>Not applicable</td>
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**SECTION 2: OVERALL ASSESSMENT OF THE STUDY**

| 2.1  | How well was the study done to minimise bias?  
*Code ++, +, or –* | 1++, because the study’s methodology had covered majority criteria with adequately addressed or above. |
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<td>2.2</td>
<td>Taking into account clinical considerations, your evaluation of the methodology used, and the statistical power of the study, are you certain that the overall effect is due to the study intervention?</td>
<td>Yes. It has a high quality methodology. The dropped out rate of participants was low. It is certain that the overall effect was due to the study intervention.</td>
</tr>
<tr>
<td>2.3</td>
<td>Are the results of this study directly applicable to the patient group targeted by this guideline?</td>
<td>Yes. The study focused similar patients group as proposed guideline focused on.</td>
</tr>
</tbody>
</table>
**Methodology Checklist 2: Controlled Trials**

**Study identification**  
*Include author, title, year of publication, journal title, pages*

### SECTION 1: INTERNAL VALIDITY

**In a well conducted RCT study...**

<table>
<thead>
<tr>
<th><strong>In this study this criterion is:</strong></th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th><strong>In a well conducted RCT study...</strong></th>
<th><strong>In this study this criterion is:</strong></th>
</tr>
</thead>
</table>
| 1.1 The study addresses an appropriate and clearly focused question. | Adequately addressed  
Focused question was clearly stated in introduction. |
| 1.2 The assignment of subjects to treatment groups is randomized | Adequately addressed  
Stratified and block of six randomization method stated. |
| 1.3 An adequate concealment method is used | Not addressed |
| 1.4 Subjects and investigators are kept ‘blind’ about treatment allocation | Adequately addressed  
Researcher responsible for allocating participants was “blinded”, but it was not applicable to “blinded” participants. |
| 1.5 The treatment and control groups are similar at the start of the trial | Adequately addressed  
Patient characteristics well balanced and reported no statistical significant between groups. |
| 1.6 The only difference between groups is the treatment under investigation | Adequately addressed  
No additional treatment was given. |
| 1.7 All relevant outcomes are measured in a standard, valid and reliable way | Adequately addressed  
All outcomes measured in a valid and reliable way. |
| 1.8 What percentage of the individuals or clusters recruited into each treatment arm of the study dropped out before the study was completed? | 1 participant dropped out in intervention, dropped out rate = 2.6% in intervention group  
0% dropped out in control group |
| 1.9 All the subjects are analysed in the groups to which they were randomly allocated (often referred to as intention to treat analysis) | Well covered  
Intention to treat was clearly stated in study. |
### SECTION 2: OVERALL ASSESSMENT OF THE STUDY

<table>
<thead>
<tr>
<th>2.1</th>
<th>How well was the study done to minimise bias? <em>Code ++, +, or −</em></th>
<th>1++, because the study’s methodology had covered majority criteria with adequately addressed or above.</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.2</td>
<td>Taking into account clinical considerations, your evaluation of the methodology used, and the statistical power of the study, are you certain that the overall effect is due to the study intervention?</td>
<td>Yes. It has a high quality methodology. The dropped out rate of participants was low. It is certain that the overall effect was due to the study intervention.</td>
</tr>
<tr>
<td>2.3</td>
<td>Are the results of this study directly applicable to the patient group targeted by this guideline?</td>
<td>Yes. The study focused similar patients group as proposed guideline focused on.</td>
</tr>
</tbody>
</table>
**Methodology Checklist 2: Controlled Trials**

**Study identification**  
*(Include author, title, year of publication, journal title, pages)*


**SECTION 1: INTERNAL VALIDITY**

<table>
<thead>
<tr>
<th>In a well conducted RCT study…</th>
<th>In this study this criterion is:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1 The study addresses an appropriate and clearly focused question.</td>
<td>Adequately addressed</td>
</tr>
<tr>
<td>The purpose of study was clearly stated in introduction, but no research question stated.</td>
<td></td>
</tr>
<tr>
<td>1.2 The assignment of subjects to treatment groups is randomized</td>
<td>Poorly addressed</td>
</tr>
<tr>
<td>Details of randomization method were not described. It has only stated randomization being used.</td>
<td></td>
</tr>
<tr>
<td>1.3 An adequate concealment method is used</td>
<td>Not addressed</td>
</tr>
<tr>
<td>Details of concealment did not mention in study.</td>
<td></td>
</tr>
<tr>
<td>1.4 Subjects and investigators are kept ‘blind’ about treatment allocation</td>
<td>Not applicable</td>
</tr>
<tr>
<td>It is unable to “blind” participants in intervention group, as they had to suck ice cubes.</td>
<td></td>
</tr>
<tr>
<td>1.5 The treatment and control groups are similar at the start of the trial</td>
<td>Adequately addressed</td>
</tr>
<tr>
<td>Patient characteristics were evenly distributed between groups, no significant different were reported before trials.</td>
<td></td>
</tr>
<tr>
<td>1.6 The only difference between groups is the treatment under investigation</td>
<td>Well covered</td>
</tr>
<tr>
<td>Interventions were the only different between groups in study, such as arm A: Chlorhexidine; arm B: normal saline; arm C: Oral cryotherapy</td>
<td></td>
</tr>
<tr>
<td>Section</td>
<td>Question</td>
</tr>
<tr>
<td>---------</td>
<td>----------</td>
</tr>
<tr>
<td>1.7</td>
<td>All relevant outcomes are measured in a standard, valid and reliable way</td>
</tr>
<tr>
<td></td>
<td>Outcomes were measured in a standard, valid and reliable way.</td>
</tr>
<tr>
<td>1.8</td>
<td>What percentage of the individuals or clusters recruited into each treatment arm of the study dropped out before the study was completed?</td>
</tr>
<tr>
<td>1.9</td>
<td>All the subjects are analysed in the groups to which they were randomly allocated (often referred to as intention to treat analysis)</td>
</tr>
<tr>
<td></td>
<td>All participants were analyzed according to their groups, but intention to treat had not specified.</td>
</tr>
<tr>
<td>1.10</td>
<td>Where the study is carried out at more than one site, results are comparable for all sites</td>
</tr>
</tbody>
</table>

**SECTION 2: OVERALL ASSESSMENT OF THE STUDY**

<table>
<thead>
<tr>
<th>Section</th>
<th>Question</th>
<th>Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.1</td>
<td>How well was the study done to minimise bias? Code ++, +, or –</td>
<td>1+, randomization process described in detail, but date of birth was not a truly randomization. Thus, it could not reach the highest quality level.</td>
</tr>
<tr>
<td>2.2</td>
<td>Taking into account clinical considerations, your evaluation of the methodology used, and the statistical power of the study, are you certain that the overall effect is due to the study intervention?</td>
<td>Yes. The study with moderate quality of its methodology.</td>
</tr>
<tr>
<td>2.3</td>
<td>Are the results of this study directly applicable to the patient group targeted by this guideline?</td>
<td>Yes. The study focused similar patients group as proposed guideline focused on.</td>
</tr>
</tbody>
</table>
### Methodology Checklist 2: Controlled Trials

**Study identification**: (Include author, title, year of publication, journal title, pages)


### SECTION 1: INTERNAL VALIDITY

**In a well conducted RCT study...**

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1.1</strong></td>
<td>The study addresses an appropriate and clearly focused question.</td>
<td>Adequately addressed</td>
</tr>
<tr>
<td><strong>1.2</strong></td>
<td>The assignment of subjects to treatment groups is randomized</td>
<td>Poorly addressed</td>
</tr>
<tr>
<td><strong>1.3</strong></td>
<td>An adequate concealment method is used</td>
<td>Not addressed</td>
</tr>
<tr>
<td><strong>1.4</strong></td>
<td>Subjects and investigators are kept ‘blind’ about treatment allocation</td>
<td>Adequately addressed</td>
</tr>
<tr>
<td><strong>1.5</strong></td>
<td>The treatment and control groups are similar at the start of the trial</td>
<td>Adequately addressed</td>
</tr>
<tr>
<td><strong>1.6</strong></td>
<td>The only difference between groups is the treatment under investigation</td>
<td>Adequately addressed</td>
</tr>
<tr>
<td><strong>1.7</strong></td>
<td>All relevant outcomes are measured in a standard, valid and reliable way</td>
<td>Adequately addressed</td>
</tr>
<tr>
<td><strong>1.8</strong></td>
<td>What percentage of the individuals or clusters recruited into each treatment arm of the study dropped out before the study was completed?</td>
<td>9 participants, 20% dropped out in intervention group. None of the participant dropped out in control group.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td><strong>1.9</strong></td>
<td>All the subjects are analysed in the groups to which they were randomly allocated (often referred to as intention to treat analysis)</td>
<td>Poorly addressed</td>
</tr>
<tr>
<td><strong>1.10</strong></td>
<td>Where the study is carried out at more than one site, results are comparable for all sites</td>
<td>Not addressed</td>
</tr>
</tbody>
</table>

**SECTION 2: OVERALL ASSESSMENT OF THE STUDY**

| **2.1** | How well was the study done to minimise bias? *Code ++, +, or –* | 1+, the study covered most of the criteria, but randomization method was poorly addressed. Thus, it could not reach the highest quality level. |
| **2.2** | Taking into account clinical considerations, your evaluation of the methodology used, and the statistical power of the study, are you certain that the overall effect is due to the study intervention? | Yes, it had a moderate methodology quality. |
| **2.3** | Are the results of this study directly applicable to the patient group targeted by this guideline? | Yes. It targeted the same target group as proposed guideline. |
**Methodology Checklist 2: Controlled Trials**

**Study identification**  
*Include author, title, year of publication, journal title, pages*

**SECTION 1: INTERNAL VALIDITY**

<table>
<thead>
<tr>
<th>In a well conducted RCT study…</th>
<th>In this study this criterion is:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1 The study addresses an appropriate and clearly focused question.</td>
<td>Adequately addressed The objective was clearly stated.</td>
</tr>
<tr>
<td>1.2 The assignment of subjects to treatment groups is randomized</td>
<td>Poorly addressed Details of randomization method did not describe.</td>
</tr>
<tr>
<td>1.3 An adequate concealment method is used</td>
<td>Not addressed</td>
</tr>
<tr>
<td>1.4 Subjects and investigators are kept ‘blind’ about treatment allocation</td>
<td>Not applicable Participants were unable to be “blinded”.</td>
</tr>
<tr>
<td>1.5 The treatment and control groups are similar at the start of the trial</td>
<td>Adequately addressed Patient characteristics were balanced between groups, not significant was reported.</td>
</tr>
<tr>
<td>1.6 The only difference between groups is the treatment under investigation</td>
<td>Adequately addressed Not additional treatment was given.</td>
</tr>
<tr>
<td>1.7 All relevant outcomes are measured in a standard, valid and reliable way</td>
<td>Adequately addressed Outcomes were measured in valid and reliable way.</td>
</tr>
<tr>
<td>1.8 What percentage of the individuals or clusters recruited into each treatment arm of the study dropped out before the study was completed?</td>
<td>0% and 5% participants dropped out in intervention and control group respectively.</td>
</tr>
<tr>
<td>1.9 All the subjects are analysed in the groups to which they were randomly allocated (often referred to as intention to treat analysis)</td>
<td>Poorly addressed All participants were analyzed according to their groups, but intention to treat had not specified.</td>
</tr>
<tr>
<td>1.10</td>
<td>Where the study is carried out at more than one site, results are comparable for all sites</td>
</tr>
</tbody>
</table>

**SECTION 2: OVERALL ASSESSMENT OF THE STUDY**

<p>| 2.1 | How well was the study done to minimise bias? <em>Code ++, +, or –</em> | 1+, it has met some of the criteria in methodology checklist |
| 2.2 | Taking into account clinical considerations, your evaluation of the methodology used, and the statistical power of the study, are you certain that the overall effect is due to the study intervention? | Yes, because it is a moderate quality study. |
| 2.3 | Are the results of this study directly applicable to the patient group targeted by this guideline? | Yes. It focused the same target group as proposed guideline. |</p>
<table>
<thead>
<tr>
<th><strong>SECTION 1: INTERNAL VALIDITY</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>In a well conducted RCT study...</strong></td>
<td><strong>In this study this criterion is:</strong></td>
</tr>
</tbody>
</table>
| 1.1 The study addresses an appropriate and clearly focused question. | Well covered  
Aim and hypothesis were clearly stated in introduction.  |
| 1.2 The assignment of subjects to treatment groups is randomized | Poorly addressed  
Details of randomization did not describe.  |
| 1.3 An adequate concealment method is used | Not addressed  |
| 1.4 Subjects and investigators are kept ‘blind’ about treatment allocation | Not applicable  
It was unable to ‘blind’ participants and evaluators.  |
| 1.5 The treatment and control groups are similar at the start of the trial | Not addressed  
It did not report and mention different between groups.  |
| 1.6 The only difference between groups is the treatment under investigation | Adequately addressed  
No addition treatment given, all possible confounding factors reported not affecting the groups.  |
| 1.7 All relevant outcomes are measured in a standard, valid and reliable way | Adequately addressed  
Outcome measurements were valid and reliable.  |
| 1.8 What percentage of the individuals or clusters recruited into each treatment arm of the study dropped out before the study was completed? | 0%. No one was dropped out in intervention and control group.  |
| 1.9 | All the subjects are analysed in the groups to which they were randomly allocated (often referred to as intention to treat analysis) | Poorly addressed | It did not report whether patients were intention to treat, but patients were analyzed to their groups. |
| 1.10 | Where the study is carried out at more than one site, results are comparable for all sites | Not applicable | Study carried in one site. |

**SECTION 2: OVERALL ASSESSMENT OF THE STUDY**

| 2.1 | How well was the study done to minimise bias? *Code ++, +, or −* | 1-, it could only met several criteria with adequately addressed. Most of the criteria could not clearly state. Higher risk bias was likely occurring. |
| 2.2 | Taking into account clinical considerations, your evaluation of the methodology used, and the statistical power of the study, are you certain that the overall effect is due to the study intervention? | Might be, due to study did not address the different between groups and poor address of randomization detail. It could have a high risk of potential bias. The secondary outcome such as pH value could not be generalized. |
| 2.3 | Are the results of this study directly applicable to the patient group targeted by this guideline? | Yes. It focused similar target group as participants in proposed guideline. |
### Methodology Checklist 2: Controlled Trials

**Study identification**  
*Include author, title, year of publication, journal title, pages*


### SECTION 1: INTERNAL VALIDITY

**In a well conducted RCT study...**  
**In this study this criterion is:**

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1</td>
<td>The study addresses an appropriate and clearly focused question.</td>
<td>Adequately addressed</td>
</tr>
<tr>
<td>1.2</td>
<td>The assignment of subjects to treatment groups is randomized</td>
<td>Adequately addressed</td>
</tr>
<tr>
<td>1.3</td>
<td>An adequate concealment method is used</td>
<td>Not addressed.</td>
</tr>
<tr>
<td>1.4</td>
<td>Subjects and investigators are kept ‘blind’ about treatment allocation</td>
<td>Not applicable</td>
</tr>
<tr>
<td>1.5</td>
<td>The treatment and control groups are similar at the start of the trial</td>
<td>Well covered</td>
</tr>
<tr>
<td>1.6</td>
<td>The only difference between groups is the treatment under investigation</td>
<td>Well covered</td>
</tr>
<tr>
<td>1.7</td>
<td>All relevant outcomes are measured in a standard, valid and reliable way</td>
<td>Adequately addressed</td>
</tr>
</tbody>
</table>
| 1.8 | What percentage of the individuals or clusters recruited into each treatment arm of the study dropped out before the study was completed? | Intervention group: 6/62 X 100% = 9.7%  
Control group: 0%  
Because participants refuse or unable to tolerate cryotherapy. |   |
1.9  All the subjects are analysed in the groups to which they were randomly allocated (often referred to as intention to treat analysis) | Results of dropped out participant were excluded.

1.10 Where the study is carried out at more than one site, results are comparable for all sites | Not applicable  
Study carried in one site only.

### SECTION 2: OVERALL ASSESSMENT OF THE STUDY

2.1  How well was the study done to minimise bias?  
*Code ++, +, or –* | 1+, it could cover most of the criteria in checklist with adequately addressed.

2.2  Taking into account clinical considerations, your evaluation of the methodology used, and the statistical power of the study, are you certain that the overall effect is due to the study intervention? | Yes, after evaluating the study methodology, the study with moderate quality.

2.3  Are the results of this study directly applicable to the patient group targeted by this guideline? | Yes. Participants were similar to targeted patients in proposed guideline.

2.4 **Notes.** Summarise the authors conclusions. Add any comments on your own assessment of the study, and the extent to which it answers your question.  
Although the study with moderate quality, compared with others similar studies folinic acid and total body irradiation (TBI) had been used in Gori et al.’s study. Cryotherapy might not have additional impact on TBI patients.
Appendix 4

Cost of setting up innovation

<table>
<thead>
<tr>
<th>Staff cost</th>
<th>Items</th>
<th>Cost (HK$)</th>
<th>Total cost (HK$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 in-charged nurse</td>
<td>1 training hour</td>
<td>$255/hr</td>
<td>$255</td>
</tr>
<tr>
<td>5 coordinated nurses</td>
<td>1 training hour</td>
<td>$220/hr</td>
<td>$1,100</td>
</tr>
<tr>
<td>60 nurses</td>
<td>1 training hour</td>
<td>$200/hr</td>
<td>($200 X 60) + ($200X5) + $255 = $13,355</td>
</tr>
<tr>
<td>Total staff training cost</td>
<td></td>
<td></td>
<td>$14,710</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Material cost</th>
<th>Items</th>
<th>Cost (HK$)</th>
<th>Total cost (HK$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ice racks</td>
<td>20</td>
<td>$20/ each</td>
<td>$400</td>
</tr>
<tr>
<td>Photocopies notes/ guideline</td>
<td></td>
<td></td>
<td>$1,500</td>
</tr>
<tr>
<td>Stationeries</td>
<td></td>
<td></td>
<td>$500</td>
</tr>
<tr>
<td>Total material cost</td>
<td></td>
<td></td>
<td>$2,400</td>
</tr>
</tbody>
</table>

**Total set up cost for innovation:** $17,110
Appendix 5

### Maintenance cost of innovation per year

<table>
<thead>
<tr>
<th>Staff cost</th>
<th>Items</th>
<th>Cost (HK$)</th>
<th>Total cost (HK$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Training cost for newly recruited staff and refreshment for current staff</td>
<td>70</td>
<td>$200/hr</td>
<td>$14,000</td>
</tr>
<tr>
<td>Total staff training cost</td>
<td></td>
<td></td>
<td>$14,000</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Material maintenance cost</th>
<th>Items</th>
<th>Cost (HK$)</th>
<th>Total cost (HK$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maintenance cost of freezers</td>
<td>2</td>
<td>$4,000/each</td>
<td>$8,000</td>
</tr>
<tr>
<td>Wear off of ice rack</td>
<td>5</td>
<td>$20/each</td>
<td>$100</td>
</tr>
<tr>
<td>Photocopies notes/guideline/protocol</td>
<td></td>
<td></td>
<td>$800</td>
</tr>
<tr>
<td>Stationeries</td>
<td></td>
<td></td>
<td>$500</td>
</tr>
<tr>
<td>Total material maintenance cost</td>
<td></td>
<td></td>
<td>$9,400</td>
</tr>
</tbody>
</table>

**Total maintenance cost of innovation:** $23,400
Appendix 6
An Evidence-Based Guideline

An evidence-based guideline on the use of cryotherapy for chemotherapy-induced oral mucositis in adult cancer patients

Introduction

Chemotherapy is one of the major treatments for cancer patients. The common adverse side-effect caused by chemotherapy is oral mucositis. The prevalence rate of chemotherapy-induced oral mucositis is approximately 30% (Etling et al., 2003; Nottage et al., 2003). In particular, studies have shown that the prevalence of oral mucositis in patients who have undergone chemotherapy scheme such as rapid intravenous chemotherapy or high dose chemotherapy can be as high as 74% (Meropol et al., 2003; Lilleby et al., 2006). The complication of chemotherapy-induced oral mucositis such as an increased risk of infection, poor nutrient, impaired quality of life, decreased tolerance of cancer treatment, and cost of huge medical burden should not be underestimated. There is an urgency to develop an evidence-based guideline to prevent the development of chemotherapy-induced oral mucositis or reduce its severity.

This guideline is based on the evidence obtained from the reviewed studies. It is established for nurses working in an oncology department of the local public hospital to prevent or reduce the incidence and severity of chemotherapy-induced oral mucositis for adult cancer patients who have undergone chemotherapy treatment. The level of evidence among all reviewed studies was rated based on the Scottish Intercollegiate Guidelines Network (SIGN, 2004). The grades of recommendations developed in this evidence-based guideline were based on the SIGN (2008). Nurses should terminate oral cryotherapy if it is considered as undesirable. The subsequent care for undesirable outcomes should be properly documented and report to the innovation in-charge nurse as soon as possible.
Objectives

The objectives of this guideline are:

1. To provide an evidence-based guideline in the use of oral cryotherapy;
2. To standardize nursing care for chemotherapy management;
3. To assist nurses in decision making for administrating oral cryotherapy and describe the subsequent management for undesirable outcomes;

Target group

This evidence-based guideline would target adult cancer patients who age 18 to 65 years old and are receiving chemotherapy as their cancer treatment only in a clinical oncology department.

If patients meet the following criteria, they will be eligible to receive oral cryotherapy,

1. Ages 18 to 65 years old;
2. Receiving chemotherapy in clinical oncology department;
3. Undergoing intravenous chemotherapy no longer than 3 hours.

Recommendation I

Oral cryotherapy should be initiated for patients receiving short half-life chemotherapy.

(Grade of recommendation: A)

Short half-life chemotherapy including 5-fluorouracil and Melphalan can benefit from oral cryotherapy (Svanberg et al., 2010, 2007; Lilley et al., 2006; Papadeas et al., 2006; Sorensen et al., 2008) (1++, 1+). Duration of short half-life chemotherapy rapidly reaches its peak level and only remains in circulation for a short period. Cryotherapy rapidly causes oral vasoconstriction and reduces cytotoxic drug flow (Lilley et al., 2006) (1+).

Oral cryotherapy can also reduce epithelial and basal cells metabolic function in oral mucosal membrane. So they can reduce the damage caused by chemotherapy (Lilley et al.,
Recommendation II

Oral cryotherapy should be administrated 5 minutes before, during and 30 minutes after chemotherapy. (Grade of recommendation: A)

Among the reviewed studies, four high to low quality studies suggested cryotherapy should be given 5 minutes before the chemotherapy infusion (Svanberg et al., 2010; Svanberg et al., 2007; Papadeas et al., 2007; Karagozoglu et al., 2005) (1++, 1+, 1-). All reviewed studies recommended oral cryotherapy should be used during chemotherapy infusion (Svanberg et al., 2010; Svanberg et al., 2007; Lilley et al., 2006; Papadeas et al., 2006; Sorensen et al., 2008; Lilleby et al., 2006; Gori et al., 2007; Karagozoglu et al., 2005) (1++, 1+, 1-). Cryotherapy should be administered in 30 minutes after the chemotherapy infusion has ended, as it is recommended in two moderate quality studies (Papadeas et al., 2007; Lilleby et al., 2006) (1+). Therefore, these schedules of administrating oral cryotherapy are suggested.

Recommendation III

Patients should be reinforced to keep their mouth constantly cool during oral cryotherapy. Oral cavity should often refill with ice to prevent ice in patient’s mouth melted completely. Size of ice should fit according to patients’ oral cavity. (Grade of recommendation: A)

All reviewed studies reinforced the importance to keep oral cavity constantly cool (Svanberg et al., 2010; Svanberg et al., 2007; Lilley et al., 2006; Papadeas et al., 2006; Sorensen et al., 2008; Lilleby et al., 2006; Gori et al., 2007; Karagozoglu et al., 2005) (1++, 1+, 1-). Keeping oral cavity consistently can reduce the quantity of drug disturbed to mouth
and reduce oral pain (Papadeas et al., 2006) (1+).

The sizes of oral cavities among patients are different. Various sizes of ice cubes will be available. It can facilitate ice cube swishes around patients’ oral cavity. Moreover, patients are instructed not to intake extremely hot or cold food. It is because the intake of extremely hot or cold food can cause further stimulation to oral cavity and increase teeth discomfort (Lilleby et al., 2006) (1+).

**Recommendation IV**

**Oral mucositis should be evaluated daily during hospitalization. (Grade of recommendation: A)**

It is important for nurses to evaluate patients’ oral mucositis daily during hospitalization in order to observe oral mucositis change. All reviewed studies reported that oral mucositis’s condition would change constantly (Svanberg et al., 2010; Svanberg et al., 2007; Lilley et al., 2006; Papadeas et al., 2006; Sorensen et al., 2008; Lilleby et al., 2006; Gori et al., 2007; Karagozoglu et al., 2005) (1++, 1+, 1-). So nurses can give corresponding nursing care according to different oral condition such as termination of oral cryotherapy.

**Recommendation V**

**World Health Organization (WHO) oral mucositis grading scale is recommended to be used as the evaluation of patients’ severity level of oral mucositis. (Grade of recommendation: RT)**

WHO oral mucositis scale is a well-known oral mucositis scale. It has been widely used in the local setting. All nurses are familiar and have sufficient skills to use the WHO mucositis grading scale. Proper documentation and mucositis grading system will be reinforced to all nurses in training sessions.
Recommendation VI
Inform physicians for medical treatment if grade 3 – 4 oral mucositis develops. (Grade of recommendation: RT)

Although oral cryotherapy is effective in reducing severity of oral mucositis and the risk for oral mucositis deterioration is low based on the reviewed studies, there is still a chance that patients may develop severe oral mucositis. As nurses would monitor patients’ oral condition daily, it is essential for nurses to inform physicians to give additional treatment. The treatment would help reduce the severity of oral mucositis once the severe oral mucositis has developed.

Recommendation VII
All patients should be able to drink a cup of water without choking. If patients choke during drinking, oral cryotherapy should not be administrated to the patient until his or her swallowing assessment is done and has been documented as without swallowing problem. (Grade of recommendation: RT)

Observing patients to drink water is a simple test for nurses to assess patients’ swallowing ability. In oral cryotherapy, patients are required to swish ice cube inside oral cavity. Ice will be melt in the procedure. Patients need to swallow the melted ice. If they have swallowing difficulty, it may cause choking or suffocation. Thus, oral cryotherapy should be withheld. If nurses have queries towards patients’ swallowing ability, patients should be assessed by a swallowing test.

Recommendation VIII
If patient suffer from suffocation during oral cryotherapy, nurses should stop administrating oral cryotherapy. In addition, nurses should remove ice from patient’s
oral cavity and inform physician immediately. Nurses should monitor patients’ peripheral oxygen saturation level every 30 minutes for 4 hours. Resuscitation should be started according to resuscitation protocol in the clinical oncology department when decreasing oxygen saturation level or decreasing conscious level occurs. (Grade of recommendation: RT)

Maintaining airway is most important when patients suffer from choking or suffocation. Removal of foreign object and give oxygen to maintain oxygen saturation level is crucial. Monitoring patients’ oxygen saturation level in the subsequent four hours is to observe for the occurrence of abnormal condition. Resuscitation or medical treatment could be given immediately according to patients’ condition.
### Appendix 7

#### Timelines for Communications, Pilot test, and Evaluation

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Appendix 8
Data collection sheet for guideline on using oral cryotherapy for a chemotherapy-induced oral mucositis in adult cancer patients

Patient characteristics
Gender:   M / F
Age:       
Smoking: Yes / No

Medical diagnosis:
______________________________________________________________

Chemotherapy scheme:
_____________________________________________________________________

Use of oral cryotherapy:   Yes □    No □
If no, reason: ________________________________

WHO oral mucositis grading system
0 = No symptoms
1 = Sore mouth; no ulcer
2 = Sore mouth with ulcers, but able to eat normally
3 = Able to eat liquids only
4 = Unable to eat and drink

Assessment of oral mucositis grading:

Before chemotherapy treatment oral mucositis grading: Grade 0 / I / II / III / IV

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<td>Oral cryotherapy duration</td>
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-84-
Assessment of oral mucositis grading (cont’d):

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Side-effects caused by oral cryotherapy:

________________________________________________________________________

Duration of oral cryotherapy:

________________________________________________________________________

Termination of oral cryotherapy: Informed innovation in-charge nurse □

Time: ____________________

Reason:

________________________________________________________________________

________________________________________________________________________

________________________________________________________________________

________________________________________________________________________

Subsequence treatment(s) provide:

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________________________________________________________________________

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Appendix 9

Self-reported Satisfaction Questionnaire for Healthcare Providers

Satisfaction towards Training Session

Please “tick” the following:

4 = Most Satisfaction; 3 = Satisfaction; 2 = Dissatisfaction; and 1 = Most

Dissatisfaction

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<td>2. Content of training session are valuable</td>
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<td>3. Duration of training session</td>
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<td>6. Self competent to use oral cryotherapy after training session</td>
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Any other comment(s)?

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Date of completion: _______________________

Name: _______________________

Title: _______________________

Ward: _______________________

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**Self-reported Satisfaction Questionnaire for Healthcare Providers**

**Satisfaction towards using evidence-based oral cryotherapy guideline**

Please “tick” the following:

4 = Most Satisfaction; 3 = Satisfaction; 2 = Dissatisfaction; and 1 = Most

**Dissatisfaction**

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<th>1. Content of guideline</th>
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<td>2. Clearness of guideline</td>
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<td>3. Guideline is user-friendly</td>
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<td>4. Resource(s) and material(s) provided</td>
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<td>5. Support and help given when necessary</td>
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<td>6. Workload after implementing innovated guideline</td>
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<td>7. Beneficence to patients after implementing guideline</td>
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<td>8. Competence of using innovated guideline in future</td>
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<td>9. Continuation using innovated guideline in department</td>
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Date of completion: _____________________

Name: ________________________________

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Ward: ________________________________
References


