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Mucositis Prevention for Patients Receiving High Dose Chemotherapy and Stem Cell Transplantation.

Preventive Strategies - There is Always More to do.

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Abstract
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The aim of this thesis was to investigate oral cryotherapy (OC) as prophy-laxis against oral mucositis (OM) in patients given high-dose chemotherapy for stem cell transplantation (SCT). A new mouth rinse device was tested for possible additive effect to OC.

For study I-III, 78 patients were randomised to OC or standard oral care (SOC). Papers I and II showed that OC patients had significantly less severe mucositis, pain, opioid use, lower C-reactive protein and less parenteral nutrition treatment (TPN).

There was no difference in relapse rate, and 5-year survival was unexpectedly significantly better in the OC group (Paper III). In paper IV, the local effect of OC on the mucosa of the mouth was investigated by the use of an infrared thermograph. Change in surface temperature in eight areas of the mouth cavity was measured after cooling of the mouth in healthy volunteers. A substantial lowering of the temperature (-12.9 °C, mean) was seen which could explain the efficacy of OC. To exclude that acute cooling in itself is traumatic, the proinflammatory cytokine IL-6 was measured in saliva and showed no increase after cooling. Paper V reported a study in 40 allogeneic SCT patients. 20 were given SOC including OC and 20 in addition received Caphosol®, a calcium phosphate mouth rinse, during chemotherapy and until day 21. Severity of mucositis, use of opioids and TPN, effects on nutrition and CRP levels were measured. No significant difference was found between the groups in any of these variables, but a non-significant trend for an advantage for the combination could be seen. IL-6 saliva levels were measured. There was a substantial increase (more than 10-fold), in mean IL-6 levels from baseline to beginning of mucositis and a weak correlation between increased IL-6 levels and severity of OM, suggesting that IL-6 in saliva may be a useful marker of the inflammatory mucosal process.

This thesis demonstrates that OC is effective as prophylaxis against chemotherapy-induced OM. As a consequence of this work, OC has been introduced as the standard of care in all SCT patients in our institution.

Keywords: oral mucositis, stem cell transplantion, oral cryotherapy, cooling, cytokine IL-6

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To Jonas, Daniel, and other loved ones that have supported and encouraged me.

List of Papers

This thesis is based on the following papers, which are referred to in the text by their Roman numerals.

I Svanberg, A., Birgegård, G., Öhrn, K. (2007) Oral cryotherapy reduces mucositis and opioid use after myeloablative therapy-a randomized controlled trial. *Support Care Cancer*, 15:1155–1161

II Svanberg, A., Öhrn, K, Birgegård, G. (2010) Oral cryotherapy reduces mucositis and improves nutrition-a randomised controlled trial. *Journal of Clinical Nursing,* 19:2146-2151

III Svanberg, A., Öhrn, K, Birgegård, G. (2012). Five year follow-up of survival and relapse in patients who received cryotherapy during high dose chemotherapy for stem cell transplantation shows no safety concerns. *European Journal of Cancer Care.* Manuscript ECC-2011-0208. Accepted 01-Jul-2012

IV Svanberg, A., Öhrn, K, Broström, H., Birgegård, G. (2012) The effect of cryotherapy on oral mucosa: a study in healthy volunteers. *Medical Oncology.Apr5 [Epub ahed of print]* DOI: 10.1007/s12032-012-0230-z

V Svanberg, A., Öhrn, K., Rönnelid, J., Lind-Norin, B, Birgegård, G. (2012) Caphosol® mouthwash gives no additional protection against oral mucositis compared to cryotherapy alone in stem cell transplantation. *Manuscript for publication.*

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Abbreviations

ALL	Acute lymphoblastic leukaemia
AML	Acute myeloid leukaemia
BMI	Body mass index
BMT	Bone marrow transplantation
CLL	Chronic lymphocytic leukaemia
CML	Chronic myeloid leukaemia
COX-2	Cyclooxygenase 2
CR	Complete remission
CRP	C-reactive protein
GVHD	Graft versus host disease
GVT	Graft veerus tumour
HD	Hodgin´s lymphoma
HDCT	High-dose chemotherapy
HLA	Human leukocyte antigen
HSCT	Haematopoietic stem cell transplantation
IL-6	Interleukin-6
i.v.	Intravenous
LREC	Local research ethics committee
MDS	Myelodysplastic syndrome
MM	Multiple myeloma
NHL	Non-Hodgkin's lymphoma
OM	Oral Mucositis
OC	Oral cryotherapy
OMAS	Oral Mucositis Assessment Scale
OMI	Oral Mucositis Index
OS	Overall survival
PR	Partial remission
QoL	Quality of Life
RCT	Randomised controlled trial
RD	Related donor
RICT	Reduced-intensity conditioning for transplantation
SCT	Stem cell transplantation
TBI	Total body irradiation
TPN	Total parenteral nutrition
TRM	Transplant-related mortality

URD	Unrelated donor
VAS	Visual analogue scale
WBC	White blood cells
WHO	World Health Organisation

Introduction

Intensive chemotherapy treatment with stem cell transplantation (SCT) often results in severe mucositis, an extremely irritating and distressing condition for patients that produces high costs and medical intervention in the form of advanced pain management and parenteral nutrition. It may even affect the delivery of optimal cancer therapy. Unfortunately, it is still the case today that toxic oral damage is an underestimated side effect.

Three of the papers in this thesis describe oral cryotherapy preventing oral mucositis (OM), its effect on patients undergoing high-dose treatment and SCT, and the outcome after 5 years. The fourth study is the first study published on the local effect of cryotherapy while the fifth study evaluates the efficacy of a new mouth rinse to improve the protective effect of cryotherapy in patients undergoing SCT. This thesis focuses on the importance of preventive treatment against oral toxic side effects that are caused by high-dose chemotherapy with SCT.

Chemotherapy

History

In the early 1900s, P. Ehrlich, a chemist, developed drugs to treat infectious diseases. He began using the term "chemotherapy", which is defined as the treatment of cancer with an antineoplastic drug or with a combination of such drugs (1). The experience of two world wars (WWI: 1914-18 and WWII: 1939-45) and an accidental spill of sulphur mustard on soldiers in a bombed ship in Bari Harbor, Italy, during World War II showed that both bone marrow and lymph nodes were affected in the men who were exposed to the gas (2, 3). Subsequent observations in the 1960s opened the possibility to use drugs in conjunction with surgery and radiation or both treatments to treat micrometastases in all breast cancer patients. Thus, the field of adjuvant chemotherapy was born (4, 5). Since then, a large number of cytotoxic agents have been developed and for a long time chemotherapy has been the backbone of cancer treatment despite a range of side effects (e.g., depression of the immune system, fatigue, gastrointestinal distress, and hair loss).

High-dose chemotherapy

High-dose chemotherapy (HDC) (myeloablative therapy) involves the administration of cytotoxic agents at doses several times greater than the standard therapeutic dose. In some cases, whole body or localised radiotherapy is also given. The rationale for HDC is the belief that many cytotoxic agents act according to a steep dose-response curve. Thus, small increases in the dosage will result in relatively large increases in tumour cell kill. However, increasing the dose also increases the incidence and severity of adverse effects (e.g., opportunistic infections, haemorrhage, and organ failure). In order to rescue the patient from the life-threatening effects of severe bone marrow depression, caused by myeloablative therapy, stem cells are transplanted from bone marrow, peripheral or cord blood stem cells, either allogeneic or autologous, to restore the bone marrow function (6, 7). The aims of myeloablative conditioning are to eliminate the malignant cells, provide space for the transplant, and achieve immunosuppression in order to rescue the patient from toxic side effects of the graft.

Stem cell transplantation

History

As early as 1891, two French physicians, Brown-Sequard and d`Arsonaval, treated a leukaemic patient by oral administration of bone marrow. The first attempts to administrate bone marrow by injection took place in 1939 (8). Barnes et al. (1956) treated leukaemic mice with supralethal irradiation followed by infusion of normal mouse marrow (9). At about the same time, Thomas et al. (1957) reported results from treatment with total body irradiation (TBI), chemotherapy, and marrow infusion (10).

Recipients of haematopoietic stem cell transplantations (HSCT), also known as bone marrow transplantation (BMT), are multiple myeloma (11) or leukaemia patients (12) who would not benefit from prolonged treatment with chemotherapy. High-risk acute leukaemia patients are transplanted after initial treatment to complete remission. Other conditions treated with stem cell transplants include sickle-cell disease, myelodysplastic syndrome, neuroblastoma, lymphoma, Ewing's Sarcoma, Desmoplastic small round cell tumour, and Hodgkin’s disease (13).

During later years, an effect on the tumour cells by the graft has been found, graft-versus-tumour effect (GVT). In patients in whom the GVT effect is important, allogeneic transplantation is the preferred choice of therapy. If the GVT effect is weak and the aim is only to be able to increase the intensity of chemotherapy, autologous HSCT is used.

More recently, non-myeloablative, or "mini-transplant," procedures have been developed that rely more on the GVT effect and require lower, less toxic doses of preparative chemotherapy and radiation. This new approach allows the application of allogeneic in the elderly and other patients who would otherwise be considered too weak to withstand a conventional treatment regimen. Currently, the most common source of stem cells for transplantation is peripheral blood stem cells.

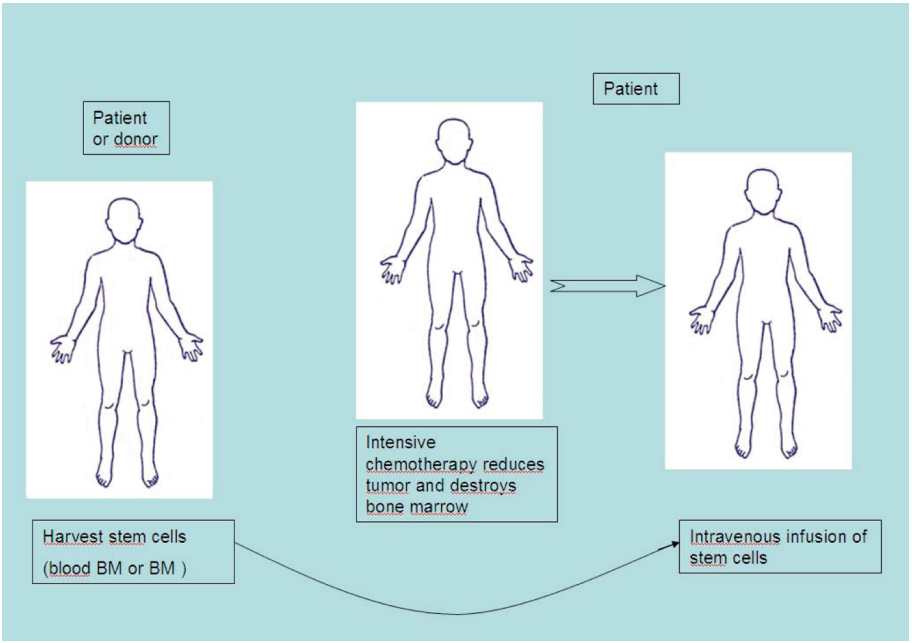

Figure 1. Autologous/allogeneic HCST involves one or two individuals; the (healthy) donor or the patient and the (patient) recipient.

Autologous

Following major efforts to determine the effectiveness of autologous SCT in the 1970s and 1980s, autologous SCT has become the therapy of choice for patients with lymphoproliferative disorders (malignant lymphoma and myeloma) and for selected patients with other malignancies. Autologous SCT requires the extraction (Apheresis) of haematopoietic stem cells (HSC) from the patient and storage of the harvested cells in a freezer (14). The patient is then treated with high-dose chemotherapy with or without radiotherapy with the intention of eradicating the patient's malignant cell population at the cost of partial or complete bone marrow ablation (destruction of patient's bone marrow function to grow new blood cells). The patient's own stored stem cells are then returned to his/her body, where they replace destroyed tissue and resume the patient's normal blood cell production (Figure 1).

Because the recovery of the immune function is rapid, autologous transplants have the advantage of lower risk of infection during the immune-compromised period of the treatment. Moreover, the incidence of patients experiencing rejection is very low because the donor and recipient are the same individual, which also eliminates the risk for graft-versus-host disease (GVHD) (15).

Allogeneic

Allogeneic SCT involves two individuals: the (healthy) donor and the (patient) recipient (Figure 1). Allogeneic HSC donors must have a tissue, human leukocyte antigen (HLA) type that matches the recipient. Matching is performed on the basis of variability at three or more loci of the HLA gene. A perfect match at these loci is preferred. Even if there is a good match at these critical alleles, the recipient will require immunosuppressive medications to mitigate GVHD. Allogeneic transplant donors may be *related* (usually a closely HLA-matched sibling), *syngeneic* (a monozygotic or 'identical' twin of the patient, which is extremely rare because few patients have an identical twin, but offering a source of perfectly HLA-matched stem cells) or *unrelated* (a donor who is not related and is found to have a very close degree of HLA matching). Allogeneic transplants are also performed using umbilical cord blood as the source of stem cells. In general, by transplanting healthy stem cells to the recipient's immune system, allogeneic SCTs appear to improve chances for cure or long-term remission once the immediate transplant-related complications are resolved (16, 17).

Reduced-intensity conditioning for transplantation (RICT) regimes

For some patients, the use of myeloablative therapy is considered too risky. RICT is considered an alternative for patients older than the accepted age restrictions for BMT and for patients with concomitant disease and organ damage (18, 19, 20). Transplant-related mortality (TRM) is lower in RICT. The development of RICT regimens seems to decrease allogeneic SCT (allo-SCT)-related toxicity and has emerged as an attractive modality in patients not eligible for standard allo-SCT (21). In recent years, RICT is being used to a larger extent with the aim of reducing TRM that is due to lower toxicity (22). Results from large, well-controlled studies are still lacking, however (21, 23).

Stem cell transplantation in haematology

Bone marrow

Bone marrow produces all cells required by the body for an intact immune system (leukocytes), coagulation (platelets), and oxygenation (red blood cells) (24).

Malignancy of bone marrow

An uncontrolled growth of pathologic leukocytes in bone marrow structures, lymphatic nodes, and peripheral blood occurs in the form of acute or chronic malignancy. Leukaemia, lymphoma, and myeloma are cancers of the bone marrow and blood (25).

Haematopoietic stem cell transplant relates to any procedure in which HSC of any donor type and any source is given to a consignee with the intention to reinstate and replace the haematopoietic system fully or partially (26).

Leukaemia

Leukaemia was officially diagnosed in 1845 by John Hughes Bennett (27). The word leukaemia is derived from the Greek words *leukos* (white) and *haima* (blood) and means "white blood" (28). Leukaemia is a rare disease with approximately 1000 new cases/year in Sweden. There are two main groups of leukaemia, namely acute (466 cases in 2003 in Sweden) and chronic (519 cases in 2003 in Sweden) leukaemia (29). Chronic leukaemia: the classification differs between type of stem cell and blastic form (influence on myeloid (CML) or lymphatic (CLL) cell line of haematopoiesis.

The course of CML has changed dramatically since the introduction of targeted therapy with tyrosine inhibitors: 5-year survival is now 90% with optimal treatment. CLL is the most common form of leukaemia in the Western world (25, 30, 31) and is the least malignant of the leukaemias with a median survival of about 9 years. Acute leukaemia is divided into two main groups: acute myeloid leukaemia (AML (~ 350 cases in Sweden, 2003)) and acute lymphatic leukaemia (ALL (~ 116 cases in Sweden, 2003) (29). The natural course of acute leukaemia is rapid and lethal. Long-term survival with cytostatic treatment alone is still poor. However, additional BMT in high risk cases has increased long-term survival over the past decade. A recent study in Sweden of adult patients with relapse of ALL (n = 71, 19-65 years) who underwent allogeneic SCT showed a 41% overall survival (OS) at a 1-year follow-up. At the 3-year follow-up, OS was 22% and at 5.5 years of follow-up 15% of the patients were still alive (all under 35) (32, 33). In a study by Chantry et al. (2006) 152 (16-69 years of age) patients with re-

lapsed AML were followed over a long period and at a 10-year follow-up OS was 32% (34).

Lymphoma

Lymphoma was first described in 1832 in a scientific article by Dr. Thomas Hodgkin (35). Approximately 2000 new cases of lymphoma are registered each year in Sweden. Lymphomas arise from lymphoid tissue. There are two main groups: Hodgkin's lymphoma (HD, 168/2003) and Non-Hodgkin's lymphoma (NHL, 1477/2003) with a number of subgroups (29). Among NHL, "low grade lymphoma" is, to a large extent, the same disease as CLL (mostly without bone marrow infiltration) and is often indolent for long periods. The treatment goal of NHL is to push back the disease and slow the progression (not cure the disease), but survival is often long. NHL may progress into HD, "high grade lymphoma" (a lymphoma that grows and spreads rapidly).

High grade lymphomas have a more dramatic course and are treated with higher-intensity chemotherapy, usually in combination with monoclonal antibodies (rituximab). Without treatment, there is generally a short survival, but treatment can lead to total cure from lymphoma. The survival rate is 60-90% after 5 years depending on type (NHL or HD) of lymphoma (36). Relapsed high grade lymphoma may be treated with high-dose chemotherapy and SCT, either autologous or allogeneic.

Myeloma

In 1844, Samuel Solley reported the first well-documented case of multiple myeloma (MM) (37). Myeloma, also known as multiple myeloma or "MM" was first mentioned as a clinical entity by J von Rustizky (1873) but described by William McIntyre in 1850 as "mollitis ossium (38). There are approximately 600 new cases/year in Sweden (29). Myeloma is a malignant tumour in the bone marrow. At diagnosis, the tumour resides at multiple sites in the bone marrow, which is why it is called MM. Patients with MM are mostly over 65 years of age. In the bone marrow, the MM tumour impedes normal haematopoiesis, and symptoms of anaemia (such as fatigue and infections) are common. The homing mechanism to the bone marrow is a characteristic feature of MM and the tumour seldom disseminates to the blood stream (39, 40, 41). Despite the breakthroughs in cancer treatment over the past years, MM is still considered incurable. SCT is regarded as an advanced palliation.

Mucositis

Mucositis is defined as inflammatory or ulcerative lesions of the oral or gastrointestinal tract that is usually caused by cancer therapies. Alimentary tract mucositis refers to the expression of mucosal damage across the continuum of oral and gastrointestinal mucosa, from the mouth to the anus. Alimentary tract mucositis has debilitating and painful side effects and adversely affects the nutrition of the patient. Treatment of oral and gastrointestinal mucositis is one of the major challenges during the period of aplasia, with risk of sepsis, which is related to degree of mucosal barrier breakdown and depth of marrow suppression. Mucositis pathophysiology occurs in five phases: initiation, upregulation and message generation, signalling and amplification, ulceration, and healing (Figure 2) (42). Nuclear factor kappa B (NF-kappaB), cyclooxygenase-2 (COX-2) as well as pro-inflammatory cytokines (in particular interleukin (IL)-1b (IL)-6) and tumour necrosis factor (TNF)) have been suggested to play a key role in this five-phase mucositis model (Figure 2). Mucositis is associated with an increased number of systemic infections, days at hospital, and overall costs and has a negative effect on health-related QoL (HRQoL) (43, 44, 45, 46, 47, 48).

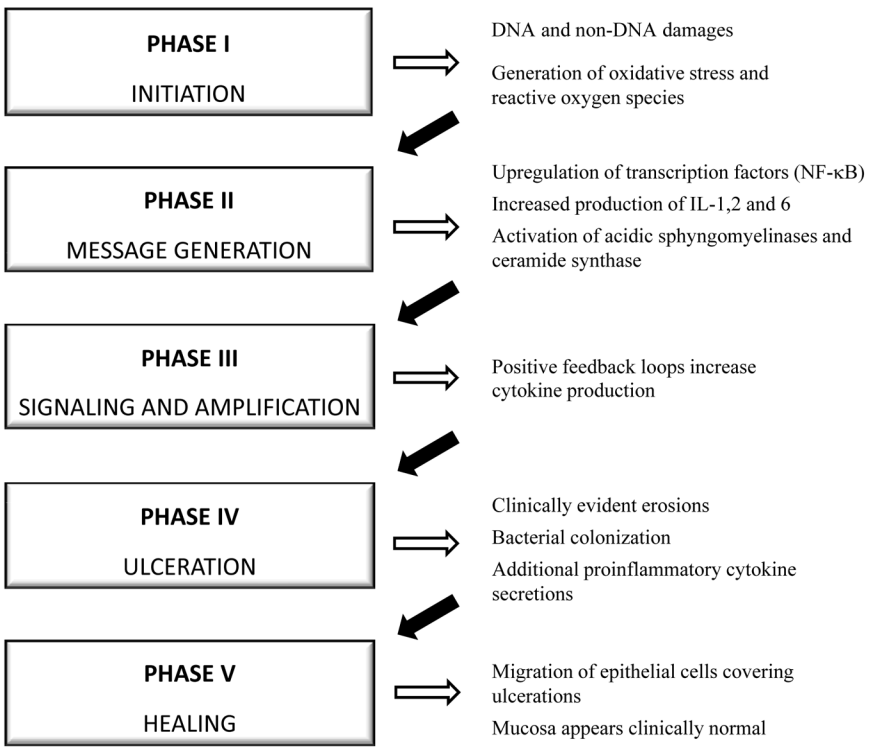

Figure 2. Flow chart of the five phases of mucositis development

Oral mucositis (OM)

Oral mucosa and saliva activity are two important barriers that prevent invasion by microorganisms (49).

Several risk factors (e.g., age and gender) are known to enhance the development of OM. Children experience more frequent and severe OM than other age groups, which is probably due to high cellular turnover. Patients over 50 years of age have a similar OM development, which is more likely because of insufficient DNA repair (50). Female patients are more likely to develop OM than male patients (51). Nutrition status, type of malignancy, dry mouth, caused by previous illness or cytotoxic treatment or irradiation, and periodontal status are risk factors that affect the development of OM (52). In addition, there is a genetic predisposition for OM (53).

Several chemotherapeutic cycles and previous episodes of OM increase the risk of developing chemotherapy-induced mucositis. TBI during myeloablative therapy for SCT also increases the risk of developing OM (54). Chemotherapy and radiotherapy impact on the rapidly renewed cells, which can lead to increased risk of toxic damage. Complications that arise include mucositis, xerostomia, reduced salivary flow, bacterial, fungal or viral infection, dental caries, loss of taste, and osteoradionecrosis, among which OM is one of the most severe side effects (55, 56, 57). Mucositis is a dose-related toxic damage in both radio- and chemotherapy (58). Cytotoxic drugs associated with severe mucositis are methotrexate (high-dose), etopoiside, and melphalan. Most frequently cytotoxic drugs linked to mucositis include alkylating agents (busulfan, cycloposphamide, procarbazine, and thiotepa), anthracyclines (daunorubicin, doxorubicin, and epirubicin), antimetabolites (cytocsine, arabinoside, hydroxyurea, 5-fluorouracil, methotrexate, and 6-mercaptopurine), and vinca alkaloids (vinblastine, vincristine, and taxanes) (59, 60, 61).

The incidence of OM can approach 90-100% in patients treated with high-dose chemotherapy or irradiation before SCT. OM is present in 40% of patients with solid tumour treated with chemotherapy, resulting in depression of bone marrow activity (43, 62). Chemotherapeutic agents that affect DNA synthesis (e.g., 5-fluorouracil, methotrexate, and cytarabine) are those that give the most prominent toxicity to the mucosa (54). OM is not only a immediate consequence of direct physical or chemical epithelial damage but also the result of a cascade of events involving the entire mucosa (Figure 3) (42). With a breach in the mucosal barrier, penetration of the epithelium into the submucosa can occur and mucosa gets prone for bacterial infection, which leads to an increase in pro-inflammatory cytokines (TNF-α, Ilβ, and IL-6) (63, 42). Patients undergoing BMT have reported acute oral pain, mucositis, and inability to eat as major sources of distress. Further, from the patients' perspective, OM is one of the most debilitating side effects of transplantation (64, 65).

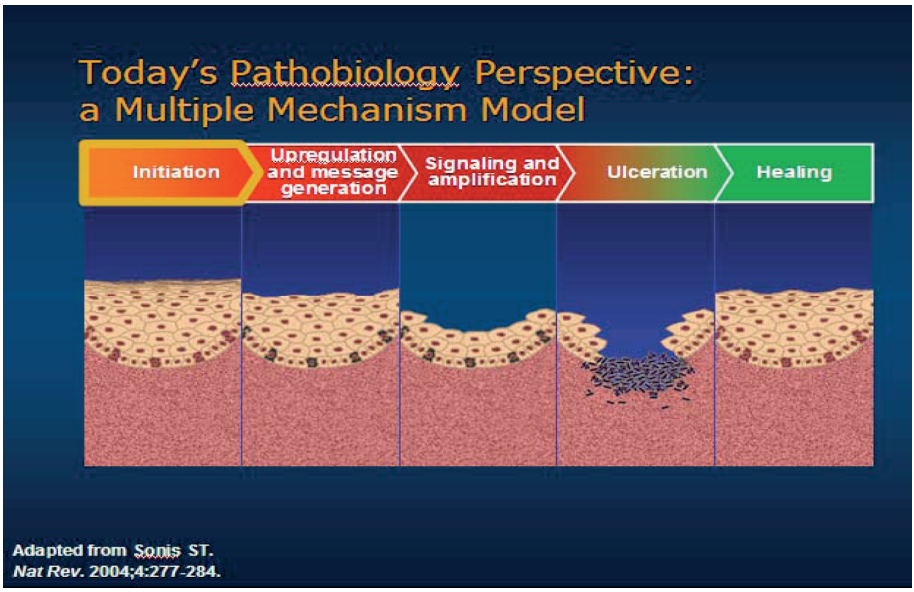

Figure 3. Pathobiology of mucositis. A five stage process.

Symptoms

Severe mucositis can greatly complicate the outcome of the chemotherapy or irradiation treatment followed by HSCT (66, 67). The primary symptom of OM is pain. Studies show that oral pain is one of the most severe side effects with an incidence of 75% in patients treated with intensive chemotherapy (68, 69, 70). Most patients who experience severe mucositis need regular pain relief that often includes opioids, which are intravenously administered in high-doses for several days (71).

Nutrition

Patients undergoing SCT are all at risk of malnutrition and it is known that well-nourished patients have a faster recovery of the graft (72). OM affects the possibility for patients undergoing BMT to consume adequate nutrition orally, which increases the risk for malnutrition (73). Severe OM may lead to problems in maintaining oral hygiene and functions such as chewing, swallowing, and even breathing via the mouth and thus interfere with eating, which would necessitate parenteral support (74). Good nutritional intake is important for patients treated with myeloablative therapy followed by BMT. Cancer per se, including haematological diseases, is often accompanied by weight loss (75, 76, 77).

Loss of taste and appetite adaptation are common side effects of both radio- and chemotherapy treatment (78, 79, 80, 81, 82, 83, 84, 77). Consequences of cancer-associated malnutrition are many, including increased risk

of infection, reduced wound healing, reduction in muscle function, and poor skin turgor resulting in skin breakdown (85). Malnutrition can also affect the patient's response to therapy (86) and increase the incidence of treatment-related side effects. Nutritional status has been empirically linked to clinical outcome (86). Malnutrition has been associated with reduced response to treatment, poorer survival, and diminished quality of life (QoL) (86, 87).

Quality of Life

One definition of QoL is ‘‘An individual’s perception of their position in life, in the context of the culture and values systems in their life, and in relation to their goals, expectations, standards, and concerns” (Definition by World Health Organisation) (88, 89).

Severe OM can have a profound impact on the life of the patient and his or her level of mental distress (90). The patient's experience of OM represents a challenge to both physical and psychological health (43). Pain that is due to OM affects the QoL during cancer treatment and is the most frequently reported patient-related complaint (42, 67).

It is a challenge in the future for stem cell transplant centres to investigate the patient’s QoL by relieving the symptoms of OM. The oral QoL survey instrument* focus on oral, taste, and smell functions that provide data on oral symptoms after chemotherapy/radiation can play an important role in future studies (91, 92).

The European Organization for Research and Treatment of Cancer (EORTC) Quality of Life (QLQ-C30) questionnaire with an addendum developed to assess oral symptoms and function.

Standard oral care in SCT

A good oral hygiene in patients treated with chemotherapy reduces infection defence and lowers the severity and duration of oral problems. Before SCT, all patients receive a dental examination. During hospital stay, patients brush their teeth using special toothpaste with an extra soft toothbrush that is changed every day. The patients are instructed to wash the oral cavity 2-3 times daily with water or NaCl. Toothpicks or dental floss is not to be used. Health care workers assist with dental care according to hospital routine when required and dental professionals are consulted if oral problems arise. The above recommendation follows the Multinational Association of Supportive Care in Cancer (MASCC)/ISOO guidelines (93).

Current management of oral mucositis

Combined prophylactics to reduce mucosal toxicity

Comprehensive patient education plays a central role and a standard oral care protocol should be applied to reduce mucosal toxicity due to high-dose chemotherapy. However, there is not enough evidence to recommend one protocol over another (94). HSCT is frequently associated with saliva hypofunction, which affects the patient's oral health. Saliva keeps the oral mucosa moistened (46). There have been several reports on the use (and efficacy) of cryotherapy to reduce OM (95, 96, 97). In addition to cryotherapy, the efficacy of a number of agents has been investigated (98, 99). In a study by Elad et al. (2006) a gel containing histamine dihydrochloride was used in the treatment of HDCT-induced OM. The study demonstrated that the gel was safe for patients without any known severe adverse events (100). A gel with high fluoride content administered in combination with a neutral, supersaturated Ca^{2+}/PO_4^{3-} mouth rinse (Caphosol®) has been studied (101, 102). This combination of the two agents was well tolerated and associated with improved OM (103, 104). The preferred regimen for the prevention of OM for patients receiving HSCT is still unclear. It is not known whether Caphosol® mouth rinsing as a complement to standard oral care, including cryotherapy, can reduce OM in connection with conditioning chemotherapy for BMT. It has been suggested, but not shown, that combining drugs in specific sequences and at different times relative to the administration of cancer therapy is probably the best solution to efficaciously manage OM (105).

Opioid treatment of severe mucositis and treatment-related side effects

Opioid-related side effects have been frequently reported in patients with neuropathic pain. OM may be due to both nociceptive and neuropathic pain (106, 107). In a study by Isitt & Murphy (2007), opioid analgesics were prescribed for 85% of the patients. Pain of the mouth and throat accounted for 78% of opioid use (108). Most patients received opioid analgesics to treat mouth and throat soreness; however, functional impairment related to mucositis persisted. Further, patients on opioids appeared to experience difficulties in their ability to eat (95).

Opioid analgesia is frequently used to treat many conditions of moderate to severe pain. However, the use of opioid analgesia is associated with side effects that can lead to undertreatment of pain. A meta-analysis of clinical research on opioid-related adverse events shows that constipation (41%), nausea (32%), vomiting (15%), pruritus (15%), and somnolence (29%) were the most frequently reported adverse events among chronic non-cancer pain

patients (109). Similarly, opioid-related side effects have been reported in patients with cancer pain (110).

Nutritional support

Most patients are not suffering from malnutrition at the start of high-dose therapy and SCT. Regardless of nutritional status at the start of high-dose therapy and SCT, a majority of patients require some form of nutritional support during the transplant period. First options for nutritional support for patients undergoing SCT are enteral and parenteral nutritional support. Weisdorf et al. (1987) found that TPN increased overall survival in paediatric and adult patients (autologous and allogeneic SCT) (111).

Enteral Nutritional (EN) support

Enteral nutrition maintains gastrointestinal functions. Several researchers advocate EN as the first choice when patients undergoing SCT are in need of nutritional support, but because of gastrointestinal side effects, this approach seems to be inappropriate in SCT patients (112). Gastrointestinal toxicity (mucositis [mouth to anus], diarrhoea, and nausea/vomiting) that is known to occur because of high-dose chemotherapy regimens in SCT affects good nutritional intake and nutritional uptake (113, 114).

Total Parenteral Nutrition (TPN)

There is a difference between allogeneic and autologous transplants with regard to the patient's need for TPN. Almost all allogeneic transplant patients require TPN, whereas not all autologous transplant patients need nutritional supplement (115). Treatment with TPN increases the risk of fluid overload and impairs liver function. In addition, TPN leads to multiple subclavian vein thrombosis, delays the regrowth of blood platelets, and increases catheter-associated infections. TPN also increases satiety and thereby prevents the feeling of hunger and appetite (116, 117). In conclusion, there is an interest in reducing the frequency and severity of OM during myeloablative therapy through oral cryotherapy to investigate the connection between nutritional status and infection rate.

Cryotherapy

Cryotherapy/the use of cold in medicine

Cold is an easily accessible element and is one of mankind's earliest remedies. The Edwin Smith Papyrus, dated 3500 BC, made numerous references to the use of cold as therapy (118).

The use of cold, or cryotherapy, to treat tetanus has been known since the time of Hippocrates (4-500 B.C) (119, 120). Today, cold is a potentially important clinical therapy in patients with severe stroke, traumatic brain injury, and newborn hypoxic –ischemic encephalopathy (121). Furthermore, cryotherapy is used as method for preventing mucositis and may reduce the incident and severity of chemotherapy-related OM (122, 123). Cryotherapy has been shown to reduce the incidence of OM by 50% following intravenous administration of 5FU (5-fluorouracil) (95, 124). Inhibition of 5FU-induced OM was achieved when cryotherapy was applied for at least 30–60 min following 5FU infusion (96).

Oral cryotherapy

There is evidence that oral cryotherapy, the application of ice chips on the mucosa of the oral cavity during the administration of antineoplastic agents, may reduce the incidence and severity of chemotherapy-related OM (123, 127, 128). The use of cryotherapy is based on the assumption that ice-induced vasoconstriction will reduce blood flow to the oral mucosa resulting in lower local concentrations of chemotherapeutic agents (129, 94). Cryotherapy has been shown to reduce the incidence of OM by 50% following intravenous administration of 5FU (5-fluorouracil) (95, 124). Oral cryotherapy has also been effective for the prevention of OM following treatment with high-dose Melphalan and autologous stem cell rescue (125, 97, 126).

At present, cryotherapy is commonly used as a primary therapy to treat many diseases ranging from traumatology to rheumatology and neurology (130). Cryotherapy is known to cause vasoconstriction but there is a lack of knowledge of the biological effects of cryotherapy on oral tissue before and after cooling with ice chips (129).

Aims of the doctoral project

The overall aim of this thesis was to investigate whether mucositis as a complication of high-intensity chemotherapy for BMT can be prevented or ameliorated. The prophylactic effect of oral cryotherapy on the development of mucositis, on opioid pain relief use, and nutrition was studied, as well as the long-term safety and whether there was a difference in survival rate for patients receiving oral cryotherapy in connection with myeloablative therapy followed by BMT compared to patients receiving routine oral care. A further aim was to study the physiological effect of cryotherapy on oral mucosa in healthy volunteers and the effect of combined prophylactics to reduce oral toxicity as well as the possibility of pro-inflammatory cytokine IL-6 levels as a marker of OM.

The specific aims of each of the five studies are listed below.

Study I

The aim of the study was to evaluate whether oral cryotherapy could delay or alleviate the development of mucositis and thereby reduce the use of opioids among patients who receive myeloablative therapy before SCT. The purpose of reducing the use of opioids was to reduce the impact of opioid side effects.

Study II

The aim was to evaluate whether reduced frequency and severity of mucositis through oral cryotherapy during myeloablative therapy would influence the patients' nutritional status and infection rate.

Study III

The study aimed to evaluate long-term safety and whether there was a difference in relapse rate and survival in patients receiving oral cryotherapy in connection with HDCT followed by HSCT compared to patients receiving routine oral care.

Study IV

The aim of this study was to investigate temperature reduction in the oral mucosa, systemic blood pressure (BP) and levels of interleukin (IL) -6 in

saliva before and one hour after cooling the oral cavity with ice in healthy volunteers.

Study V

Study V aimed to evaluate whether the addition of Caphosol® mouth rinse to oral cryotherapy alone could further alleviate the mucositis and thereby reduce the use of opioids and TPN. Moreover, the study attempted to determine whether the cytokine IL-6 levels in saliva could be a marker of mucosal damage.

Materials and Methods

This thesis consists of five studies (Papers I-V). In all five studies, quantitative methods were used (Table 1).

Table 1. Overview of the study design, sample, measurements, and data analysis.

Paper	Design	Sample	Measurements	Data analysis
I-II	RCT* to study oral cryotherapy or standard oral care.	N=78 (EXP**=n39, CTR**=n39)	**I**. Opioid use, OMAS. CRP **II.**Temperature, infection, nutrition	ITTB***. Chi 2 and t-test
III	A 5-year follow-up study of study **I**	N=78 (EXP**=n39, CTR**=n39)	Overall survival. Disease-free survival. Relapse rate	The Kaplan-Meier method and Cox regression analyses. Chi 2 and t-test
IV	Healthy volunteers. Cooling oral cavity.	N=12	Temperature measurement, blood pressure and saliva sample	Paired t-test, non-parametric Wilcoxon signed-rank test.
V	RCT* to study standard treatment or Caphosol®.	N=40 (EXP**=n20, CTR**=n20)	Oral mucositis and pain. IL-6 levels in saliva. Nutritional status.	ITTB***, t-test, Wilcoxon signed-rank test and Spearman rank-order correlation

* randomised controlled study, ** group, ***ITTB=Intention to Treat Basis

Paper I-II

Design

Study I and II was a randomised controlled trial with random assignment to either the experimental (EXP, receiving oral cryotherapy) or control (CTR, receiving standard oral care) group. Study II was a part of the first study. A stratified randomisation was used regarding type of transplantation (autologous versus allogeneic/unrelated donor (URD)). A power analysis was carried out with the number of days of opioid use as the primary outcome measure. A statistically significant reduction in number of days with i.v. opioids was found and reported in study I. Additional outcome measures were nutrition and infection rate reported in study II. In study I, after informed consent had been obtained, patients in the EXP group were instructed to either suck on ice chips or rinse with ice cold water, depending on their own preferences, during the administration of chemotherapy. They were informed about the importance of keeping the oral cavity constantly cool. The oral cryotherapy started in direct connection with the chemotherapy session and lasted until the end of the session. The use of cryotherapy was evaluated with a questionnaire after each chemotherapy cycle. Deviation from the goal of constant cooling was recorded and is reported in the Result section of this thesis. Special procedures and instruments for recording of oral problems and mucositis were used (see Procedure and data collection).

Subjects, paper 1-II

Between January 2002 and August 2004, data were collected on 78 patients. Eligible to participate in the study were patients > 18 years of age, being able to communicate in Swedish, and scheduled for SCT at the Akademiska University Hospital in Uppsala, Sweden. The final sample consisted of 78 patients. Thirty-nine patients (31 autologous SCT and 8 allogeneic/URD SCT) were randomised to the EXP group (oral cryotherapy) and 39 (31 autologous SCT and 8 allogeneic/URD SCT) were randomised to the CTR group (standard oral treatment). No significant differences could be found between the EXP and CTR groups on gender, age, or tobacco use. All patients suffered from haematological or oncological malignancies. The different diagnoses were evenly distributed between the two groups (Table 2).

Table 2. Patient characteristics, diagnoses, and chemotherapy regimen

	Experimental group n=39 (%)	Control group n=39 (%)	Total
Female (42.3%)	13 (39)	20 (61)	33
Autologous	10 (40)	15 (60)	25
Allogeneic/URD	3 (38)	5 (62)	8
Male (57.7%)	26 (58)	19 (42)	45
Autologous	21 (57)	16 (43)	37
Allogeneic/URD	5 (62)	3 (38)	8
Age, mean ± SD	49.8 ± 14.4	54.3 ± 11.0	
Smokers/snuff users	7	6	13
Diagnosis			
Lymphoma	15	16	31
Myeloma	12	16	28
Testis cancer	1	1	2
Acute lymphocytic leukaemia	4	1	5
Acute myeloid leukaemia	2	3	5
Other*	3	2	5
Myeloablative therapy regimen			
High-dose melphalan	13	16	29
BEAM	0	2	2
BEAC	15	13	28
Testis cancer protocol	1	1	2
ALL conditions + TBI	4	1	5
AML conditions	2	3	5
CML	2	0	2
Other**	2	3	5

* This category includes amyloidosis, plasmocytoma, myelofibrosis, hypoplastic anaemia, and prolymfocytic leukaemia.

** Other regimes; Fludarabin + Busulfan, Cyklofosfamid + Busulfan + Total body irradiation (TBI)

The intervention

A questionnaire on the use of oral cryotherapy was evaluated after each chemotherapy session. Deviation from the goal of constant cooling was recorded and is reported in the Result section. Special procedures and instruments for recording of oral problems and mucositis were used (see Procedure and data collection).

Routine oral care

All patients followed the standard treatment for oral care during BMT. Standard oral care protocol includes examination of the oral cavity and necessary dental treatment provided by a hospital dentist before the start of chemotherapy, followed by oral examination by the nursing staff at the ward. The patients received information and instructions on oral hygiene from the nursing staff at the ward and were recommended a soft toothbrush and gentle toothpaste, which was provided at the ward. When the patients complained about oral manifestations, the hospital dentistry unit was consulted if deemed necessary.

Medical treatment

All patients received intravenous conditioning chemotherapy and (when required) TBI on the basis of diagnosis. Conditioning therapy and supportive care were administrated according to institutional practice. Out of 78 patients, 13 in the CTR group and 13 in the EXP group received filgrastim, a human granulocyte colony-stimulating factor (G-CSF) subcutaneously (s.c.) as prophylactics according to the Nordic treatment protocol (NMSG # 7/98) for patients with myeloma. Treatment with G-SCF was given from day 4 after BMT and was stopped when white blood cells (WBC) reached

$\geq 1.0 \times 10^9$/l. Chemotherapy regimens are presented in detail separately in Appendix 1 (Paper I). There were no significant differences between the EXP and the CTR groups in the distribution of chemotherapy regimens or TBI.

Pain relief

Opioids used in the study were mainly morphine, orally, subcutaneously, or intravenously administrated. Many patients used sublingual fentanyl. Some examples of non-opioids were tablet/mixture of paracetamol or Xylocain® viscous (for local oral pain relief).

Parenteral nutrition

TPN was given when patients were unable to satisfy their nutritional needs orally. Mucositis was the dominant cause of reduced food intake. Calorie intake was calculated twice a week as a routine at the ward or more often when ordered by the physician in charge. TPN was given if the daily intake was less than 25 calories per kilo.

Procedure and data collection

Patients were invited by mail to participate in the study. Randomisation to the EXP or CTR group was performed in blocks of six outside the clinic by an independent centre. Assessment started in connection with the start of myeloablative treatment at day 0. Patients included in the EXP group started

with oral cryotherapy less than 5 min before the nurse started to administer chemotherapy. Thirteen patients received a cytostatic regimen of 1 day; for the remaining patients, the cytostatic regimen was administered from 2-6 days. Oral pain was reported verbally twice to a nurse (in the morning and in the afternoon). A visual analogue scale (VAS) was used to assess the level of pain of the patients (0 = no pain and 10 = worst imaginable pain). The nurse in charge recorded oral pain on a specific questionnaire kept in the nursing charts. When patients rated their pain level to 6 on the VAS despite using non-opioid pain relief, these patients were offered opioids. Mucositis was assessed daily with a modified version of the Oral Mucositis Assessment Score (OMAS) (131). The nurse in charge examined the oral cavity daily and measured temperature twice a day. Fever was defined as a single axillary temperature measurement of ≥ 38.5°C or a temperature ≥ 38°C in two measurements within 12 h in the absence of obvious environmental causes. Infection rate was assessed as neutropenic fever and by the use of i.v. antibiotics. Nutrition was measured as weight, administration of TPN, and S-Albumin (reference value 37-48 g/l) from day 0-21. All nurses and assistant nurses were specially trained, both practically and theoretically, in the assessment and grading of mucositis by an experienced dental hygienist (KÖ). In total, 45 staff members participated in the assessment. The daily oral examination was evaluated from the start of chemotherapy until day 21. The duration as well as doses of i.v. opioids and other pain-relieving drugs, absolute neutrophil count, and C-reactive protein (CRP) were collected from the patients' medical records. Time to death after HDC with HSCT was collected from the patients' medical records ≥ 5 years after the start of HDC/HSCT. Relapse, number of days at hospital, number of days with fever, and OM were also collected from the patients' medical records. The use of cryotherapy was evaluated by questionnaire after each chemotherapy session.

Data analysis

In study I, the total dose of opioids was calculated by transforming both i.v. morphine and other opioids (such as fentanyl products) into a comparable dose of morphine administered orally. In study II, the mucositis index was converted into the WHO scale. The analysis was made on an intention-to-treat basis in study I and II. Differences between the groups (study I-III) were analysed with Chi-square for categorical data and Student's *t*-test for numerical data. The software Statistical Package for the Social Sciences (SPSS) 12.0 was used for statistical analysis. A p-value < 0.05 was considered significant.

Paper III

Subjects, paper III

All 78 patients from study I (Table 2) were followed-up to assess relapse and survival 5 years after transplantation.

Design

In study III, primary endpoints were overall survival (OS) (time from HSCT until death, or last follow-up at ≥ 5 years), disease-free survival (time from HSCT until disease relapse, or last follow-up at ≥ 5 years), and rate of disease progression (time from HSCT until relapse).

Data analysis

OS was estimated by the Kaplan-Meier method (132) and analysed with the Cox regression model for comparisons between patients who underwent oral cryotherapy and those who received standard oral care to determine the extent of differences among the two groups. The software Statistical Package for the Social Sciences (SPSS) 12.0 was used for the analyses. Statistical significance was set to $p < 0.05$.

Paper IV

Subjects

In study IV, locking at the effect of oral cryotherapy on oral mucosa, levels of inflammatory cytokine saliva IL-6, and systemic BP measurements were performed in 12 healthy volunteers. The volunteers were students recruited from the Faculty of Medicine, Uppsala University (n=4), students from the Swedish University of Agricultural Sciences (n=5), or nurses from the Akademiska University Hospital (n=3). The study was balanced for gender and age and they were non-smokers/snuff users among the healthy volunteers. The participants used no medication that might have influenced cardiovascular disease.

Method

The patients were instructed to keep the oral cavity constantly cool by sucking on crushed ice chips for 1 h. Temperature measurements were performed in the oral mucosa using infrared thermography following a flowchart protocol. BP was measured with a sphygmomanometer. Saliva was analysed for inflammatory cytokine IL-6 using an enzyme-linked immunosorbent assay (ELISA) (133).

Procedure

The procedure was explained verbally to each subject and informed consent was obtained from the subjects before being included in the study. The volunteers were asked not to consume alcoholic or caffeinated beverages, food, or any medication for at least 1 h before measurements were taken. The volunteers were placed in an acclimatised room (temperature 22 °C) for about 30 min before measurements were made. Initially, baseline saliva samples were collected and BP was measured. Baseline temperature in the oral cavity was measured in the following regions: buccal mucosa right, buccal mucosa left, labial mucosa upper, labial mucosa lower, tongue dorsal anterior, tongue dorsal posterior, tongue dorsal ventral, and hard palate. Next, the oral cooling experiment started with intake of crushed ice for 1 h. The crushed ice was taken from the same sources throughout the study. The volunteers were asked to provide new portions of crushed ice as soon as the prior ice had melted. After 1 h, the patients were again asked to leave a saliva sample, BP was measured and the thermographic measurements were repeated.

Statistical analysis

Differences in temperature, cytokine IL-6, and BP were analysed by the paired t-test. P-value < 0.05 was deemed statistically significant.

Paper V

Design

The study was a randomised, controlled, open study to compare standard treatment (including cryotherapy) with cryotherapy plus Caphosol® mouth rinse. The randomisation was done using a random computer table by an independent nurse and the patients were informed about which group they were assigned.

Subjects

Qualified to participate in the study were all patients > 16 years of age, able to communicate in Swedish, and who were scheduled for SCT at the Akademiska University Hospital in Sweden. Between September 2010 and October 2011 data were collected on the final sample (n = 40) of patients. Twenty patients were randomised to the EXP group and 20 patients to the CTR group. Patients in the CTR group followed the standard treatment for oral care during BMT (including oral cryotherapy). Patients in the EXP group were instructed to use Caphosol® mouth rinse four times a day as a complement to standard treatment. No statistically significant differences were found in gender or age between the CTR and EXP group. There were seven diagnoses evenly distributed between the EXP and CTR group

Medical treatment

All patients received intravenous conditioning chemotherapy and (when required) TBI in accordance with diagnosis. Supportive care and conditioning therapy were performed according to hospital practice. There were no significant differences between the EXP and CTR group regarding conditioning therapies. Treatment with RICT was evenly distributed between the CTR and EXP group. I.v. pain relief included morphine (strong opioid), Tramadol (week opioid), tablet/mixture/iv paracetamol (peripherally acting analgesic), or viscose/mouth rinse for local oral pain.

Instruments

Mucositis was assessed with the World Health Organization (WHO) scale, combining objective signs of mucositis (erythema and ulcer formation) with subjective and functional outcomes (pain and ability to eat) (134). Pain was assessed with a 10 cm VAS from 0 (no pain) to 10 (worst imaginable pain). The start and duration of i.v. opioids in days and other pain relieving drugs, CRP, and number of days at hospital were collected from patient medical records. Nutrition was measured as weight, body mass index (BMI), start and number of days with total parental nutrition (TPN), and S-albumin (reference values 36-48). Renal function was measured as S-creatinin (reference values: men 60-105; women: 45-90). The pro-inflammatory cytokine IL-6 levels in saliva were analysed using ELISA (133).

Procedure

Data were collected over 22 days (day 0 - day 22). Patients scheduled for BMT at the Akademiska University Hospital in Uppsala, Sweden were asked if they would like to take part in a study to evaluate whether Caphosol® mouth rinse could alleviate OM and thus reduce the use of i.v. opioids and TPN. The nurse responsible for the study presented the information both orally and in writing when the patient arrived at the ward. Those patients who agreed to participate gave their written consent and were then randomly assigned to either the EXP or CTR group. The assessment started at day 0 in connection with myeloablative or RICT therapy. The patients used the VAS to rate oral pain verbally twice a day to the nurse in charge. Mucositis was measured with the WHO scale. The nurse in charge of the study patients examined the oral cavity on a daily basis as part of the morning routine care from the start of chemotherapy (day 0) until day 21 (n=22 days). Number of days of i.v. opioids and other pain-relieving drugs, as well as TPN, CRP, S-Albumin, and S-Creatinin were collected from the patients' medical records. Study patients were instructed to spit into a sampling tube (at least 1 ml of saliva) for detection of the pro-inflammatory cytokine IL-6 twice during the transplant period (day 0 and at the beginning of OM).

Data analysis

Data on all patients were analysed on an intention-to-treat basis. EXP and CTR groups were compared in the total material. For comparison between EXP and CTR groups, the unpaired *t*-test and the Mann-Whitney U-test was applied. For comparison between the first and the second sample of IL-6 levels the non-parametric Wilcoxon signed-rank test was used. The correlation between saliva IL-6 levels and mucositis was assessed with Spearman rank-order correlation. A p value <0.05 was considered statistically significant.

Ethical considerations

The Local Regional Research Ethics Committee (LREC) approved the studies (Dnr; 02-137. Dnr; 2010/134).

Before participation in study I-V, the study participants received written information about the study and the procedures in the studies were verbally explained. Participation was voluntary and all data were treated confidentially and available only to the investigating physicians. The study subjects could refuse participation or could quit the study at any time without indicating the reason.

Results

Oral cryotherapy reduces mucositis and opioid use after myeloablative therapy (Paper I).

No severe oral problems were presented at study start (day 0). All patients (n=78) had a WBC $\geq 1.5 \times 10^9$/l. Twelve patients (6 in the EXP group and 6 in the CTR group) started the study with an evaluated value of CRP (>10). The assumption that sucking on ice cubes would cause discomfort (e.g., tooth pain or nausea) because of the abundance of water by melting ice did not prove to be a major problem.

The intervention -- sucking on ice chips during chemotherapy administration -- was well tolerated by the patients in the EXP group. In the EXP group, 58-75% of the patients managed to keep the oral cavity constantly cooled all the time and 71-100% kept the oral cavity cooled more than half of the time, depending on the chemotherapy regimen, and consequently, the number of days with oral cryotherapy. Seven patients (18%) found cryotherapy unpleasant; of those seven patients, four (10%) experienced cryo cooling as very unpleasant, mostly because of shooting pain from the teeth. The EXP group had significantly fewer days with i.v. opioids ($p=0.045$). When subgroup analysis was performed (autologous versus allogeneic/URD group), the pattern of mucositis, WBC, and CRP differed. Patients receiving autologous transplantation had their nadir of WBC count, the highest CRP, and the highest mucositis scores around days 9-11, whereas patients in the allogeneic group reached corresponding scores around days 16-18. This finding was not unexpected because of the different myeloablative therapies, given expected subsequent development of OM in the allogeneic group of patients. The degree of mucositis differed between patients receiving autologous versus allogeneic transplantation. In the autologous transplant group (EXP), there was a significantly lower mucositis score on day 10 ($p = 0.042$), whereas the allogeneic group of patients (EXP) showed a significantly lower mucositis score on day 16 ($p = 0.021$).

The nutrition in the EXP group was improved as compared with the CTR group and there was a trend that patients in the EXP group received less antibiotics than those in the CTR group (Paper II).

As noted in Study I, oral cryotherapy was well tolerated by the patients. According to the WHO scale, cooling of the oral mucosa had an effect on the grading of OM. There were significantly ($p=<0.05$) fewer patients suffering from severe OM in the EXP group (WHO, grade 3-4). When it came to OM grade 2 on the WHO scale, the same pattern was found. All patients (n=78) lost weight during their hospital stay. In the autologous group, the difference in weight between baseline and discharge was significant (AT-EXP 79.1 kg/baseline - 76.5 kg/discharge, AT-CTR 75.6 kg/baseline - 73.5 kg/discharge, $p=<0.001$). The nutrition status appeared to be better preserved in the EXP group. The S-albumin level in the EXP group supported the results in the sense that it was better preserved within the reference value and there were more patients receiving TPN for more days in the CTR group. We could not detect any significant differences between the EXP and CTR groups in the number of days with fever, positive cultures, or the use of intravenously administered antibiotics. A significant difference ($p=<0.05$) in the EXP group in the number of days in hospital among patients receiving allogeneic/URD BMT was found.

A significant difference was seen regarding 5-year overall survival between patients who received oral cryotherapy and patients given standard oral care during myeloablative therapy followed by SCT (Paper III).

At the 5-year follow-up, 51.3% (40/78) of the patients were still alive. We found a significant positive difference in overall survival between the EXP group and the CTR group ($p=0.025$). Sixty-four per cent (25/39) in the EXP group were alive at the 5-year follow-up compared with 38% (15/39) in the CTR group. There were no differences in number of patients with relapse or number of days to relapse between the groups. Statistically, oral cryotherapy seems to be a prognostic factor to overall survival ($p=0.009$, odds ratio [OR] 2.74, confidence interval [CI] 1.29-5.83). Looking at complete remission status at transplantation, there were significantly more patients in complete remission in the EXP group (n=13) than in the CTR group (n=6) ($p=0.047$). There were no significant differences in patient characteristics for gender, age, diagnosis, high-dose chemotherapy treatment, remission status, or BMI between patients who survived and those who died at baseline.

Temperature measurements in the oral cavity revealed a significant difference before and 1 h after cooling with crushed ice. Systolic blood pressure (BP) was significantly affected by oral cooling (Paper IV).

Among the healthy volunteers (n=12), two felt discomfort during the period of oral cooling. Nevertheless, both of these volunteers completed the cooling session despite the discomfort. Temperature in the oral cavity was measured at eight sites with a mean difference of 12.9°C. No differences between men and woman were observed. The difference in temperature measurement in the oral cavity at all surfaces was significant ($p=0.002$). Oral cooling affected BP. Only systolic BP showed a significant result with a higher measured level (125.8 vs 120 mmHg, $p=0.019$). In this study, cytokine IL-6 levels were measured in saliva. No difference was noted in cytokine IL-6 levels before or after oral cooling with crushed ice.

No statistically significant difference was seen in mucositis scores between the EXP group (Caphosol® mouth wash added to standard oral care) and the CTR group (standard oral care) (Paper V, manuscript submitted for publication).

Out of 20 patients in the EXP group, 17 completed the use of Caphosol® mouthwash. There were no significant differences between the EXP and CTR groups in mucositis scores, oral pain, days/doses of i.v. opioids or opioid tablets or in the use of TPN. The study demonstrated that patients in the EXP group started to use i.v. opioids and TPN 2 - 3 days later than patients in the CTR group, although this difference was not statistically significant. In the CTR group, a trend could be discerned towards more use of pain relief with administered orally of weak opioids and paracetamol on day 11 - 19 and use of oral intake of strong opioids on day 19 – 21.

There was a more than 10-fold increase in mean IL-6 levels in the saliva from baseline to the second sample, which was taken at the onset of mucositis, 113.22 pg/mL vs 1345.5 pg/mL, $p<0.001$. There was also a correlation between mucositis severity and IL-6 levels at day 9 ($Rho=0.483$, $p=0.058$).

Discussion

Paper I

This was a study with a new approach to alleviate OM for patients treated with myeloablative therapy and SCT at the Akademiska University Hospital, Uppsala, Sweden. The aim was to provide relief from OM by using oral cryotherapy during high-dose chemotherapy infusion, which, in turn, would reduce the need for i.v. opioid analgesics. The results indicate that oral cryotherapy is protective against the development of mucositis and alleviates oral pain. Concerning i.v. opioid use, the results demonstrate a reduction in the number of days and dose with i.v. opioids. These findings are consistent with previous results of reduced frequency and intensity of OM (68, 45, 135, 136, 137, 124, 138, 139, 123) and are in accordance with updated guidelines from the MASCC (140). One of the important findings in this thesis was that sucking on ice chips during myeloablative therapy was well tolerated by the patients. Concerns about sensitive teeth or other dental problems proved almost groundless, with only a few of the patients complaining of its unpleasantness. The incidence and severity of OM and pain due to OM varied within the groups (autologous/allogeneic/URD), which could partly depend on different chemotherapy regimens. However, there were no significant differences in the distribution of the chemotherapy regimens between the EXP and CTR groups. Therefore, the notion that oral cryotherapy can reduce the number of days and doses of i.v. opioids was supported.

Paper II

This study aimed to evaluate whether the use of oral cryotherapy reduced both severity and frequency of OM and whether this reduction affected nutritional status and infection rate. The results according to the development of severe mucositis (WHO scale grade 3-4) observed in the EXP group of autologous transplanted patients were consistent with previous studies (124, 128, 138). We also detected a trend towards less need for TPN in the EXP group. Fewer patients needed TPN fewer days compared with the CTR group. The assumption is that the nutrition in the EXP group improved more compared with the CTR group. Weight loss in this specific group of patients is common and often under-treated. In this study, all patients, regardless of

group, lost weight from treatment start to discharge from hospital. The S-Albumin level was better preserved in the EXP group, which supports the pattern that the EXP group was in less need for i.v.-administered nutritional support. However, the weight loss data indicated that both groups suffered from malnutrition. A well-known difficulty in haematology patients concerns calculating the rate of infection. Neutropenic fever, the standard indicator, may give both false positive and false negative cases depending on the fact that inflammatory processes other than infection may cause fever and all infections do not reach the fever criteria. On the other hand, a quickly rising CRP may be an indication as much as microbial cultures for infections requiring antibiotic therapy. In this study, we looked at both markers to detect infection. The results showed a trend whereby treating patients with oral cryotherapy during myeloablative therapy resulted in fewer antibiotics in comparison with the CTR group. In paper I, CRP values closely followed the mucositis scores and there was a significant difference between the groups when each subgroup was analysed separately. The autologous EXP group had a lower value than the CTR group on day 11 ($p=0.039$) and the allogeneic EXP group had a significantly lower value of CRP than the CTR group on days 20 and 21 ($p=0.014$).

A number of years have now passed since the data were collected for this study, but surprisingly few studies have been published on the use of oral cryotherapy to prevent and treat OM in patients receiving high-dose chemotherapy and SCT.

Paper III

Despite the positive outcome of using oral cryotherapy to prevent severe OM, few haematological centres in Sweden have established cryotherapy as a routine prophylaxis. The reason for not using cryotherapy may be fear of the theoretical possibility that malignant leukaemia cells will lodge in the oral mucous membranes and thus be inaccessible or do not respond to chemotherapy treatment when using oral cryotherapy. This concern seems to be built on a single case report (141). However, we found in our 5-year follow-up study of survival a significantly better survival rate in the group of patients receiving oral cryotherapy 5 years after SCT. Patients pre-treated with oral cryotherapy experienced less pronounced OM (grade 3-4) and a better 5-year survival benefit. The result is consistent with previous studies that established a link between severe mucositis and survival after SCT (142, 45, 143). Particularly noteworthy was the finding of no difference in the time to relapse or in the number of early deaths between the EXP and the CTR groups. A possible explanation may be that more patients in the EXP group were in complete remission from their disease at the time of SCT. However, when all living and dead patients were evaluated for remission rate, there

was no correlation, which speaks against remission rate being the explanation for this finding. Another possibility is that the limited size of the sample caused the statistical difference in favor of cryotherapy. At any rate, our results indicate that oral cooling does not have any recognisable disadvantages or a higher relapse rate. We cannot exclude the positive effect of the reduction of inflammatory reaction to be one explanation to the unexpected effect on survival in the cryotherapy group.

Paper IV

We established that oral cooling among healthy volunteers was well tolerated, just as it is for patients treated with oral cryotherapy in connection with myeloablative therapy and SCT (127, 144, 145). To our knowledge, local reaction on oral cavity to oral cooling has not been previously investigated. We found a profound effect on mucosal temperature, with a mean temperature of 12.9°C. General cooling is known to induce vasoconstriction and a reduction in blood flow (146, 147). A marginal increase in systolic BP of no clinical significance was found. However, a problem that arose in one patient was that the cold led to bleeding at the tip of the tongue, which could be a problem if patients with neutropenia and a low level of thrombocytes suffer from similar effects by oral cooling. Therefore, further studies are required to determine the time frame for the cooling of the oral cavity to achieve a protective effect against toxic lesions. The study also aimed to determine whether cytokine IL-6 levels in saliva could be a marker of mucosal damage in connection with oral cooling.

Pro-inflammatory cytokine IL-6 together with TNF-α and Ilβ is known to react when there is a breach in the mucosal barrier (63, 42). We found no apparent association between oral cooling and any immediate inflammatory reaction in healthy volunteers. Our study strengthens the hypothesis that cooling of the oral mucosa is harmless.

Infrared thermography is a simple and reliable method to measure oral cavity temperature. Setting the distance between the mouth and the infrared camera and automatic entry of data from the measurements was obtained smoothly. Future studies should investigate the possibility to use an infrared thermal camera to examine the mouths of patients during treatment with high-dose chemotherapy associated with SCT. The equipment must be able to guarantee cleaning that meets hygienic requirements for patients protected with insulation because of neutropenia. It would be of interest to investigate whether temperature increase in the mucosa, as measured by thermography, is an early marker of developing mucositis, i.e. before visible lesions are present or biochemical markers indicate inflammation.

Paper V (Manuscript, submitted for publication)

Since oral cryotherapy began to be used as a standard procedure to prevent OM in our department, the most severe oral mucositis decreased significantly with a concomitant decrease in the use of opioids. However, there is still a need for further improvement, especially in allogeneic SCT. By paying attention to the five stages of OM development, it may be possible to design preventive strategies based on biological grounds. We know that oral cryotherapy has a positive impact on reducing the duration of mucositis (93). In our study we wanted to add another method of treatment in order to enhance the efficacy of the preventive strategy. Thus, we combined oral cryotherapy with Caphosol® mouthwash. Caphosol® mouthwash is a neutral supersaturated Ca^{2+}/PO_4^{3-} mouth rinse (104). However, Caphosol® mouthwash has not been incorporated into the MASCC/ISOO mucositis guidelines because of a lack of controlled studies. One study shows that Caphosol® and an additional preparation with topical fluoride treatment improve OM after high-dose chemotherapy (104). In our study, we did not find a positive effect when adding Caphosol® with oral cryotherapy. However, several patients reported that rinsing with Caphosol® gave immediate relief of pain in the oral cavity. One possible explanation why no effect was found for Caphosol® in our study is the small sample of patients. The substantial increase in saliva IL-6 levels from baseline to the onset of mucositis indicates that IL-6 may be an early marker of mucositis, and the correlation with severity of mucositis may indicate that it is a marker of mucositis severity. These results must be further explored in larger studies.

Methodological considerations

The relatively small sample size of patients and healthy volunteers (study I-V) limits the conclusions of the present studies. Another limitation of the present studies is that only one centre was investigated, which may limit the generalisation to centres with a different patient and staffing composition. Predisposing factors for mucositis have not been investigated. For practical reasons, more samples could not be obtained in these studies. One strength of these studies was that there were few patients who dropped out or did not choose to participate. In the 5-year follow-up, no patient was lost to follow-up. Another strength is that most instruments used in this study (OMAS, WHO, VAS, and EORTC-QLQ-C30) have been well established and meet acceptable standards. A further strength is that the oral problems were visualised among ward staff and were recognised as a serious side effect to myeloablative treatment and SCT.

General aspects, paper I-V

This thesis concerns the study of OM, a severe side effect of high-dose chemotherapy that is associated with HSCT.

The goal was to investigate cryotherapy as a preventive therapy to alleviate/reduce OM and its symptoms and thereby reduce the need for opioids and parenteral nutrition, which also have side effects. Furthermore, paper IV explored how oral mucosa was affected by cooling with ice cubes and if there were other side effects of the cooling procedure that needs to be taken into account. The study was conducted in healthy volunteers.

Paper V included only allogeneic transplant patients. The purpose of the study was to investigate whether a calcium/phosphate mouth rinse, previously shown to reduce mucositis, could add to the effect of cryotherapy and thus further alleviate OM. The patients' oral cavity was examined daily during the study period by the nurse in charge of patient care. The nurse was told to have patients suck on ice pieces to keep the oral cavity cooled while they were undergoing high-dose chemotherapy. In addition to cryotherapy, the patients were asked to rinse their mouth four times a day with a calcium/phosphate mouth rinse.

During hospitalisation, it is important that nurses and assistant nurses are able to assess and rate mouth status and oral pain in patients with OM. Furthermore, they need to be able to perceive the relationship between severe OM and its side effects. Such knowledge and awareness would increase the ability to provide adequate pain relief and be instrumental in the care of the mouth cavity. For study I and V, the health professionals in our haematological institution have been trained to assess oral status. Some studies (148, 149) have shown that most health care professionals were unwilling to examine the oral cavity of patients. Discussing problems with patients related to the mouth have also been perceived as troublesome. Health care providers experience this as an invasion of patient privacy (149). Stokman et al. (2005) showed that assessment of oral mucositis significantly improved if staff has been trained to use assessment instrument (150). The results of an observational study conducted by Voruka et al. (2011) show that patients who do not use oral cryotherapy during high-dose chemotherapy in combination with SCT are at increased risk of developing OM (151). Our findings suggest the need to further study oral cryotherapy in this specific group of patients in order to determine the optimal time and cooling medium for the mouth. Furthermore, the present results suggest that cryotherapy is a safe procedure to prevent OM and that more patients would benefit from using it during treatment with high-dose chemotherapy in conjunction with SCT.

A number of years have now passed since the data were collected for this study. Yet, surprisingly few studies have examined the use of cryotherapy to prevent cancer therapy-induced OM in patients receiving high-dose chemotherapy.

This thesis concerns the prevention of OM, a common severe side effect in patients treated with myeloablative therapy in combination with SCT. The major conclusions of this study are as follows:

- Most patients who are given oral cavity cooling (cryotherapy) during myeloablative treatment and SCT tolerate the extreme coolness taking place in the oral cavity. Cryotherapy seems to alleviate mouth ulcers (OM) and reduce opioid use and the side effects associated with it.

- In addition to alleviating OM and the need for opioids, oral cryotherapy preserved nutritional status and reduced the need for TPN. A trend toward less use of antibiotics in patients treated with oral cryotherapy may be due to lower infection rate.

- Cryotherapy patients followed-up 5 years post-SCT showed no survival disadvantage or a higher relapse rate.

- Oral cryotherapy causes a marked temperature reduction in the oral mucosa, causing reduced blood flow and explaining the protective effect against cytostatic agents.

- Oral cryotherapy raises no safety concerns among healthy volunteers.

- Rinsing the oral cavity with supersaturated Ca^{2+}/PO_4^{3-} mouth rinse (Caphosol®) proved to be safe. However, the mouth rinse, in combination with cryotherapy, did not give any additional positive effects. Pro-inflammatory cytokine IL-6 may act as a marker of mucositis severity.

Clinical implications and further research

This research began with question related to how to help patients reduce the risk of OM. Previous studies have shown that sucking ice chips reduced OM in patients treated with chemotherapy in oncological settings. This gave suggestions for the use of oral cryotherapy in an effort to reduce and relieve OM and thus reduce the use of opioids in oral pain treatment. The results from

paper I was promising and supported by other studies. All this led to that oral cryotherapy is now included in the standard treatment for patients undergoing SCT at our institution. A possible model for further studies would be to use different agents at different time points during treatment with myeloablative therapy and SCT adapted to the five stages of OM development. In addition, it would be of interest to find a marker for OM using saliva samples to detect pro-inflammatory cytokines, such as IL-6 and TNF-α. It would also be of interest to investigate whether infrared thermography could be used to detect inflammatory processes at an early stage of the disorder. To ensure adequate sample size in future work it would be useful to perform multicentre studies.

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