Effectiveness of Oral Cryotherapy in the Reduction or Prevention of Chemotherapy Induced Oral Mucositis

by

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ABSTRACT

TITLE: Effectiveness of Oral Cryotherapy in the Reduction or Prevention of Chemotherapy Induced Oral Mucositis

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Oral mucositis is characterized by inflammation and ulceration of oral mucosal tissues. Approximately 40% of patients receiving chemotherapeutic agents for the treatment of cancer develop oral mucositis or secondary oral complications as a result of mucositis. One study has shown that oral cooling with ice chips, termed oral cryotherapy, may reduce the severity of oral mucositis associated with the chemotherapy regimen, 5-fluorouracil/leucovorin (5-FU/LV). In this study, a modified technique of oral cryotherapy was used to improve patient tolerance and possibly improve its efficacy.

A sequential comparison experimental design was selected to test the effects of oral cryotherapy on the incidence and severity of 5-FU/LV associated mucositis in patients with colon cancer. Patient tolerance of oral cryotherapy was evaluated by oral pain ratings prior to, during, and immediately after the procedure. A total of 6 subjects, age 26 to 72, were tested. All patients demonstrated evidence of oral mucositis during the previous course of chemotherapy.

Oral cryotherapy was performed during chemotherapy administration in a private medical clinic. The oral cavity was cooled with a polyurethane bag filled with ice. 5-FU was administered 10 minutes after beginning the procedure and oral cryotherapy was continued for 25 minutes following the injection. Assessment of the oral cavity was performed during the previous chemotherapy course when mucositis was present, and on days 5, 10 - 12, 15, and 29 following chemotherapy. Oral pain ratings related to mucositis and pain associated with oral cryotherapy, were measured at the same time periods. The worst oral mucositis and oral pain scores obtained from the prestudy chemotherapy course and the oral cryotherapy course were compared to determine if the experimental treatment was associated with a reduction in the incidence or severity of oral mucositis.

Five of six subjects demonstrated reduction in oral mucositis scores during the experimental course. Two subjects had complete protection from 5-FU/LV induced oral mucosal toxicity. Three subjects experienced clinically significant improvement, although mild pain or redness was still present. A reduction in oral pain ratings during the experimental course, compared to the baseline course was observed in 5 of the 6 patients. The patient who showed no change in mucositis or oral pain scores nonetheless reported a subjective benefit from oral cryotherapy.

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CHAPTER I

INTRODUCTION

Statement of Problem

Oral mucositis is a painful condition characterized by inflammation and ulceration of oral mucosal tissues (Sonis, 1989). Also termed stomatitis, oral mucositis is a frequent and distressing side effect of many chemotherapeutic agents used for the treatment of cancer. Approximately 40% of patients receiving chemotherapy will develop primary mucositis or secondary oral complications (Sonis, 1983), which include impaired nutrient intake (Ohnuma & Holland, 1977), periodontal disease (Rosenberg, 1986), and increased risk of life threatening infection (Dreizen, McCredie, & Keating, 1981). Over one million people will be diagnosed with cancer in the United States this year (Boring, Squires, & Tong, 1993), and the National Institutes of Health (NIH) (1989) estimates that approximately 400,000 of these individuals will be afflicted with oral mucositis or secondary chemotherapy related oral complications.

Unfortunately, the standard approach for the treatment of mucositis is limited to palliation of symptoms (Sonis, 1989). No treatments are utilized in general practice to prevent the development of this condition. To encourage investigations designed to reduce the incidence and morbidity associated with oral mucositis, the NIH (1989) has outlined specific research priorities for oral complications of cancer therapies. The recommendations include investigation to (a) develop accurate, quantifiable, reproducible criteria for assessing and classifying oral mucositis and secondary

chemotherapy related oral complications, (b) correlate risk factors for mucositis with types of secondary oral complications observed, (c) reduce secondary infection, and (d) test agents that may protect oral tissues from harmful effects of chemotherapy and radiation therapy. The systematic study of "agents which control mucositis in specified patient populations" has been identified as a national research priority (p. 22).

Oral mucositis is commonly associated with chemotherapy regimens used for colon cancer (Poon et al., 1989). With the advent of new chemotherapy combinations, cure may be attainable for patients previously expected to succumb to the disease (Cohen, Shank, & Friedman, 1989). However, these potentially curative combinations have an associated incidence of mucositis which dramatically exceeds that reported for earlier single drug regimens (Poon et al., 1989).

Colon cancer is a common malignancy with a projected incidence in the United States of approximately 152,000 in 1993 (Boring, Squires, & Tong, 1993). Approximately 55,000 patients per year are diagnosed with locally advanced disease which is surgically resectable (Adjuvant Therapy, 1990). However, at least 35% of patients receiving surgery alone will develop a recurrence of their disease, which ultimately cannot be controlled by any therapeutic modality (Sugarbaker, Gunderson, & Wittes, 1985). Recent advances in colon cancer research have prompted the NIH (1990) to advise physicians to consider adjuvant chemotherapy, including the drug 5-fluorouracil, for patients in whom large or locally advanced cancers were found at the time of surgery. Although this subset of patients may have had all visible cancer

surgically removed, they are believed to be at high risk for future development of metastatic disease (Cohen, Shank, & Friedman, 1989).

The antimetabolite, 5-fluorouracil (5-FU), has been considered the "backbone" drug in the treatment of advanced colon cancer for 30 years (Gomez & Pazdur, 1991). Recent trials combining 5-FU with the folate analog leucovorin (LV) have improved clinical responses from a dismal 15% historically documented with single agent 5-FU to at least 40% (Hines, Zakem, Adelstein, & Rustum, 1988; Machover et al., 1986; Poon et al., 1989). These studies have shown that improved tumor response, measured by reduction in tumor mass(es) by at least 50%, has translated into a significant survival advantage. Unfortunately, enthusiasm generated by this successful chemotherapy combination has been tempered by the significant toxicity reported. Up to 80% of patients develop oral mucositis during 5-FU/LV therapy (Poon et al., 1989). Furthermore, Petrelli et al. (1989) reported an alarming 5% mortality due to severe diarrhea which may be a manifestation of ulceration and denudation of the entire gastrointestinal tract mucosa. Although a reduction in drug dosage frequently decreases future development of these side effects, dose attenuation may jeopardize the effectiveness of chemotherapy in achieving control of the disease (Poland, 1991).

Clinical manifestations of mucositis include oral pain, mucosal edema, erythema, and ulceration. The pain associated with mucositis can impair intake of food and fluids. Disruption of the oral mucous membranes can lead to local infection requiring antibiotic, antiviral, or antifungal therapy. Additionally, mucositis can exacerbate pre-existing periodontal disease, thus inducing oral infection by a secondary mechanism

(Sonis, 1989). Severe mucositis may require hospitalization for intravenous fluid support and pain control. Consequently, the morbidity associated with severe oral mucositis can impact the patient's physical health, quality of life, and performance of usual activities of daily living.

Interventions designed to reduce mucositis may improve the patient's nutritional status and quality of life. Although numerous treatments are employed to control local pain, remove oral debris, and treat infection, no standard therapies are utilized to prevent mucositis from occurring (Lydon, Purl, & Goodman, 1990). Evidence supporting the use of prophylactic measures such as pharmacologic antidotes or antimicrobial oral rinses is lacking. Thus, a practical method to reduce oral mucositis associated with chemotherapy is urgently needed in the clinical setting.

A recent trial by Mahood et al. (1991) suggests that oral cryotherapy, or cooling the oral cavity with ice during the injection of certain chemotherapy drugs, may reduce the severity of mucositis. Cold induced vasoconstriction appears to decrease exposure of oral mucosal cells to chemotherapy drugs by temporarily shunting blood flow away from mucosal tissues. Additional study was needed to confirm the benefits of oral cooling in reducing oral mucositis in patients receiving the 5-FU/LV drug combination for treatment of colon cancer.

Purpose

The major purpose of this study was to determine whether oral cryotherapy would reduce the incidence and severity of oral mucositis in patients receiving combination 5-FU/LV chemotherapy for colon cancer. An alternate method was used to cool the

mouth in an attempt to reduce oral pain and the potential risk of dental damage due to prolonged contact with ice. Oral cooling was administered via a flexible ice filled plastic bag held in the mouth for a 35 minute period during chemotherapy administration. Patients receiving the oral cryotherapy treatment during a course of 5-FU/LV therapy were hypothesized to develop a lower incidence of mucositis, reduced severity, or both, as compared to those who received chemotherapy without concurrent oral cooling. Two secondary purposes of the study were to (a) assess patient tolerance of oral cryotherapy and (b) determine if scores on two instruments for assessing oral mucositis were associated with one another.

Significance to Nursing

Clark and Slevin (1985) described mucositis as "one of the most distressing side effects of 5-FU therapy" (p. 268). The problem is further magnified by the addition of LV to the treatment regimen. The frequency of mucositis in patients undergoing chemotherapy makes prevention of this painful and potentially life threatening toxicity a primary concern for oncology nurses (Daeffler, 1980).

Disruptions in oral health impact a patient's general well being in a multitude of ways. Disruption in mucosal integrity associated with severe mucositis often results in oral infection and periodontal disease. Oral pain related to mucositis can limit oral intake and compromise the nutritional status of the patient receiving chemotherapy. Ensuing malnutrition may diminish resistance to infection and the ability to tolerate or optimally respond to antineoplastic therapy (Szeluga, Groenwald, & Sullivan, 1990).

Mucositis may create psychosocial consequences as well. For example, severe oral pain may lead to decreased verbal communication, inability to share meals with family members, and subsequent social isolation. Thus, interventions which effectively reduce threats to physical, emotional, and social well-being caused by mucositis are significant concerns for oncology nursing.

Nurses are responsible for selecting oral hygiene agents and administering oral care to acutely ill patients (Beck, 1992; Passos & Brand, 1966). Therefore, the implementation of oral care regimens to reduce or ameliorate mucositis is within the scope of nursing practice. An ideal nursing intervention to prevent mucositis or reduce its severity would be easy and quick to implement; require few, if any, expensive technologic accoutrements; and would present negligible risk or discomfort to the patient. In addition, little specialized training would be required and the intervention would be easily adaptable to the outpatient clinical oncology setting. The application of oral cryotherapy as used in this study strived to satisfy all of these conditions.

CHAPTER II

REVIEW OF THE LITERATURE AND CONCEPTUAL FRAMEWORK

Oral mucositis occurs as a result of damage to rapidly dividing cells in the basal layers of the oral mucosa. The following summary reviews characteristics of the normal oral mucosa and the pathophysiology of mucositis. The biochemical effects of 5-FU/LV and mechanisms of 5-FU/LV mucosal toxicity are examined, as are other variables which influence oral mucositis. Interventions for treatment of oral mucositis are reviewed. Finally, the scientific basis for using local hypothermia and oral cryotherapy to reduce chemotherapy induced toxicity is explored.

The Oral Mucosa

The tissues of the oral mucosa are constantly exposed to environmental insults as a result of normal daily wear and tear. In fact, "no other part of the body is as routinely and repeatedly exposed to as much chemical, physical, thermal, microbial, and mechanical trauma as the mouth" (Dreizen & Brown, 1983, p. 43). Mastication and intake of foods with various textures and acidity cause constant shedding and damage while vocalization causes drying and subsequent sloughing of superficial mucosal cells. Heavy colonization by resident flora and constant exposure to nonresident organisms create a potential portal of entry for systemic infection (Sonis, 1983). However, oral mucosal integrity, salivary flow, abundant neutrophils, and salivary antibodies provide protection against the continual barrage of potential environmental pathogens while keeping normal flora in check (Dreizen, 1978).

In order to determine the pattern of division and renewal, Gillespie (1969)

observed the replication and replacement of oral mucosal cells after labelling them with tritiated thymidine. He found that cells in the basal layer have a high mitotic index, indicating that a large percentage are actively replicating. Although the time for migration of cells from the basal layer to superficial layers of the oral epithelium is variable, the process takes approximately 5 days. Thus, the oral mucosa is a metabolically active tissue in a constant state of renewal. Replacement of superficial layers is maintained in careful balance in the healthy mouth.

Pathophysiology of Mucositis

Sonis (1983) attributes the development of chemotherapy induced oral mucositis to both direct and indirect effects. Direct stomatoxicity is due to direct damage to cells of the oral mucosa, while indirect stomatoxicity is a result of effects on other tissues, primarily those comprising the hematopoietic system. Disruption in hematopoietic function may be manifested by oral conditions such as infection and bleeding.

Direct Stomatoxicity

Direct exposure to cytotoxic agents such as 5-FU decreases cellular proliferation of the mucosal basal layer. Renewal of the epithelium is slowed and migration of new cells to the superficial mucosal surfaces is impaired (Guggenheimer, Verbin, Appel, & Schmitz, 1977). As a result, the rate of superficial shedding exceeds that of cellular replacement. Epithelial thinning and superficial sloughing leads to ulceration (Dreizen, 1978). Microscopically, basal cells appear dysplastic. Collagen degeneration, epithelial hyperplasia, and atrophy are associated findings. These

observations are limited to the nonkeratinized epithelium and rarely involve tissues beyond the mucocutaneous junction of the lips (Lockhart & Sonis, 1981). On clinical examination, inflammation, pain, burning sensation, mucosal and glossal edema, and secondary infection are gross manifestations of the histologic changes (Beck, 1979). The signs and symptoms of mucositis generally appear 4 to 7 days following chemotherapy administration and persist for up to 14 days (Sonis, 1983).

Indirect Stomatoxicity

Indirect stomatoxicity is related to cytotoxic effects on tissues other than the oral mucosa. Damage to hematopoietic cells alters the oral mucosal environment, setting the stage for secondary oral complications such as infection and hemorrhage (Sonis, 1983). The onset, severity of disruption, and recovery of the oral mucosa from cytotoxic chemotherapy tends to mirror the fall and subsequent recovery of peripheral blood leukocyte and platelet counts (Lockhart & Sonis, 1979).

Myelosuppression, the impaired replication and maturation of hematopoietic cells of the bone marrow, presents the most significant indirect effect on the health of the oral mucosa. Chemotherapeutic drugs can impair replication of hematopoietic elements by the same mechanisms that impair buccal mucosal proliferation. Toxicity to myeloid precursors in the bone marrow leads to neutropenia and predisposes the patient to infection. Sites at risk in the oral cavity include areas of periodontal infection, pulpal disease, and mucosa denuded by ulceration (Dreizen, McCredie, & Keating, 1981; Rosenberg, 1986). Alterations in the microbial balance of the oral cavity develop in association with mucositis as absolute numbers of resident flora

increase. Overgrowth of opportunistic organisms such as *Candida subspecies* or activation of latent *Herpes simplex* are commonly seen in the neutropenic patient. Oral ulcerations may become colonized with gram negative bacilli from species such as *Pseudomonas aeruginosa, Enterobacter cloacae*, or subspecies of *Klebsiella* and *Hemophilus* (Dreizen & Brown, 1983). Secondary oral infection may ultimately lead to life threatening systemic infection in patients with concomitant chemotherapy induced myelosuppression (Peterson & Sonis, 1982).

Mucositis Associated with 5-Fluorouracil/Leucovorin

Chemotherapeutic agents differ in their stomatoxic potential. Antimetabolites such as 5-FU display a high propensity for causing oral mucositis (Chabner & Myers, 1989). The addition of LV to a 5-FU regimen enhances therapeutic efficacy and increases toxic effects on normal tissues as well. In order to understand the mechanisms responsible for development of mucositis, the pharmacology of 5-FU/LV and the cytotoxic effects of this drug combination on oral mucosal cells will be reviewed.

Biochemistry of 5-Fluorouracil/Leucovorin

5-FU is a pyrimidine analog belonging to the antimetabolite class of antineoplastic drugs. The drug mimics the base uracil in essential cellular processes involving RNA and DNA synthesis. Substitution of uracil with this fluoridinated analog results in inhibition of the enzyme thymidylate synthase, a crucial step in the synthesis of DNA precursors. Incorporation of 5-FU into RNA prevents formation of messenger RNA and reduces stability of this nucleotide complex, thereby interfering with DNA

synthesis by a secondary mechanism (Ardalan & Glazer, 1981). Thus, the cytotoxic effects of 5-FU are due to inhibition of both cell replication through effects on DNA synthesis and interference in vital cellular metabolic processes conducted by RNA.

Reduced folates, such as folinic acid (LV), are not inherently cytotoxic. When administered with 5-FU, LV stabilizes the complex which inhibits thymidylate synthase. Consequently, 5-FU cytotoxicity is increased and improved antineoplastic activity is observed in tumors that are sensitive to 5-FU (Gomez & Pazdur, 1991). The increased cytotoxicity of 5-FU combined with LV is also exhibited in normal cells undergoing active replication, particularly those cells of the gastrointestinal tract and hematopoietic system.

Gastrointestinal Toxicity of 5-Fluorouracil/Leucovorin

Toxic effects of antimetabolites, such as 5-FU, have a predilection for tissues of the gastrointestinal tract. The common association of these drugs with the development oral mucositis has resulted in the label "stomatoxic" when discussing the toxicity profile observed. Calabresi and Chabner (1990) suggested that cells of the oral mucosa may be particularly sensitive to inhibition of RNA function. The 5-FU metabolite, FdUMP (5-fluoro-2'-deoxyuridine-5'-monophosphate), probably contributes to the development of mucositis by potent inhibition of thymidylate synthase, thus blocking DNA synthesis. Dependence on thymidylate synthase is correlated with the proliferative activity of the cell (Ardalan & Glazer, 1981). Cells demonstrating high mitotic activity, such as oral mucosal cells, are prime targets for the cytotoxic effects of 5-FU.

Oral mucositis is a visible reflection of what may be widespread mucosal ulceration of the gastrointestinal tract. While oral pain and ulceration are manifestations of toxicity in the proximal gastrointestinal tissues, diarrhea commonly occurs in the lower intestinal tract and may progress to hematochezia, proctitis, and even intestinal perforation (Chabner & Myers, 1989). In clinical studies, the schedule of drug administration is associated with different toxicity patterns. Oral mucositis tends to be the dose limiting toxicity for patients receiving a five day treatment schedule of 5-FU/LV which is repeated every 28 days, whereas diarrhea is the most troublesome toxicity associated with weekly drug administration.

Clinical Reports of Mucositis Associated with 5-Fluorouracil/Leucovorin

5-FU alone is associated with an incidence of mucositis ranging from 15 to 66% (Hines, Zakem, Adelstein, & Rustum, 1988; Petrelli et al., 1989). The degree of mucositis appears to be dependent on the total dose and schedule of administration. Poon et al. (1989) evaluated six different regimens containing 5-FU, including two 5-FU/LV schedules, in 429 patients with advanced colorectal cancer. Therapeutic superiority, defined as an overall improvement in survival, was demonstrated in groups receiving 5-FU combined with either low dose or high dose LV, compared to 5-FU alone or in combination with methotrexate or cisplatinum ($p=.05$ using the Gehan-Wilcoxon statistic and corrected for prognostic variables). Ulcerative mucositis was the dose limiting toxicity affecting one third of the subset receiving 5-FU with low dose LV administered for five consecutive days and repeated every 28 days.

Erlichman, Fine, Wong, and Elhakim (1988) administered six 8 week courses of

5-FU alone or in combination with high-dose LV to 130 patients with advanced colorectal carcinoma. When the incidence of mucositis was analyzed during each course, moderate to severe mucositis was observed more frequently in the first three courses as opposed to the latter three courses. Although the investigators did not attribute the reduced incidence to attenuation in 5-FU dose, this appears to be a logical assumption as frequent dose reductions were described in their analysis.

Personal Variables Affecting Mucositis

Individual tolerance for a given dose of an antineoplastic drug varies widely. However, little variation occurs within the same individual if the drug dose and schedule are held constant. Thus, a patient who develops mucositis with the first exposure to chemotherapy is almost certain to suffer similar toxicity with subsequent treatment courses unless the dose is reduced (Dreizen, McCredie, & Keating, 1981). However, maintenance of the initial dose may be crucial to the ultimate benefit the patient derives from therapy (Dreizen, 1978).

Age

Age may be an important predictor for mucositis risk. Mucositis tends to be more severe in young individuals, although they experience a more rapid recovery rate than those in older age groups (Sonis, 1983). Up to 90% of patients under 20 years of age exhibit chemotherapy induced mucositis, while approximately 15% of patients over age 60 develop this side effect. Although the wide discrepancy in age related mucositis incidence is due, in part, to different malignancies and chemotherapy regimens, physiologic changes are partially responsible. The increased rate of buccal

mucosal renewal observed in younger individuals may help explain this finding (Sonis, 1983).

Nutritional Status

Malnutrition and cachexia are serious complications associated with cancer. The presence of the tumor itself increases the basal metabolic rate, thereby creating greater nutrient demands (Szeluga, Groenwald, & Sullivan, 1990). Gastrointestinal toxicities from chemotherapy can exacerbate nutritional deficiencies by reducing food intake and absorption. Ohnuma and Holland (1977) state that "the alimentary canal is one of the most vulnerable targets of chemotherapeutic agents" (p. 2397). Anorexia, nausea, vomiting, diarrhea, and taste changes are treatment related side effects which threaten the oncology patient's nutritional status. Importantly, pain associated with mucositis may profoundly impair oral intake and further compromise nutritional balance in the patient receiving chemotherapy.

Histologic findings of decreased buccal cell renewal and migration are evident in cases of starvation and protein malnutrition. Consequently, diminished nutrient intake secondary to mucositis may intensify pathologic effects of preexisting malnourishment on buccal mucosal cells and further inhibit the renewal of oral tissues (Williamson & Chir, 1978).

Periodontal Disease

Patients with preexisting periodontal or dental pulpal disease have a higher incidence of oral complications following chemotherapy, including infection, abscesses, and pulpal necrosis (Peterson, 1983). These conditions place the patient at

significant risk for systemic infection when myelosuppression is present (Peterson & Sonis, 1982). Goldman and Cohn (1968) found that up to 98% of healthy individuals displayed some evidence of periodontal disease. Similarly, Harrell and Damon (1989) found that 100% of the 81 postoperative adult patients in their sample demonstrated some degree of gingivitis. Therefore, thorough dental evaluations combined with adequate treatment of periodontal or pulpal disease are strongly recommended prior to instituting chemotherapy in order to prevent painful and potentially serious infections (Peterson & Sonis, 1982; Rosenberg, 1986).

Other Variables

Additional factors may contribute to the development of mucositis associated with chemotherapy. Chemical irritants such as tobacco, alcohol, and coarsely textured foods can impair mucosal cell function or increase cell sloughing. Medications such as antibiotics alter the balance of oral microbes while steroids modify cellular function and immune response, thus increasing an individual's risk of secondary oral infection (Lydon, Purl, and Goodman, 1990; Pizzo & Meyers, 1989).

In summary, personal variables including age, nutritional status, and dental condition influence the development of chemotherapy associated oral mucositis. Medications and certain foods contribute as well by altering either immune cell function or the oral microenvironment.

Interventions for Oral Mucositis

Oral Hygiene

Despite the widespread adoption of oral care guidelines by cancer institutions

across the United States, few randomized trials have tested the efficacy of these regimens (Daeffler, 1980). Dilute hydrogen peroxide continues to be used despite its known irritant effects (Daeffler, 1981; Karl, 1982; Lydon, Purl, & Goodman, 1990). Antimicrobial oral rinses may reduce oral infection; however, the severity of mucositis is not altered (Weisdorf, Bostrom, & Raether, 1989). Beck (1979) evaluated the systematic use of conventional oral care including toothbrushing and the use of Cepacol® mouthwash in the first published trial evaluating oral care in the prevention of mucositis. Her approach continues to be used today in patients without evidence of mucosal irritation or ulceration. However, once mucositis is present, normal saline rinses, topical anesthetics, and dilute oxidizing agents such as hydrogen peroxide are recommended, despite the absence of documentation supporting their effectiveness (Lydon, Purl, & Goodman, 1990; Beck, 1992).

Simply rinsing the mouth does not produce sufficient removal of dental plaque and debris. When mucositis is present, usual measures of flossing and brushing may be performed inadequately, or abandoned altogether due to pain associated with these procedures. This neglect may cause further deterioration in the condition of gingival tissues, with increased pain and dysphagia developing as a consequence (Poland, 1991). Subsequent accumulation of dental plaque in concert with mucous membrane ulceration can lead to oral infection or dental decay (Peterson & Sonis, 1982). Measures that reduce or prevent painful oral mucositis will promote oral comfort, thereby facilitating oral hygiene measures necessary for dental health in patients receiving chemotherapy.

Allopurinol Rinses

Allopurinol mouthwashes have been tested by several investigators as a topical therapy to prevent mucositis associated with 5-FU. The rationale for using allopurinol is based on scientific evidence that systemic administration of the drug inhibits formation of active 5-FU metabolites (Fox, Woods, Tattersall, Piper, & Sampson, 1979; Howell, Woods, Tattersall, & Brodie, 1979). Consequently, allopurinol mouthwashes were tested to determine if topical administration would reduce the cytotoxicity effect of 5-FU on oral mucosal cells.

Two small nonrandomized trials evaluated allopurinol mouthwashes in patients who had previously developed 5-FU associated mucositis (Clark & Slevin, 1985; Tsavaris, Caragiauris, & Kosmidis, 1988). Both studies, testing 6 and 16 patients respectively, reported a reduction in severity of mucositis with allopurinol mouthwashes, although the strength and frequency of use was not comparable between studies.

Loprinzi, Dose, Burnham, Hagen, Cross, and Fischer (1990) conducted a randomized, placebo controlled, double blind, crossover trial of allopurinol mouthwash in 77 patients receiving 5-FU alone or 5-FU/LV. The lack of efficacy observed with allopurinol during interim analysis prompted the investigators to close the study prior to the planned enrollment of 120 patients. In short, the hypothetical protective effect of topical allopurinol in reducing 5-FU induced mucositis was not supported in this well controlled clinical trial.

Local Hypothermia

Local hypothermia was initially tested in the chemotherapy setting as an approach to decrease drug induced hair loss, or alopecia (Hunt, Anderson, & Smith, 1982). Although alopecia is not life threatening, temporary baldness is a distressing side effect which may reduce self esteem and stigmatize the individual as a "cancer patient" (Lydon, Purl, & Goodman, 1990). Hence, considerable work has been done in an attempt to reduce alopecia. Doxorubicin, an antitumor antibiotic, is associated with total or nearly total alopecia in over 90% of patients receiving the agent (Chabner & Myers, 1989). Since doxorubicin is a highly active drug in a number of malignancies, many patients receive this drug and ultimately develop alopecia.

Hunt et al. (1982) evaluated the topical application of cold, using an ice cap, in an effort to reduce drug toxicity to the hair follicles, thereby limiting hair loss. The rationale for local hypothermia was two-fold. First, cold induced vasoconstriction in the scalp was purported to diminish the amount of cytotoxic drug delivered to sensitive, rapidly dividing cells of the hair follicle. Secondly, the investigators hypothesized that active transport mechanisms which permitted entry of doxorubicin into the cell were impaired by cooling, thus reducing cellular uptake of the drug in the scalp. An ice cap was placed on the patient's head for 15 minutes prior to doxorubicin administration and continued for 45 minutes after the injection. The duration of scalp hypothermia was derived from pharmacokinetic data indicating the drug distributes quickly to the tissues with a sharp drop in plasma levels after 15 to 30 minutes, followed by a relatively long terminal half life of 25 to 28 hours (Chabner &

Myers, 1989).

Scalp hypothermia in this trial was beneficial to 22 of the 28 subjects (79%), demonstrated by either no hair loss or minimal loss which did not require use of a wig (Hunt et al., 1982). These results are impressive in a setting where marked hair loss is expected in over 90% of patients who receive the drug. However, the incidence of alopecia is dose dependent, with most cases occurring at doses of 50 mg/m^2 or more. All but two of the patients in this study received dosages below this level and thus, may not have been at risk for significant alopecia. Additional study limitations included variable durations of chemotherapy treatment and a small sample size.

Dean, Griffith, Cetas, Mackel, Jones, and Salmon (1983) compared the commercially produced Kold Kap® to crushed ice contained in plastic bags as methods of local hypothermia to reduce doxorubicin induced hair loss. The sample consisted of 64 patients with breast cancer or other solid tumors who were beginning combination chemotherapy with doxorubicin 30 to 37.5 mg/m^2 intravenously on day 1 and cyclophosphamide 150 to 200 mg/m^2 orally on days 1 through 3. The first 35 patients received the crushed ice method while the succeeding 29 patients were treated with the Kold Kap®. Scoring of hair preservation was rated excellent (0 to 25% loss), good (25 to 50% loss), moderate (50 to 75% loss), or poor (75% to total loss). Assessments of the scalp were based on nurse ratings and further documented by scalp photographs taken from five different views.

Compared to historical experiences of the investigators, a notable reduction in the epiliatory effects of doxorubicin was demonstrated with scalp hypothermia. Prior to

the use of scalp hypothermia, over 90% of patients receiving the identical drug regimen developed moderate or total hair loss. Over an average of eight months of therapy, 63% percent of patients using the Kold Kap® experienced a minimum hair preservation rating of good. Similarly, of the 35 patients in the crushed ice group, 56% qualified as having a good response.

Contrary to the experiences of Hunt et al. (1982) and Dean et al. (1983), a negative study of scalp hypothermia was reported by Wheelock, Myers, Krebs, and Goplerud (1984). The authors applied the Kold Kap® scalp hypothermia device to 11 patients during their first course of chemotherapy for gynecologic cancer. The scalp hypothermia method, consistent with that of Dean et al., (1983) involved applying the Kold Kap® 15 minutes prior to chemotherapy administration and discontinuing scalp hypothermia 45 minutes after the injections were completed. All patients received identical dosages of doxorubicin (50 mg/m^2, or an average total dose of 72 mg) and methotrexate 20 mg/m^2, followed by cisplatinum 50 mg/m^2 via intravenous infusion. Five patients received cyclophosphamide 500 mg/m^2 as well. The study was terminated prematurely after 10 out of 11 patients experienced severe alopecia, defined as over 50% loss of hair and/or the patient's subjective need to wear a wig. Wheelock et al. (1984) suggested that the higher dose of doxorubicin may have influenced their findings. Additionally, failure of scalp hypothermia in this study may have been related to the use of combination regimens containing moderately high dose cyclophosphamide, which is also known to cause alopecia. Considering the 1 to 4 hour plasma half life of cyclophosphamide (Chabner & Myers, 1989) and the high

intravenous dose, 45 minutes of scalp hypothermia following chemotherapy injection may have been insufficient to reduce exposure of the hair follicles to the drug. Furthermore, transport of cyclophosphamide into the cell may not be as temperature sensitive as doxorubicin transport processes. Hence, the Kold Kap® may not play a role in preventing alopecia associated with chemotherapy regimens employing doxorubicin and high dose cyclophosphamide.

Hillen, Breed, and Botman (1990) employed a novel method of scalp hypothermia with 48 patients receiving one of three combination chemotherapy regimens, two of which contained doxorubicin. Compressed air was directed through a T shaped vortex tube constructed for the purposes of the study. High and low velocity air flow patterns were produced due to the geometric properties of the tube, resulting in separate columns of warm and cold air. After the cold air temperature reached 12°C, it was diverted from the vortex tube to a hairdryer cap which was placed on the patient's head. Cold air circulated under the hairdryer cap to cool the scalp. Thirteen additional patients received scalp hypothermia with cryogel packs, and the results of both methods were reported in the total sample of 61 patients.

Prior to implementation in the treatment setting, a pilot study was conducted in the laboratory. Healthy subjects donned the cold air caps, then epidermal and intradermal temperature was measured for 60 minutes. Scalp blood flow was calculated with a laser Doppler flowmeter. After ten minutes of cooling, a 50% reduction in scalp blood flow had been achieved, corresponding to an epidermal temperature of 16°C and an intradermal temperature of 31 to 32°C. Blood flow

continued to decrease to approximately 60% below baseline at 15 minutes and 63 to 65% below baseline at 30 minutes (Hillen et al., 1990).

The results of the therapeutic trial by Hillen et al. (1990) were variable and related to the chemotherapy combination used. For patients receiving combination therapy without doxorubicin, 95% (21 of the 22 patients) experienced little or no hair loss, while alopecia was marked or total in 69% (9 of 13) of those receiving doxorubicin and 100% (13 of 13) of patients receiving the doxorubicin analog, epirubicin. Although the study was not designed to be comparative, 13 patients treated with cryogel caps had similar results. Consistent with previous research, the investigators found that the forced air technique of local hypothermia was not effective in regimens and doxorubicin doses associated with a very high incidence of alopecia. However, Hillen et al. (1990) suggested that the protective effects of scalp hypothermia they observed in some patients could not be attributed to vasoconstriction alone, since a 50 to 60% reduction in blood flow would allow some drug to be distributed to the scalp. Furthermore, modest benefits observed with drugs possessing long half lives, such as cyclophosphamide, may be explained by the inhibitory effect of local hypothermia on cellular uptake and metabolism of cytotoxic agents, rather than temporary vasoconstriction.

In summary, published reports on scalp hypothermia have suggested that local cooling has a role in preventing chemotherapy induced alopecia. Scalp hypothermia does appear to benefit some patients who would otherwise experience significant hair loss. A number of hypotheses exist to explain the mechanisms in which local

hypothermia exerts its protective effect. Whether vasoconstriction results in reduced drug delivery or tissue cooling decreases cellular uptake or intracellular incorporation of cytotoxic drugs, evidence exists to support the hypothesis that local cooling reduces toxicity of some agents to dividing hair follicle cells.

In response to studies supporting its use, scalp hypothermia devices have been commercially available for over 10 years. Unfortunately, investigators neglected to fully evaluate the risks involved with reducing cytotoxic drug delivery to an area of the body known to develop metastatic cancer. Several patients using scalp hypothermia experienced scalp metastases and some deaths were reported. In 1990, the Food and Drug Administration banned the sale of commercial scalp hypothermia devices until sufficient data is collected to determine the relative risk of scalp metastases associated with their use (Camp-Sorrell, 1991).

Oral Cryotherapy

Interest in the use of oral cooling to prevent chemotherapy induced mucositis has been documented for nearly a decade (Peterson & Sonis, 1982). However, the concept has been implemented in the clinical setting only recently (Mahood et al., 1991). Oral cooling or "cryotherapy" is based on data derived from scalp hypothermia studies and available pharmacokinetic data of various chemotherapeutic drugs. The oral cavity is cooled with ice prior to administration of the stomatoxic drug, 5-FU. Oral cryotherapy is continued for 25 minutes, until the 10 to 20 minute plasma half life of the drug is passed (Chabner & Myers, 1989). Hypothetically, drug delivery to oral mucosal cells is decreased by cold induced vasoconstriction. In

addition, cellular uptake of 5-FU may be inhibited by cryotherapy. However, reports of effects of temperature on cellular uptake of chemotherapy drugs are limited to studies of doxorubicin (Herman, Baustian, & Kundrat, 1981).

Mahood et al. (1991) conducted the only prospective randomized trial of oral cryotherapy for the prevention of chemotherapy induced mucositis. The authors studied 95 patients receiving 5-FU/LV chemotherapy, 50 of whom were randomized to receive the oral cryotherapy treatment. Patients in the cryotherapy group swished ice chips in their mouths for 5 minutes prior to and 25 minutes following the 5-FU injection. Mucositis was rated on a five category scale as 0 (none), 1 (mild), 2 (moderate), 3 (severe), and 4 (requiring intravenous feeding). The authors controlled for drug dose and schedule. Furthermore, patients were stratified by age and dentition, although the age ranges and numbers of patients in each subset were not described. Smoking status was accounted for, however, periodontal disease and nutritional status are variables which may have had an effect and were not controlled or accounted for in the study.

Severity of oral mucositis was reported to be significantly reduced in patients receiving oral cryotherapy compared to patients who did not receive the intervention. The mean severity of mucositis for the experimental group was 0.7 while the control group's mean score was 1.6 ($p=.02$) on a scale of 1 to 4. One interesting finding was that 8 of 45 patients in the control group experienced grade 3 stomatitis, while only 5 of 50 patients in the oral cryotherapy group received a rating this high. Two patients in the control group required intravenous hydration (grade 4), while none of

the patients in the experimental group required intravenous support. Oral cryotherapy was described as well tolerated, with adverse effects being limited to temporary oral numbness, headache, and nausea. However, the authors noted that nausea may have been related to the 5-FU rather than oral cryotherapy.

Strengths of this study include selection of patients with the same malignancy receiving the same chemotherapy regimen at identical dosages per m^2 of body surface area, thus controlling for potential variability in treatment intensity and duration. The randomized prospective design may have served to evenly distribute influencing variables, such as individual responses to stomatoxic agents, age, and dental disease between the two treatment groups. Hence, the observed differences between the groups was most likely due to the experimental treatment rather than chance alone.

Since the authors did not measure oral temperature during the cryotherapy procedure or describe the amount of ice used, it is difficult to determine if uniform oral cooling was achieved. Individual variation in tolerance of continuous cooling with ice chips may have influenced the amount of ice in the mouth at any one time, producing a potential difference in the amount of cooling attained in different subjects. Subjects in the study were undergoing their first chemotherapy course, thus, it is difficult to ascertain the extent to which mucositis severity was affected by sample selection and the influence of intervening variables. Nevertheless, oral cryotherapy seems to have produced the statistically significant reduction in mucositis reported. In fact, two large scale clinical trials in colon cancer have recommended the oral cryotherapy procedure described by Mahood et al. (1991) in the supportive care

section of each protocol (Fisher, 1991; Haller, McDonald, Mayer, & Zalcberg, 1988). Thus, hundreds of patients may be offered oral cryotherapy based on the results of a single study. Confidence in the effectiveness of oral cryotherapy may be strengthened by a conceptual replication and extension of that study.

Effects of Local Cooling

Scalp Temperature

Dean et al. (1983) performed body temperature measurements during scalp hypothermia as an adjunct to an alopecia prevention trial. Three healthy subjects underwent subcutaneous scalp temperature measurements during scalp hypothermia with the Kold Kap®. A four channel thermometry system was used to measure temperature on various areas of the scalp. Body temperatures including esophageal, oral, rectal, and tympanic measurements were taken to determine if core temperature varied during scalp hypothermia. The scalp temperatures obtained by the researchers demonstrated a range from 22 to 34°C, indicating lack of uniformity in scalp cooling. Systemic temperatures fluctuated less than 0.5°C from baseline, with the exception of tympanic temperature which revealed a slight downward trend.

Cold Vasodilation

Cold vasodilation is an intermittent phenomenon which has been observed when peripheral blood vessels are subjected to temperatures below 12°C. After tissue temperatures are maintained below this level for several minutes, brief episodes of vasodilation occur followed by strong vasoconstriction. This phenomenon has been observed primarily in localized vascular beds. For example, one digit may exhibit

cold vasodilation while the perfusion of the adjacent digit remains extremely reduced (Keatinge, 1980).

Work by Keatinge (1958) and Folkow, Fox, Kroy, Odelran, and Thoren (1963) suggests that cold vasodilation may be the result of paralysis of peripheral blood vessels. Below 12°C, these vessels fail to respond to the potent vasoconstrictor, norepinephrine, resulting in relaxation of affected vessels. The magnitude of cold vasodilation varies in different areas of the body and appears to correlate with the number of arteriovenous anastomoses present. The preponderance of evidence for this phenomenon is described in studies of cutaneous vessels in the digits. Proximal cutaneous vascular beds, such as those in the forearm, exhibit variable evidence of cold vasodilation at temperatures below 12°C. Furthermore, proximal cooling of an extremity greatly reduces both distal blood flow and cold vasodilation of the digits; thus overall blood flow remains less than usual levels (Keatinge & Harmon, 1980).

Cold vasodilation is an area of potential concern when a therapeutic intervention is based on vasoconstriction induced by the application of cold. The rationale for the use of oral cryotherapy is primarily to produce constriction of the oral mucosal vessels, thereby shunting cytotoxic drugs away from these sensitive tissues. Reflex vasodilation could mitigate the beneficial effects of cryotherapy by allowing stomatoxic amounts of 5-FU to enter the mucosal cells. However, reports on cold vasodilation are limited to the cutaneous vasculature of the extremities, and no evidence exists that this phenomenon occurs inside the mouth or on the scalp. Dean et al. (1983) did not achieve sufficient temperatures to cause cold vasodilation in their

scalp hypothermia study. Research describing tissue temperatures achieved with procedures analogous to oral cryotherapy has not been identified following an exhaustive review of the literature. It was impossible to determine if cold vasodilation would have an adverse effect or occur at all in this study.

Conceptual Framework

The physiologic and hypothetical relationships between personal and treatment variables predisposing the patient to oral mucositis and the protective effects of local hypothermia on oral mucosal cells are illustrated in Figure 1.

Variables

Personal variables including age, nutritional status, condition of the periodontal tissues, and smoking can influence the susceptibility of the oral mucosa to chemotherapy induced damage. Specific treatment variables, including drug type, dosage, schedule, concomitant medications, and concomitant toxicities such as myelosuppression, interact with personal variables to determine the degree of damage to oral mucosal cells. Observable characteristics of oral mucosal damage are ulceration, bleeding, edema, erythema, and infection. Subjective findings are oral pain and interference in ability to eat solids and/or drink liquids.

Assumptions

The predicted benefit of oral cryotherapy is based on four assumptions. First, a reduction in oral mucosal blood flow by at least 50% decreases local drug delivery sufficient to reduce toxicity to the oral mucosal cells. Second, administration of oral cryotherapy during 5-FU reduces uptake of the drug by oral mucosal cells. Third,

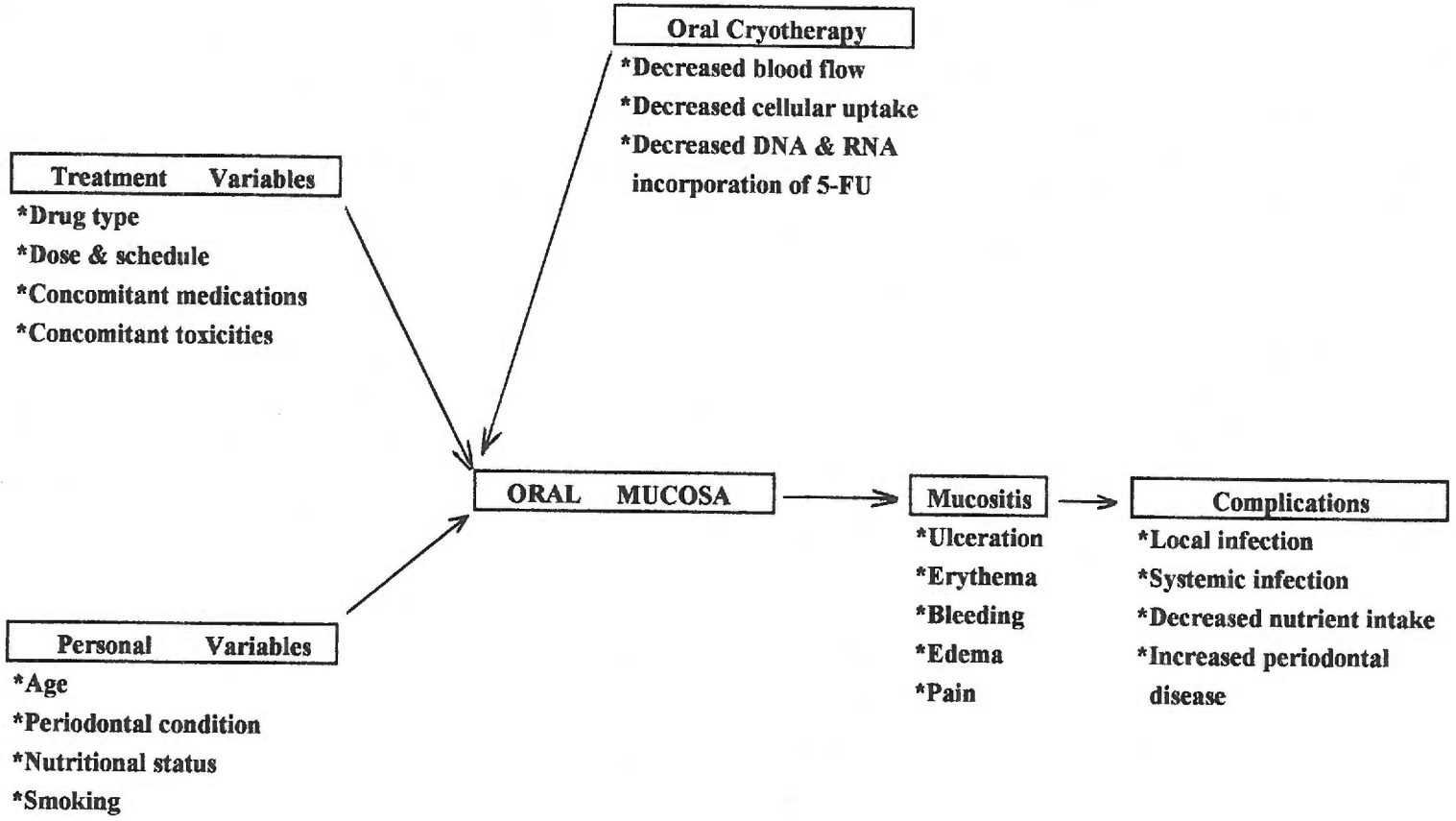

Figure 1. Relationships between personal variables, treatment variables, and the proposed effect of oral cryotherapy on the development of oral mucositis.

enzymatic processes within oral mucosal cells are slowed by cooling; thus inhibiting intracellular incorporation of 5-FU into metabolic processes. Finally, cooling of oral mucosal tissues sufficient to achieve both a 50% reduction in local blood flow and slowing of cellular metabolic processes can be achieved with an ice filled bag held in the mouth.

Modification of the oral cryotherapy protocol described by Mahood et al. (1991) was based on the following considerations. First, the adequacy of cooling the buccal mucosa is questionable if the patient simply eats ice chips. Ice tends to be located in the center of the mouth rather than distributed to all areas at risk for mucosal damage. Secondly, the ice chips melt quickly and frequent replenishment is necessary. This requires regular checks by nursing staff to assure that oral cooling remains constant. Finally, the direct contact of ice with the oral mucosa can be painful and may create dental complications such as cracking of teeth and pulpal damage. A preliminary investigation of 5 individuals using ice chips revealed significant oral and dental pain after less than 5 minutes of contact with the oral cavity. The cryotherapy regimen described by Mahood et al. (1991) was modified in order to accomplish the following aims: (a) improve the uniformity of oral mucosal cooling by employing an ice filled plastic bag designed to cool both central and buccal areas, (b) improve patient tolerance of the procedure, and (c) reduce nursing time necessary to implement the intervention.

CHAPTER III

METHODS

The study used a sequential comparison experimental design (Mitchell, 1988) to determine the effects of oral cryotherapy on the incidence and severity of 5-FU/LV associated mucositis as measured by two oral assessment scales. Tolerance of oral cryotherapy was evaluated by an oral pain rating scale completed by the patient during and immediately following the administration of each treatment. Finally, mucositis scores obtained on two oral assessment scales during the experimental course were compared. The detailed study protocol is presented in Appendix A.

Sample and Setting

The initial study plan included a projected minimum of 10 and a maximum of 30 subjects. Following a data collection period of approximately 10 months, the study was closed after a total of six subjects had been tested. Eligible subjects were at least 18 years of age, were receiving a regimen of 5-FU/LV for colon cancer, and had evidence of oral mucositis during a previous course of chemotherapy. The 5-FU was administered by bolus injection over 1 to 10 minutes and was repeated for 5 consecutive days. LV was administered by bolus or infusion on the same schedule as 5-FU. Each treatment course was repeated every 28 days. The treatment intent of 5-FU/LV was either adjuvant, to improve the probability of cure following surgical resection, or palliative, to control symptoms and progression of unresectable disease. A minimum 5-FU dosage of 370 mg/m^2 administered with a minimum dose of 20 mg/m^2 LV was initially designated in the eligibility criteria to eliminate the chance

that oral mucositis would not occur due to low treatment doses. However, three subjects treated at 5-FU doses below 370 mg/m^2 (minimum dose of 224 mg/m^2) continued to demonstrate significant toxicity, including mucositis, diarrhea, and fatigue and were included in the sample.

Exclusion criteria included concurrent radiation therapy since it could intensify mucositis by other cytotoxic mechanisms. Subjects with brain metastases were excluded due to a relatively short estimated survival and the possibility of cognitive changes which could influence the ability to give informed consent.

Subjects received their examinations and chemotherapy in clinic areas designated for oncology practice. Chemotherapy was administered in private rooms by registered nurses certified to administer cytotoxic drugs. Subject recruitment, instrument administration, baseline oral assessments, and oral cryotherapy was conducted on site. Follow up assessments were conducted at the clinic if the subject was scheduled for a visit or, alternatively, in the subject's home.

Recruitment Strategies

Subjects were recruited from four clinics served by seven oncologists. Recruitment strategies consisted of a letter (see Appendix H) and brochure (see Appendix I) mailed to each physician explaining the purpose of the study, subject eligibility, and oral cryotherapy procedures. The investigator personally discussed the study with chemotherapy nurses in three clinics where five of the seven physicians treat their patients. Additionally, an article describing the study was published in the newsletter for the local chapter of the Oncology Nursing Society.

Despite the numerous efforts to recruit patients, resistance to the study was encountered from nurses at two of the four clinics. Both clinics had instituted prophylactic oral cryotherapy using the procedure described by Mahood et al. (1991) to all patients beginning with their first course of 5-FU/LV chemotherapy. Thus, an untreated baseline course did not exist for this group of patients. The investigator was concerned that patients were receiving oral cryotherapy when oral mucositis had not been documented. At least one third of these patients would not be expected to develop oral mucositis; hence, they were unnecessarily subjected to a potentially uncomfortable and inconvenient procedure. Following several discussions between the investigator and nurses regarding the ethical issues of providing oral cryotherapy to those who may not need it, a total of six patients were referred from these two clinics. However, only one subject qualified and entered the study. The remaining five subjects were recruited from the other two oncology clinics.

Intervention

Oral cryotherapy, the independent variable in the study, was defined as experimental cooling of the oral cavity as a therapeutic modality intended to reduce the incidence or severity of oral mucositis. The procedure was initiated 10 minutes prior to each 5-FU injection and was continued during the injection and for 25 minutes afterward. The LV injection was administered either 1 hour or approximately 1 minute prior to 5-FU, depending on the treatment protocol prescribed by the physician. Since LV is not toxic to mucosal cells, timing of its administration did not influence timing of oral cryotherapy.

The only published oral cryotherapy study (Mahood et al., 1991) employed a 5 minute cooling period prior to 5-FU injection. However, the investigators failed to provide data describing the amount of vasoconstriction achieved at the time 5-FU was administered. Scalp hypothermia data by Hillen et al. (1990) suggested blood flow was reduced by 50% following 10 minutes of scalp cooling. Similar to scalp hypothermia, the primary objective of oral cryotherapy was to produce local vasoconstriction, thereby reducing drug delivery to the oral cavity. Based on the data from Hillen et al., a 10 minute cooling interval was used prior to injection of 5-FU. In addition, the 25 minute post-injection cooling period used by Mahood et al. (1991) was adopted for this study.

Oral cryotherapy was administered with an oral ice bag, consisting of a soft, 16 by 20 cm polyurethane freezer bag which meets U. S. Department of Agriculture standards for nontoxic food grade materials. Each bag was filled with 3 tablespoons of crushed ice, punctured 5 to 6 times with a toothpick to allow air and melting ice to escape, and the end was tied in a knot to close the opening. Oral ice bags were shaped by hand to resemble the configuration of the oral cavity and kept on ice in a clean container prior to use. Each device measured approximately 8 cm in transverse dimension, by 7 cm in anterior-posterior dimension, by 1 cm in height. The oral ice bag was designed to initiate and sustain local vasoconstriction, while providing some insulation between ice and oral tissues. This design was chosen to enhance patient tolerance of oral cryotherapy over that reported with ice chips and assure relatively constant cooling throughout the procedure.

Subjects were instructed to place the device inside the mouth behind the front teeth. The tied end of the bag extended out through the center of closed lips, allowing subjects to adjust the position of the device as needed for comfort and uniform cooling. Subjects wearing dentures removed them prior to initiating the procedure. As ice melted in the bag, subjects were instructed to swish the ice water around inside the mouth and then swallow it. The investigator checked the cooling device every 3 to 5 minutes to assure that frozen contents remained. When a device had thawed, it was replaced with another frozen one. On average, eight oral ice bags were used for each oral cryotherapy treatment.

Pilot Study

A pilot study was conducted with two healthy adults, a practicing oncologist and a certified oncology nurse, prior to submission of the research study for human subjects review. The purpose of the pilot study was to evaluate adequacy of mucosal cooling obtained with the oral ice bag by measurement with the 8000A Digital Multimeter (John Fluke Manufacturing Company,Inc., Seattle, WA), and to evaluate tolerance of the procedure.

The oral cryotherapy procedure was conducted in the identical fashion described in this study proposal. First, baseline oral temperatures were obtained, then oral cryotherapy was administered with the oral ice bag for a total of 35 minutes. Oral mucosal temperatures were obtained at 5 minutes, then every 10 minutes from the superior surface of the tongue and the right and left buccal mucosa. Temperature readings and oral pain ratings are displayed in Table 1. Oral cryotherapy was well

Table 1

Oral Mucosal Temperature and Oral Pain Ratings During Oral Cryotherapy

	Subject 1			Subject 2		
	Oral Temperature (°C)					
Minutes of Cryotherapy	Right	Left	Tongue	Right	Left	Tongue
5	19	18	19	17	15	15
10	17	14	20	16	14	15
20	13	13	15	12	13	14
30	11	11	16	13	12	14
	Pain score[a]					
4	1 (mild)			1 (mild)		
35	2 (discomforting)			2 (discomforting)		

Note. Temperature was obtained from right buccal mucosa, left buccal mucosa, and superior central portion of the tongue, respectively. [a]Oral pain was rated with the Present Pain Intensity Scale (Melzack, 1975) found in Appendix D.

tolerated, with side effects limited to mild to moderate dental pain, burning and numbness of the cheeks, and a sensation of feeling cold, all of which resolved within 30 minutes after completing the procedure. Approximately 12 hours after oral cryotherapy, small aphthous ulcers (canker sores) and mild irritation developed on the lateral aspect of the tongue in one subject and resolved untreated within 36 hours. No choking or gagging sensations were experienced.

Evaluation of Oral Mucositis

Oral mucositis was defined as erythema and ulceration of oral mucosal tissues. Oral mucositis was scored with two instruments, the Common Toxicity Criteria (CTC) Stomatitis Scale (National Cancer Institute, 1989) and the Oral Assessment Guide (OAG) (Eilers, Berger, & Petersen, 1988). Subject reporting of oral pain was assessed by the Present Pain Intensity Scale (PPI), a part of the McGill Pain Questionnaire (Melzack, 1975). Oral assessment was performed at six time points during the study. Initial evaluation, termed baseline, was performed by physician examination with the CTC Stomatitis Scale when mucositis was present during the previous course of chemotherapy. Subsequent evaluations were performed by the investigator using the CTC Stomatitis Scale, the OAG, and the subject's rating on the PPI Scale. The second evaluation, day 1, was performed prior to chemotherapy administration on the first day of the experimental course. The purpose of this evaluation was to describe the baseline condition of the oral mucosa. Postcryotherapy evaluations were conducted at four time points (days 5, 10 to 12, 15, and 29) following implementation of the experimental treatment to determine the worst degree

of mucositis which developed during the treatment course.

Common Toxicity Criteria Stomatitis Scale

The CTC Stomatitis Scale, a component of the CTC (National Cancer Institute, 1989), was the first tool used for evaluating mucositis (see Appendix B). The CTC Stomatitis Scale provided a functional rating of the subjects's ability to eat and the presence of soreness or ulcers. Ratings for mucositis included 0 (none), 1 (painless ulcers, erythema, or mild soreness), 2 (painful erythema, edema, or ulcers but can eat), 3 (painful erythema, edema, or ulcers and cannot eat), and 4 (requires enteral or parenteral support).

The complete CTC are a comprehensive list of drug related toxicities universally used by national organizations conducting cancer clinical trials. Use of a standard scale allows consistent reporting of drug toxicity within each trial and across trials of different cancer types. Organ system abnormalities and symptoms are rated in terms of severity. For example, hematopoietic toxicities, such as anemia, and constitutional symptoms, such as fatigue, are described and rated from 0 to 4 as follows: 0 (none), 1 (mild), 2 (moderate), 3 (severe), and 4 (life threatening). Scores are not added or averaged. Instead, guidelines for modifying drug doses or radiation schedules are based on the severity of specific toxicities. Despite the fact that rigorous reliability and validity testing has not been done, the applicability of the criteria and general use in cancer research support face validity of the CTC. Inclusion of the CTC Stomatitis Scale in this study facilitated comparison of results with previous oral mucositis studies reported in the literature.

Oral Assessment Guide

The OAG, shown in Appendix C, was the second tool used to provide an objective score of each subject's oral condition (Eilers et al., 1988). The OAG categorically rated the degree of disruption in oral mucosal condition by scoring observations of eight oral characteristics including the voice, swallowing ability, lips, tongue, saliva, mucous membranes, gingiva, and teeth or denture bearing areas. Each category received a numerical score ranging from 1 for normal condition to 3 for marked dysfunction or disruption. The scores for each of the eight categories were totaled for a possible range of 8 to 24. The instrument provided an ordinal level score which reflected overall oral condition as well as disruption in any single category. Eilers et al. evaluated content and consensus validity by an extensive review of the literature. Moreover, confirmation of the content areas was validated with a panel of experts consisting of three dental professors from two universities in Omaha, NE and one attending dentist from Memorial Sloan-Kettering Cancer Center, New York, NY. Interrater reliability was reported as .91 (Eilers, et al., 1988).

Eilers et al. (1988) developed and tested the OAG with 20 critically ill patients undergoing high dose chemotherapy or chemoradiotherapy and bone marrow transplantation. Severe mucositis is universal in patients undergoing this type of therapy. OAG scores were obtained on each patient daily until recovery, death, or initiation of mechanical ventilatory support. The latter condition prevented thorough oral assessment. Total scores in the sample ranged from 8 to 22, while mean scores in individual patients ranged from 9.4 to 14.8.

Examination procedures required to complete the OAG are noninvasive, easily performed by trained nursing personnel, and require equipment commonly found in a medical clinic. If necessary, equipment can be easily transported to the patient's home to perform examinations when a clinic visit is not scheduled. Thus, the OAG was well suited to evaluation of patients treated with stomatoxic drugs in an outpatient setting. Since the OAG had been designed for patients with oral mucositis and had been previously tested in this population, it was considered appropriate in this study.

Present Pain Intensity Scale

Temporary oral discomfort may result from the cryotherapy procedure, while persistent pain is associated with moderate to severe mucositis. Subjective measurement of oral pain was assessed with the PPI Scale (Melzack, 1975). The PPI Scale is a six item verbal descriptor scale ranging from (0) no pain, to (5) excruciating (see Appendix D). Reliability testing has generated variable results. A report by Reading (1980) compared pain measurement with the PPI Scale to a 10 point visual analog scale in postpartum women with episiotomy pain. His results showed a moderate but significant correlation between the PPI Scale and a visual analog scale measure of pain (r= .57 to .71). Validity and reliability may be superior in verbal descriptor scales compared to visual analog scales, since the former tend to be easier to understand. Furthermore, subjective rating of pain with a list of descriptive words, such as those used in the PPI Scale, is generally accepted as a valid measure of the subjective pain experience (McGuire, 1988).

For the purposes of the study, subjects were asked to rate oral pain related to

mucositis and the oral cryotherapy procedure with the PPI Scale. During the day 1 evaluation, the PPI Scale was used to obtain a retrospective rating of oral pain related to mucositis experienced during the previous chemotherapy course. Subsequent rating of oral pain was performed in conjunction with the OAG and CTC Stomatitis Scale at the same time points. Rating of pain related to oral cryotherapy was performed prior to each procedure, after 5 to 9 minutes of cryotherapy, and at completion. Instructions on administration were provided with the tool and each subject was asked to read the instructions then select the term which best describes their degree of pain. All six subjects were literate, capable of reading the instructions, and selecting a verbal descriptor to reflect their pain level.

Oral examination

A complete examination of the oral cavity, was conducted by adopting the method described by Schweiger, Lang, and Schweiger (1980). The procedure includes careful examination of the lips, buccal mucosa, tongue, gingiva, and palate with a dental mirror and gloved hands. The pharynx is evaluated by visual inspection with use of a tongue blade combined with changes in voice character and subject reports of throat pain. The equipment and procedures are described in the data collection protocol found in Appendix A.

Influencing Variables

Variables which may influence the severity and duration of mucositis and were controlled in the study included the type of cancer and the chemotherapeutic drug combination, dosage, and schedule of administration (Sonis, 1989). Additional

variables were accounted for which could have a minor or unknown impact on the outcome of the intervention, or were unrealistic to control within the context of the study. Personal variables which were accounted for include age, height, weight, body surface area, weight loss since diagnosis, smoking history, documented periodontal disease, and dentition (Peterson, 1983; Sonis, 1983; Sonis, 1989; Szeluga, et al., 1990). Dentition was rated by the investigator in five categories: excellent (no evidence of periodontal disease), good (mild dental decay or slight periodontal disease), fair (moderate dental decay, gingival redness, or mild gum retraction evident) poor (severe gum retraction, loose and severely decayed teeth, and/or extreme periodontal disease), or edentulous. Treatment variables which were accounted for included previous cancer therapy, number of prior 5-FU/LV treatment courses, total dose of 5-FU and LV, and the clinic where treatment was administered. Influencing variables were recorded on the Background Data Collection Form (see Appendix F).

Variables which were not controlled or accounted for include the relationship of treatment administration to the patient's circadian rhythms, detailed dental history including the number of crowns and fillings, and concurrent medical illnesses such as heart disease and pulmonary disease.

Protection of Human Subjects

The study proposal and patient consent form were approved by the Oregon Health Sciences University Committee on Human Research prior to commencement of data collection. All patients provided written informed consent prior to study participation.

Patient records were maintained in a locked file, and individual patient data was coded and reported by number rather than name to protect confidentiality.

Although minimal risk was predicted for oral cryotherapy, there are reports in children of a subcutaneous inflammatory process caused by contact with frozen foods such as popsicles and ice cream for at least 5 minutes (Epstein & Oren, 1970). The process, termed "popsicle panniculitis," is self limiting, resolves untreated in several days, and has only been reported in infants and young children. A similar syndrome, "french vanilla frostbite," has been described in an 18 month old child who developed blistering of the lips following 30 minutes of contact with a vanilla ice cream cone (Peterson & Peterson, 1982).

Hypothetical risks to extreme cooling of the teeth included cracking of the enamel and dentin or pulpal damage due to restricted blood flow (M. Bartley, D. M. D., personal communication, August 15, 1991). However, clinical studies supporting these hypotheses were lacking. The primary risks expected in the study were identified by the pilot study and prior researchers (Mahood et al., 1991) and included oral discomfort, nausea, and headache. These risks were expected to be mild and completely reversible following termination of the procedure.

Data Analysis

Small sample or single case designs are useful when there are considerable differences between subjects on the variables being studied (D. Berry, personal communication, April 30, 1993). Small sample studies help explain the effects of a specific variable or changes in phenomena within each subject rather than between

subjects. Mitchell (1988) suggests these study designs are particularly applicable to nursing since they "preserve the uniqueness of the individual" (p. 200).

Despite the small sample size of 6 subjects, the amount of data collected was considered adequate to describe patterns of response to oral cryotherapy in each subject. The sequential comparison or A - B design used in this study helped explain how the experimental treatment, oral cryotherapy, affected the development of oral mucositis in each subject over a period of 29 days. Detailed descriptions and graphic presentations of each subject's data were performed to analyze and compare individual characteristics and responses to oral cryotherapy. Descriptive statistics, specifically median scores and ranges, were employed to summarize the data.

To determine if oral cryotherapy administered during 5-FU/LV chemotherapy affected the subsequent development of mucositis, the incidence and severity of oral mucositis during the study course were compared to the preceding course in which oral cooling was not employed. Scores obtained when mucositis was present during the baseline course were compared to scores on obtained during the experimental course. Ratings of oral pain during the baseline and experimental courses were compared at the same time points to determine if oral cryotherapy affected the severity of oral pain related to mucositis. Oral pain ratings obtained immediately before and during the oral cryotherapy procedure were compared separately to evaluate patient tolerance of the procedure. Finally, scores on the CTC Stomatitis Scale and OAG obtained during the experimental course were compared to determine if increases in CTC Stomatitis scores were associated with comparable increases in OAG scores.

CHAPTER IV

RESULTS

The major purpose of this study was to determine whether oral cryotherapy reduced the incidence and severity of oral mucositis associated with 5-FU/LV chemotherapy. The CTC Stomatitis Scale and the OAG were the instruments employed to measure the effects of the independent variable, oral cryotherapy, on the presence and severity of the dependent variable, oral mucositis. Oral pain from mucositis was rated by the PPI Scale as was tolerance of oral cryotherapy during and immediately following each treatment. Individual subject scores on the CTC Stomatitis Scale and OAG during the experimental course were compared.

Characteristics of the Study Sample

A convenience sample of six subjects receiving combination 5-FU/LV chemotherapy for colon cancer was studied. Individual characteristics are displayed in Table 2. They ranged in age from 26 to 72 with a median of 63.5 years. Four women and one man were receiving 5-FU/LV as palliative treatment for unresectable disease, while a single woman was undergoing adjuvant therapy to prevent disease recurrence. Two subjects were current smokers; one subject was a past smoker but had not smoked for several years. Only one subject had poor dentition and one was edentulous.

Seven additional patients were referred for oral cryotherapy but were ineligible to participate. Three patients received 5-FU by daily continuous intravenous infusion rather than daily bolus injection, two did not receive a second course of therapy due to

Table 2

Subject Characteristics

Subject	Age (years)	Sex	BSA (m^2)	Dentition[a]	Current Smoker
1	26	Female	1.78	Excellent	No
2	72	Female	1.68	Fair	No
3	69	Male	2.05	Excellent	No
4	61	Female	1.35	Poor	No (past)
5	55	Female	1.57	Edentulous	Yes
6	66	Female	1.54	Good	Yes

[a]Excellent = no evidence of periodontal disease; good = mild dental decay or slight periodontal disease; fair = moderate dental decay, gingival redness, or mild gum retraction evident; poor = severe gum retraction, loose and severely decayed teeth, and/or extreme periodontal disease.

severe toxicity during the initial course, one patient had only four rather than five days of 5-FU/LV during the baseline course, and one was unknown to the investigator until after the experimental course of chemotherapy had begun.

Five subjects were treated in private physician's clinics, while one was treated in the hospital in order to receive insurance reimbursement. All chemotherapy was administered during daytime hours between 9 a.m. and 5 p.m. As shown in Table 3, four of the subjects received identical drug dosages during both treatment courses while two subjects had dose reductions during the experimental course. Chemotherapy consisted of a minimum 5-FU dose of 224 mg/m^2 (Md = 387) administered with a minimum LV dose of 19 mg/m^2 (Md = 21.5) on a 5 day schedule which was repeated every 28 days. Drug doses during the baseline and experimental courses are shown in Table 3.

Responses to Oral Cryotherapy

The incidence and severity of oral mucositis during the experimental chemotherapy course was compared to the preceding course in which oral cooling was not employed, using the worst scores obtained on the CTC Stomatitis Scale. To evaluate tolerance of oral cryotherapy, oral pain ratings were obtained immediately before and during the procedure. Scores on the CTC Stomatitis Scale and OAG during the experimental course were compared to determine if an increase in the CTC Stomatitis Scale score on day 10 to 12 was associated with a comparable increase in the OAG score on day 10 to 12.

The following individual summaries of subject data include a general description

Table 3

Chemotherapy Doses During Baseline and Experimental Courses

Subject	Baseline				Experimental				
	Chemotherapy course	5-FU dose	LV dose	Cumulative 5-FU[a]	Chemotherapy course	5-FU dose	% 5-FU reduction	LV dose	Cumulative 5-FU
1[b]	3	309	492	4,958	4	309	0	492	6,503
2	1	372	21	1,860	2	342	8	21	3,570
3	1	402	20	2,012	2	402	0	20	4,024
4	1	407	22	2,037	2	407	0	22	4,074
5	1	408	22	2,038	2	408	0	22	4,076
6	1	357	19	1,786	2	224	37	19	2,906

Note. All doses are in milligrams per meter squared of body surface area. [a]Cumulative 5-FU dose at the end of the chemotherapy course. [b]Patient 1 received concomitant interferon alfa-2_b, 9×10^6 units on days 0 (beginning the day before 5-FU/LV) through 6 of each course.

of the subject, the incidence and severity of oral mucositis during the baseline course and experimental courses of chemotherapy, and available information regarding continuance of oral cryotherapy after the study. Each subject's scores on the CTC Stomatitis Scale, OAG, and PPI Scale at baseline and days 1, 5, 10 to 12, 15, and 29 are presented in graphic form. Baseline OAG scores were not available in five of the six subjects. A comparison of subject data follows the individual summaries.

Subject 1

Subject 1 was a 26 year old female whose colon cancer was diagnosed three months after giving birth to her first child. Following a hemicolectomy to remove a large lesion in the transverse colon, she enrolled in a clinical trial evaluating the efficacy of 5-FU combined with high-dose LV and interferon alfa 2_a. She did not smoke and her dentition was excellent.

Subject 1, in contrast to the other five subjects, had received more than one prior chemotherapy course. Baseline data were obtained during her third course. Her cumulative 5-FU dose after the baseline (third) course was 4,958 mg/m^2 compared with a range of 1,786 to 2,038 mg (*Md* = 2012 mg) for the other subjects (see Table 3). She had experienced grade 2 to 3 oral mucositis by CTC criteria during all three previous courses. At day 10 of the baseline course she had a CTC score of 2 and a retrospective oral pain rating of 4 in spite of a reduction in 5-FU dose from 370 mg/m^2 to 309 mg/m^2. The OAG score was unavailable. Oral mucositis was generalized, involving the buccal mucosa, palate, and tongue along with pharyngeal pain that limited oral intake to liquids. She experienced moderate nonmucosal

toxicities during all three courses as well (see Table 4). Concomitant interferon alfa-2_b is known to intensify mucosal, hematologic, and gastrointestinal toxicity of 5-FU/LV (Grem, Chu, Boarman, Balis, Murphy, McAtee, et al., 1992).

During the experimental course of chemotherapy in which oral cooling was used, Patient 1 demonstrated a virtual absence of oral lesions with a CTC score of 0. Her only complaint was mild pharyngeal pain which did not interfere with eating. Mild soreness on swallowing resulted in an OAG score of 9. She rated oral pain on the PPI Scale as 0 (see Figure 2). Table 4 shows that non-mucosal toxicity during the experimental course was similar to the baseline course.

Subject 1 electively continued oral cryotherapy for one additional course of chemotherapy with only slight benefit (CTC grade 2, primarily pharyngeal soreness). However, she left the clinic prior to completing the prescribed cooling period and it is unknown if she continued cooling for the full 25 minute period after 5-FU. Nausea, which she attributed to the ice, led her to refuse oral cooling during her sixth and final treatment course. Oral mucositis and pharyngeal soreness was evident during this course as well (CTC = 2).

Subject 2

Subject 2, a 72 year old woman with metastatic colon cancer to bone, lungs, and liver, was the oldest subject treated. She had undergone a segmental colon resection and was found to have a primary colon tumor with extensive hepatic metastasis. After her first course of therapy, she developed sciatic pain that required oral narcotic analgesics and eventually was treated with local radiation therapy.

Table 4

Nonmucosal Toxicities by Common Toxicity Criteria Grade During Baseline Course and Experimental Course

Subject	Toxicity	Baseline	Experimental
1	Diarrhea	2	2
	Nausea/Vomiting	2	1
	Fatigue	2	2
2	Diarrhea	2	0
	Nausea/Vomiting	1	2
3	Diarrhea	1	3
	Nausea/Vomiting	0	1
4	Diarrhea	1	0
5	Diarrhea	2	0
	Nausea/Vomiting	0	1
6	Diarrhea	1	4
	Fatigue	3	2
	Infection	4	0

Note. 0 = none; 1 = mild; 2 = moderate; 3 = severe; 4 = life-threatening.

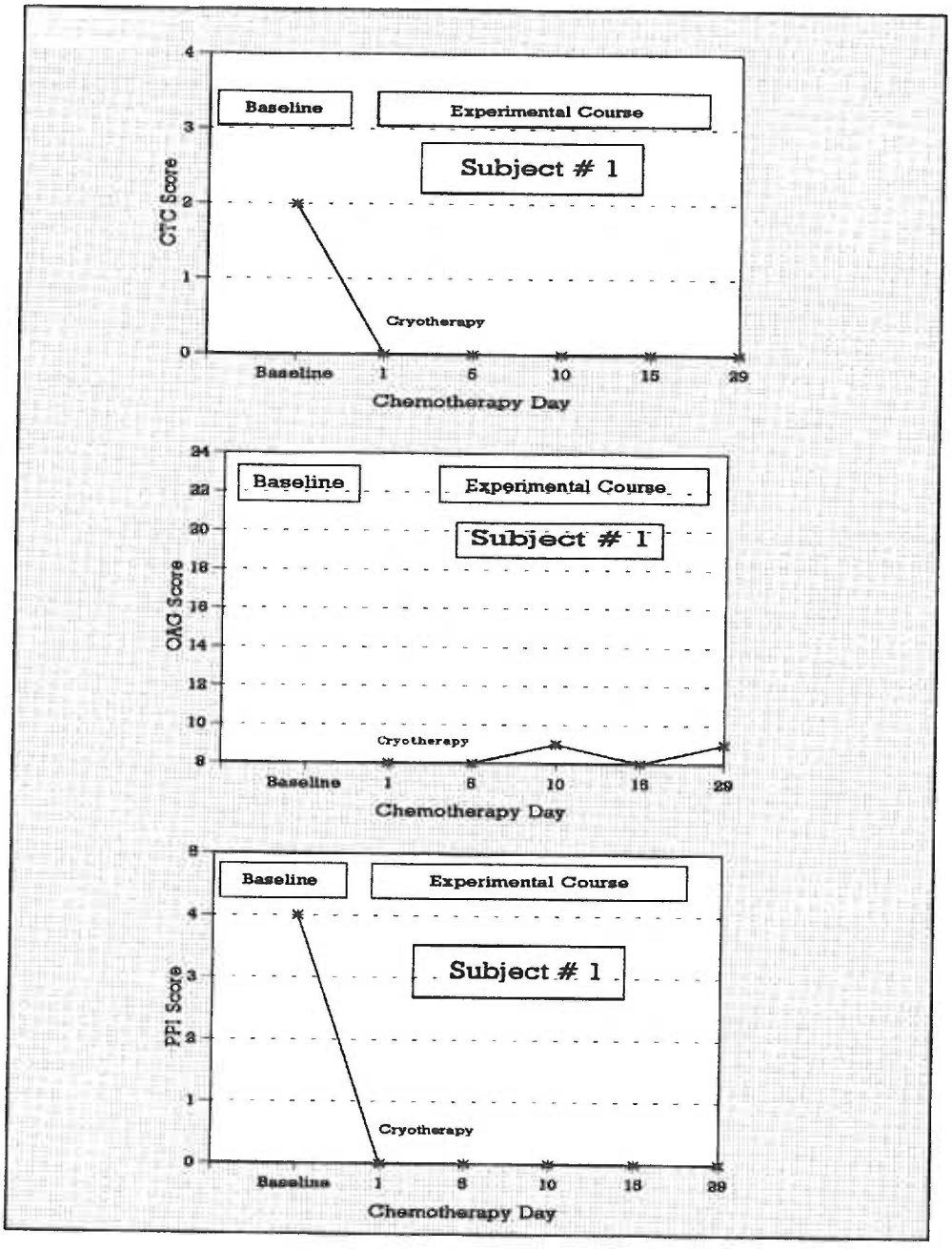

Figure 2. Scores on the Common Toxicity Criteria Stomatitis Scale (top), Oral Assessment Guide (middle), and Present Pain Intensity Scale (bottom) during baseline and experimental courses for Subject 1.

Following administration of the baseline course, she experienced moderate oral mucositis (CTC grade 2). Oral pain was rated at 2 on the PPI Scale (see Figure 3). She noted ulcers on her lip line and lower gingiva, however, oral intake was not restricted. She explained her palate felt "pebbly" and rough. The prominent non-mucosal toxicity during the baseline course was diarrhea (see Table 4).

An 8% dose reduction in 5-FU was ordered by the physician due to oral mucositis and diarrhea experienced during baseline. The physician and the investigator did not believe this modest dose reduction would ameliorate 5-FU toxicity; therefore, oral cryotherapy was instituted to reduce subsequent mucositis. A definite benefit was seen after oral cryotherapy was administered. Oral pain was absent and the only evidence of mucosal toxicity was a mild "scratchy" throat and a pinpoint sized erythematous lesion on upper anterior buccal mucosa noted on day 10 (see Figure 3). She was too ill to be seen for the final assessment on day 29. Persistent nausea, vomiting, and pain caused her to withdraw from therapy and she expired 3 months thereafter.

Subject 3

Subject 3, a 69 year old male, was the only subject with a history of prior chemotherapy exposure. He had received a year of adjuvant treatment with methyl CCNU, vincristine, and 5-FU from August 15, 1988 to June 30, 1989 following complete surgical resection of a sigmoid colon cancer. Unfortunately, he developed a recurrence of his colon cancer 36 months later, and he elected to undergo palliative 5-FU/LV therapy.

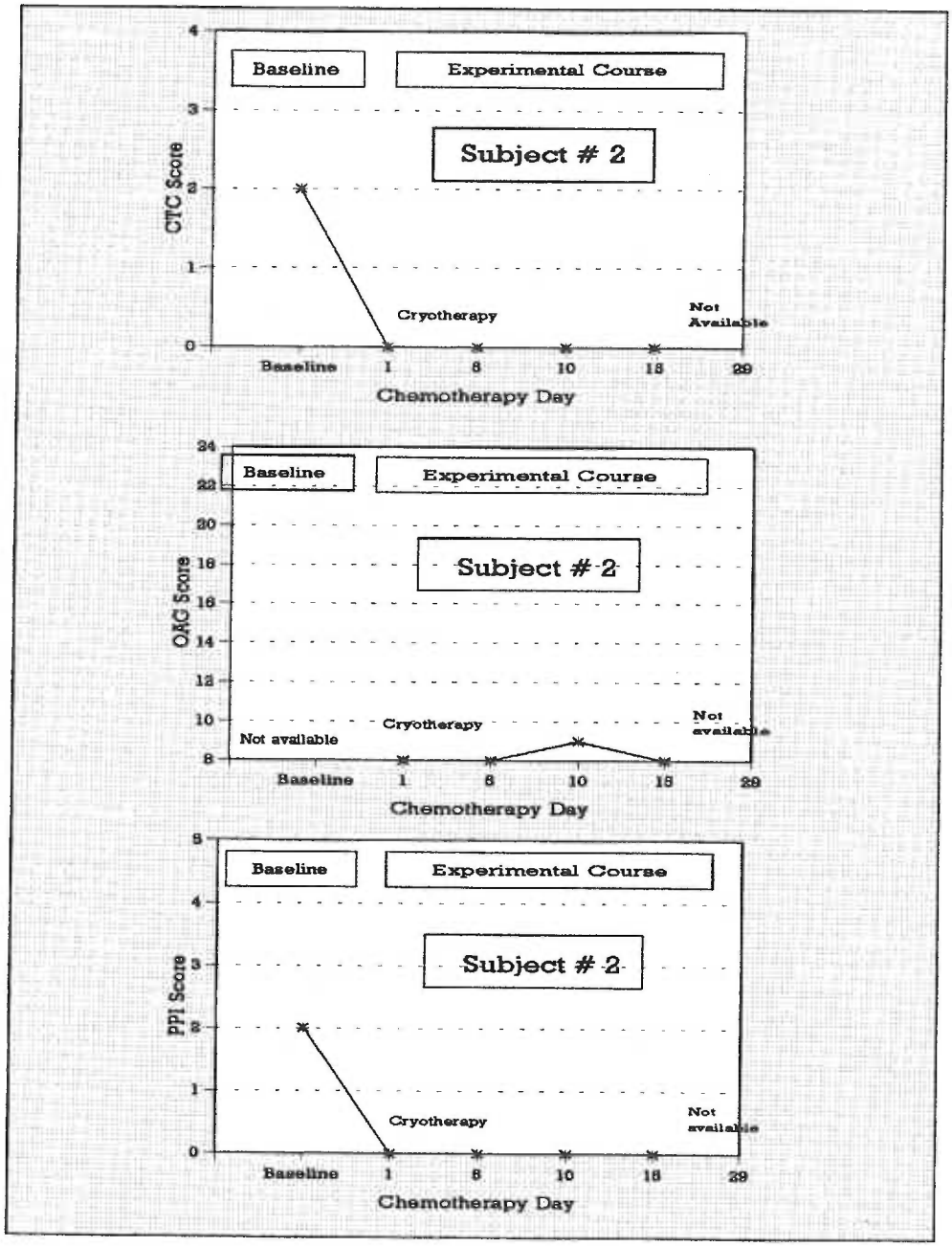

Figure 3. Scores on the Common Toxicity Criteria Stomatitis Scale (top), Oral Assessment Guide (middle), and Present Pain Intensity Scale (bottom) during baseline and experimental courses for Subject 2.

During the baseline course, he experienced moderate oral mucositis (CTC = 2) and rated oral pain as "horrible" (PPI = 4). OAG scores were not available during baseline. Nonmucosal toxicity was limited to mild diarrhea.

During the experimental chemotherapy course, he noted mild oral and throat soreness on day 10, (CTC = 1, OAG = 9, PPI = 2), although observable mucositis was absent (see Figure 4). The CTC score decreased from 2 at baseline to 1 during the experimental course. Oral pain ratings decreased from a score of 4 during baseline to 2 during the experimental course. Subject 3 believed that believed that oral cryotherapy was so successful that he continued to use the procedure for 8 additional courses of chemotherapy with complete prevention of oral mucositis. However, he switched from the oral ice bag used in the study to ice chips after his third course due to nausea associated with the taste of the plastic bags. He reported that ice chips were slightly more effective in his case, achieving subjectively cooler oral temperatures than reached with the ice bag.

Subject 4

Subject 4, a slight 61 year old woman with diffuse peritoneal carcinomatosis, underwent a partial resection of her colon tumor prior to initiating palliative 5-FU/LV therapy. She had extremely poor dentition and was a past smoker, although she had not smoked for several years.

Subject 4 was the only subject available for direct oral assessment by the investigator during the baseline course. Her oral exam at that time was remarkable for marked dental decay, gingival atrophy, and inflammation. During the baseline

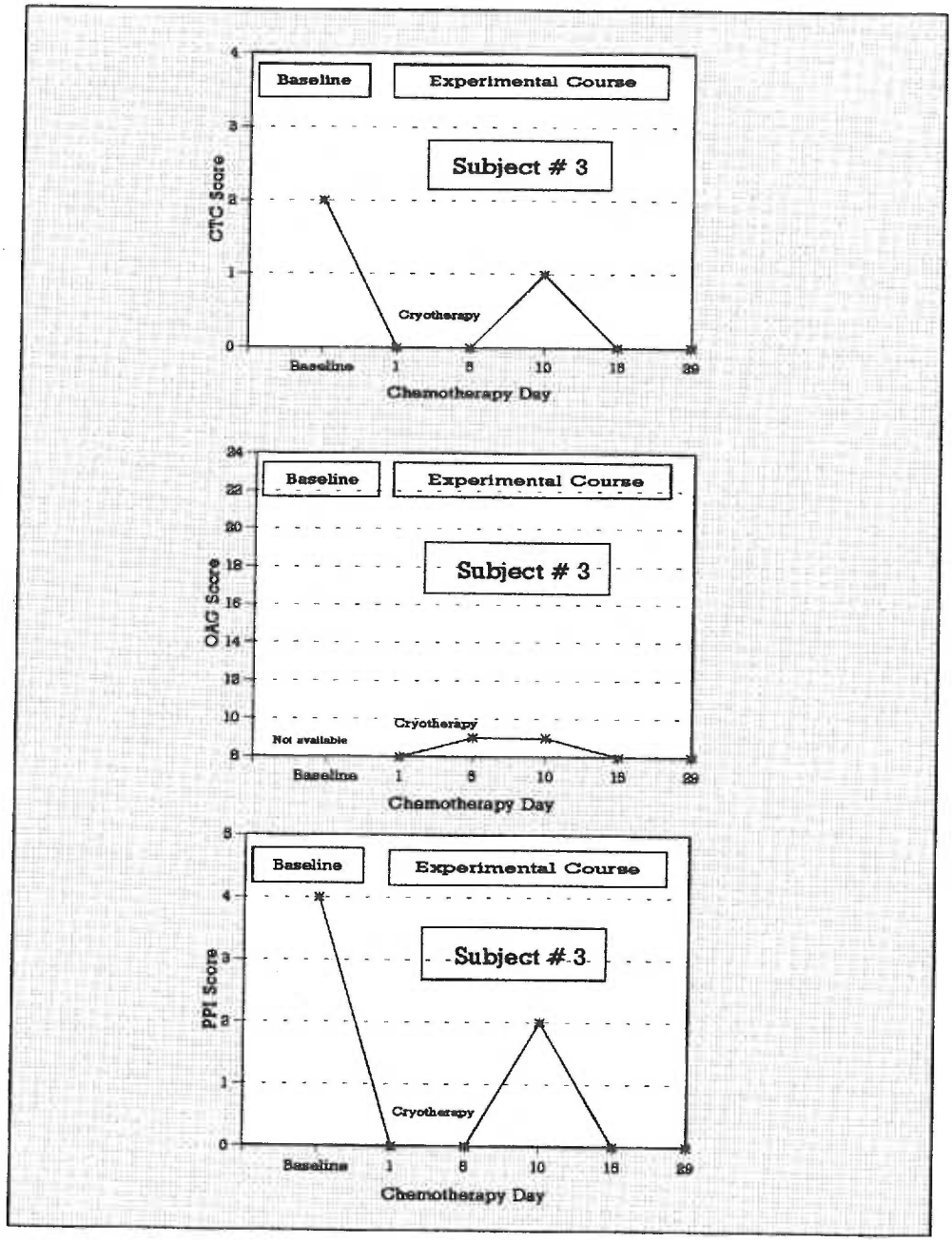

Figure 4. Scores on the Common Toxicity Criteria Stomatitis Scale (top), Oral Assessment Guide (middle), and Present Pain Intensity Scale (bottom) baseline and experimental courses for Subject 3.

course, she experienced severe oral mucositis (CTC = 3) and rated oral pain as "horrible" (PPI = 4). The baseline OAG score was 16. Mild diarrhea was the only nonmucosal toxicity.

Subject 4 improved to an OAG score of 10 prior to initiation of the experimental course on day 1, but severe periodontal disease (gingival irritation, heavy plaque on teeth) precluded a normal OAG score of 8. Therefore, an elevated OAG score in this was not necessarily indicative of oral mucositis. During the experimental chemotherapy course, she reported mild lip soreness and slightly reddened gingiva (CTC = 1, OAG = 12, PPI = 2) on day 12 (see Figure 5). Unfortunately, this subject did not return on day 15 as scheduled and did not have a telephone. However, on day 29, she stated that she had improved and wished to continue cryotherapy. She received 6 additional chemotherapy courses and achieved comparable benefit with oral ice bags.

Subject 5

Subject 5, a 55 year old female smoker with pulmonary metastasis, was diagnosed with colon cancer after a 4 month history of intermittent rectal bleeding. A pulmonary lesion was identified which was consistent with metastatic disease. She was otherwise healthy with the exception of hay fever, and took an antihistamine/decongestant to control symptoms of nasal congestion and sore throat.

During the baseline course, subject 5 developed oral mucositis which was confined to the lips and anterior buccal mucosa (CTC = 2). Oral intake was restricted due to oral pain (PPI = 3), although she was able to eat after applying

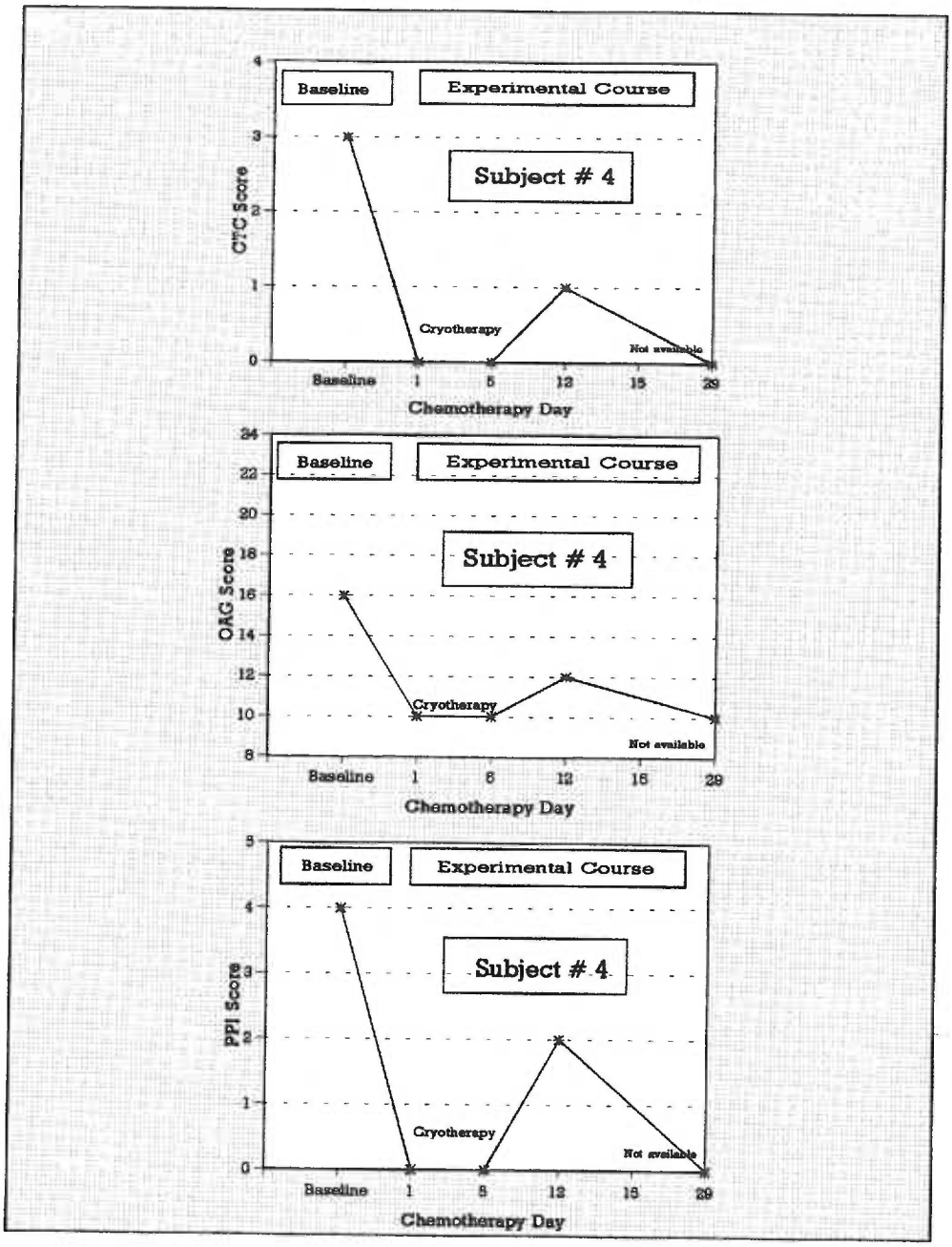

Figure 5. Scores on the Common Toxicity Criteria Stomatitis Scale (top), Oral Assessment Guide (middle), and Present Pain Intensity Index (bottom) during baseline and experimental courses for Subject 4.

viscous xylocaine to her lips. Diarrhea was the only documented nonmucosal toxicity.

On day 5 of chemotherapy, subject 5 left for vacation and returned just prior to the next chemotherapy course. Objective assessments on days 10 and 15 of the experimental course were not possible, but subject 5 was contacted by telephone to obtain subjective CTC and oral pain ratings (OAG scores could not be done). On day 10, she reported moderate throat soreness and at least one ulcer (CTC = 2, PPI = 3) (see Figure 6). Unfortunately, she was not available by telephone on day 15 for assessment. Overall, comparison of baseline and subjective experimental scores on day 10 indicate no benefit was derived from oral cryotherapy. Evaluation of allergic symptoms during the experimental course was not done and aggravation of chemotherapy induced pharyngitis by allergic phenomena cannot be excluded.

Subject 5 returned to the clinic on day 29 requesting continuation of oral cryotherapy. However, she complained that waiting in the clinic for 25 minutes to complete cryotherapy was inconvenient and nausea associated with drinking melted ice was problematic. Instead, she wished to use an unopened, plastic covered popsicle to cool the oral cavity. She hoped this method would prevent nausea when using the ice bag and allow her to leave the clinic immediately after the chemotherapy injection. Subject 5 has continued with oral cryotherapy using the covered popsicles for five additional chemotherapy courses. She reported complete relief from oral mucositis and full chemotherapy doses were maintained.

Subject 6

Subject 6, a 66 year old female, had a long oncologic history including carcinoma

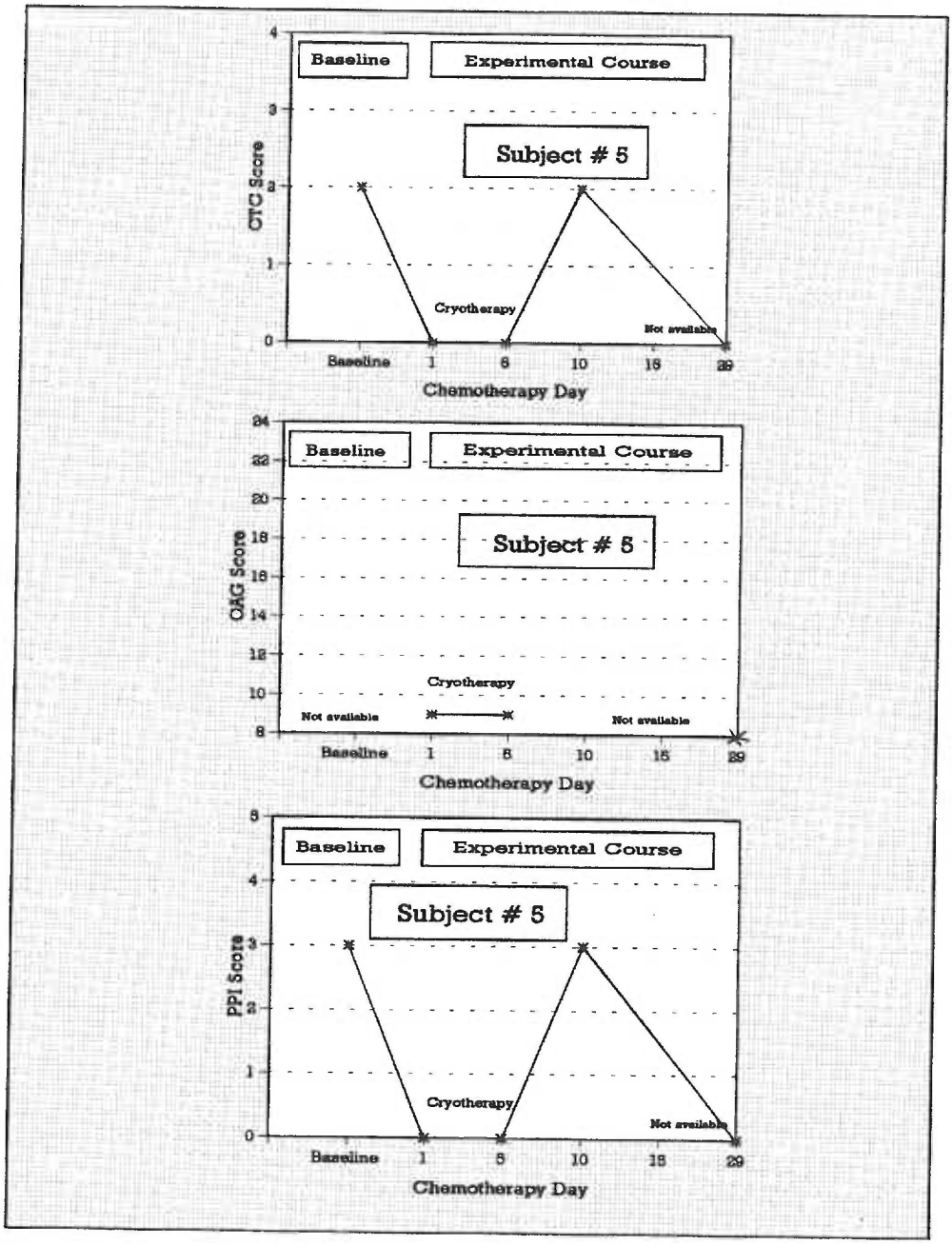

Figure 6. Scores on the Common Toxicity Criteria Stomatitis Scale (top), Oral Assessment Guide (middle), and Present Pain Intensity Scale (bottom) during baseline and experimental courses for Subject 5.

of the stomach, uterus, colon, as well as lymphoma. This combination of malignancies, associated with the presence of keratoacanthomatosis (precancerous skin lesions), is known as Torre's syndrome. She had undergone numerous bowel resections resulting in chronic diarrhea due to short bowel syndrome. She had reluctantly agreed to undergo chemotherapy following her most recent cancer diagnosis, colon carcinoma with liver metastasis.

Subject 6 exhibited the highest CTC mucositis score (CTC = 4) during the baseline course, although she had the lowest cumulative 5-FU dose of all subjects in the study sample. Following the baseline course, she was hospitalized for 14 days with sepsis, diarrhea, and severe mucositis requiring intravenous hydration. She rated her oral pain score as 4.

During the experimental course, the 5-FU dose was decreased by 36% due to the severe toxicity associated with the initial doses. On day 12, subject 6 noted mild throat soreness and two small painless white patches were present on her oral mucosa. The CTC score decreased from 4 at baseline to 1 during the experimental course (see Figure 7). The maximum OAG score of 10 was recorded on day 8. Oral pain ratings decreased from a score of 4 during baseline to 0 during the experimental course. Although she had no oral pain, the CTC and OAG scores remained slightly elevated due to the presence of small painless white ulcerations on the palate, compatible with mild oral candidiasis. The improvement in oral mucositis ratings during the experimental course could have been a consequence of the 5-FU dose reduction. However, significant non-mucosal toxicity including CTC grade 4 diarrhea

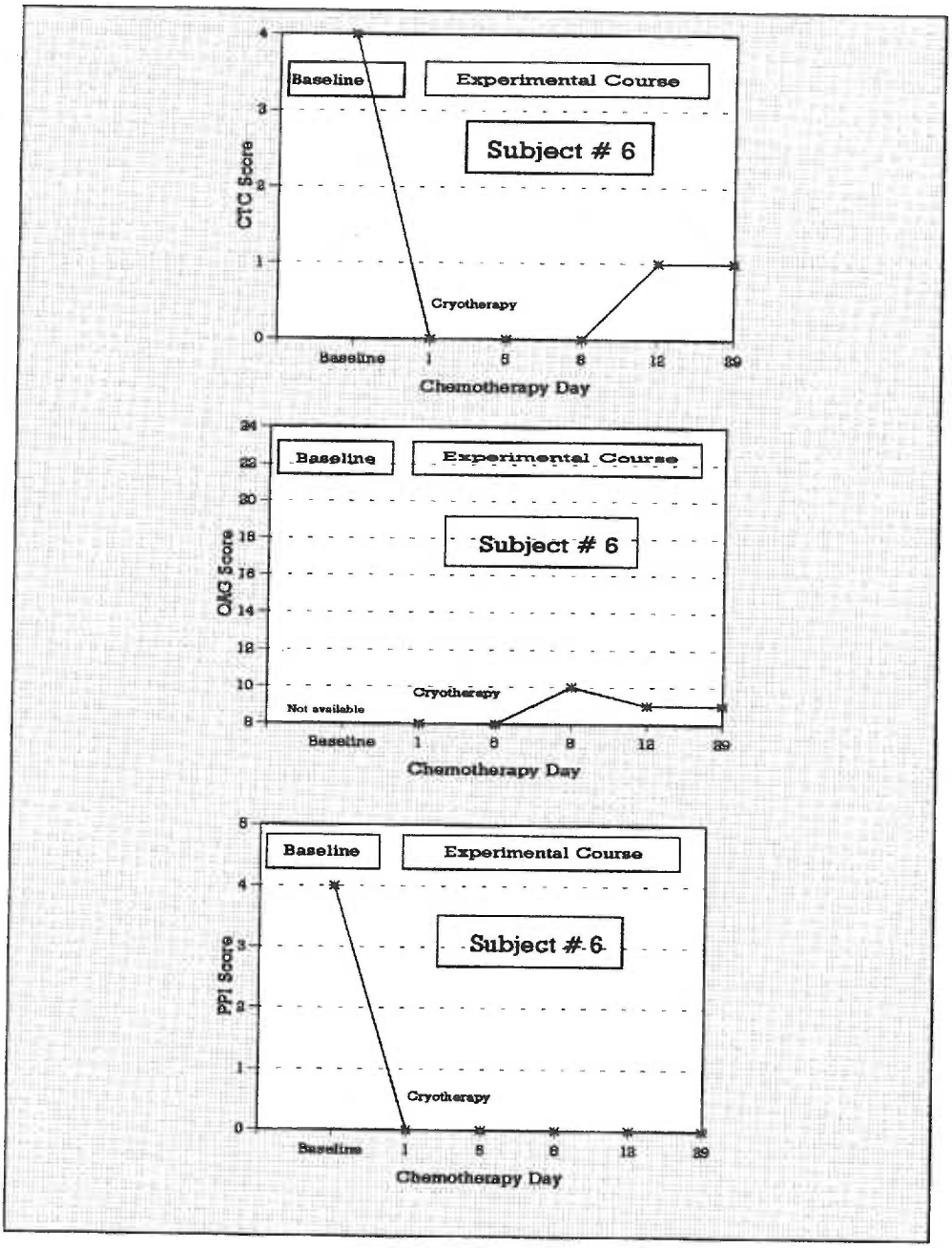

Figure 7. Scores on the Common Toxicity Criteria Stomatitis Scale (top), Oral Assessment Guide (middle), and Present Pain Intensity Scale (bottom) during baseline and experimental courses for Subject 6.

(> 10 liquid stools per day, IV hydration required) and fatigue also developed. Hence, it is a plausible speculation that oral mucositis would have recurred if oral cryotherapy had not been used.

Subject 6 continued to use oral ice bags during three subsequent courses of 5-FU/LV therapy and she reported complete absence of oral mucositis. Non-mucosal toxicity, primarily diarrhea, improved with tincture of opium and intravenous hydration.

Comparison of Responses

Scores obtained with the CTC Stomatitis Scale at baseline (days 8 to 11 of the baseline course) and the experimental course (days 10 to 12) when oral mucositis was expected to be at its worst severity, are displayed in Figure 8. Group OAG scores during the experimental course are found in Figure 9, and PPI Scale scores at baseline and day 10 to 12 of the experimental course are shown in Figure 10.

Common Toxicity Criteria Stomatitis Scale Scores

All subjects, with the exception of subject 5, demonstrated a reduction in mucosal toxicity scores. Subjects 1 and 2 experienced complete absence of 5-FU induced oral mucositis. Subjects 3, 4, and 6 experienced clinical improvement, however, mild pain or redness was still present. Although subject 5 had no change in CTC scores, the pattern of oral mucositis was altered favorably. Soreness and ulceration of the lips and anterior buccal mucosa which were present during the baseline course did not occur during the experimental course. However, irritation of the posterior pharynx increased during the experimental course compared with baseline.

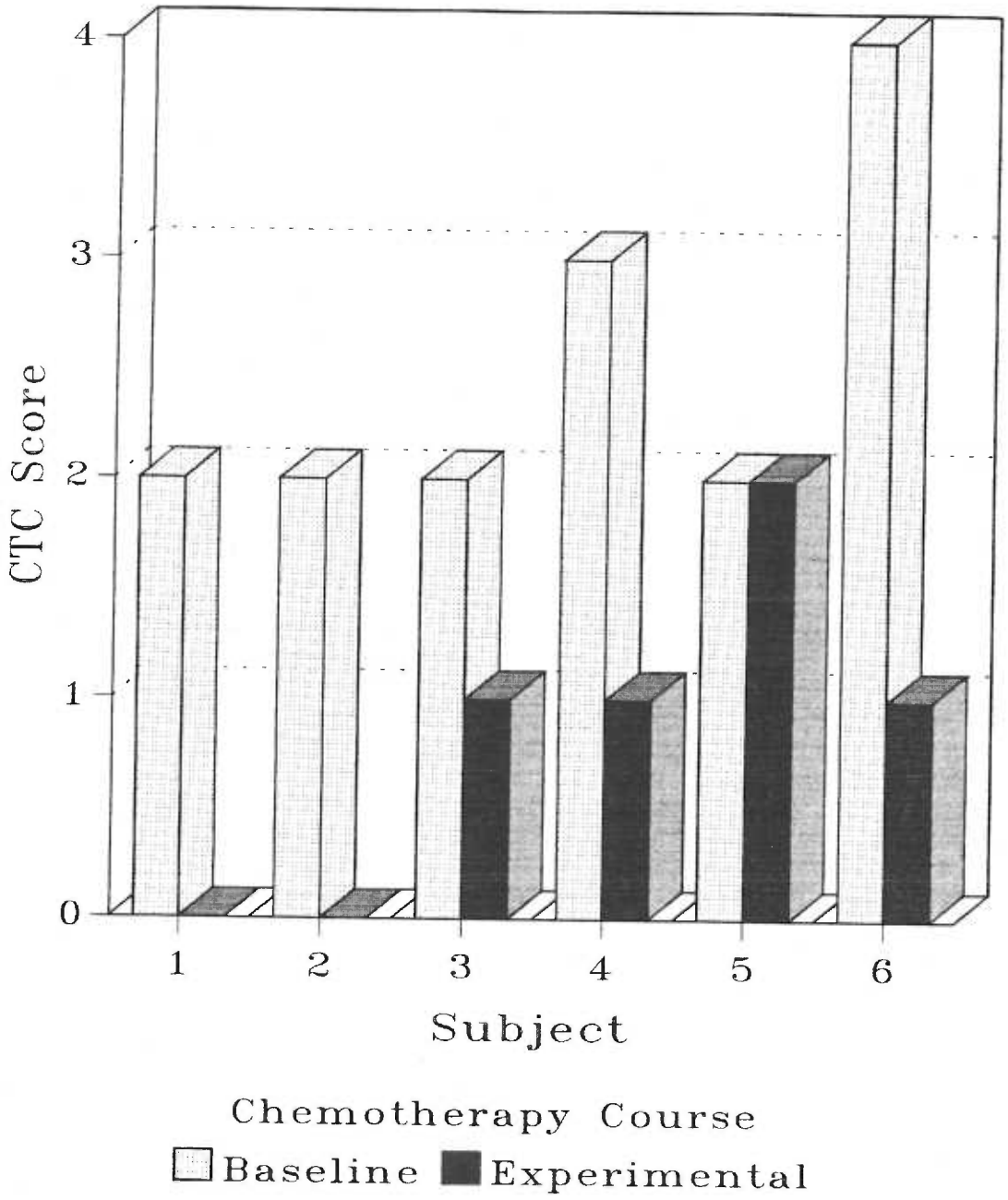

Figure 8. Comparison of the worst CTC Stomatitis Scale scores during baseline and experimental courses of chemotherapy in the six study subjects.

Oral Assessment Guide

Oral examinations were not performed at baseline on five subjects since the investigator was unable to travel to the clinic to examine subjects on short notice. On several occasions the investigator was contacted by a physician when a potential subject was waiting in the clinic. The investigator did not inconvenience potential subjects by asking them to wait for her arrival to obtain a baseline OAG score. However, one subject was scored since she had an appointment at a clinic when the investigator was already present.

Use of the OAG in the study is limited to comparison of scores during the experimental course of chemotherapy. OAG scores on day 1 and days 10 to 12 of the experimental course are displayed in Figure 9. One subject was on vacation and unavailable for assessment at the latter time. Slight increases in OAG scores were observed in the five subjects on days 10 to 12 when compared to day 1 scores. In subjects 1 and 2, slight increases in OAG scores were not accompanied by the presence mucosal ulceration. In both cases, the OAG score of 9 was due to mild pharyngeal pain. Subjects 3, 4, and 6 demonstrated an increase in OAG scores with mild oral pain or painless ulceration.

Comparison of CTC Stomatitis Scale and OAG Scores

A secondary purpose of the study was to compare subject scores on two instruments designed to measure the presence of oral mucositis. However, two factors prevented meaningful comparison of these instruments in the study. Scores on the OAG during the baseline course were not available in five of the six subjects studied.

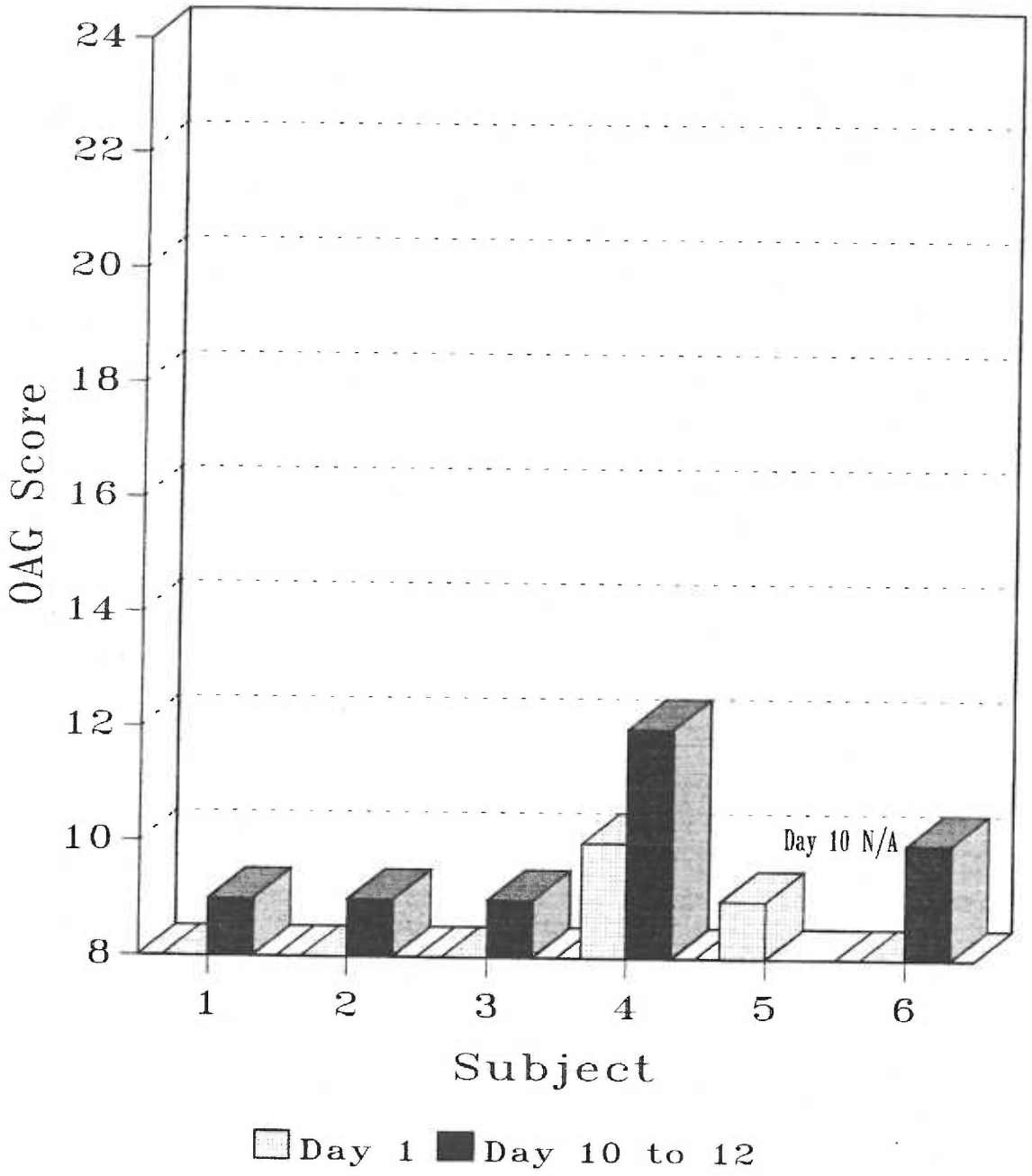

Figure 9. Comparison of OAG scores on day 1 and days 10 to 12 of the experimental course of chemotherapy for the six study subjects.

In addition, the comparison of available OAG and CTC Stomatitis Scale scores on only six subjects did not provide sufficient data for valid statistical correlation. Hence, comparison of scores obtained on these instruments was performed in a descriptive rather than statistical manner.

Five subjects had CTC Stomatitis Scale and OAG scores available for days 10 to 12. Two subjects had a CTC score of 0, indicating no mucositis was present. However, their corresponding OAG scores were elevated from an 8, or normal, to a 9 due to mild pharyngeal soreness. The remaining three subjects all had a CTC score of 1 for mild pain or redness on days 10 to 12 while the OAG scores for these subjects were 9, 12, and 10. In the latter cases, a slight increase in the CTC score from 0 to 1 was accompanied by an increase in the OAG of 1 to 2 points over baseline.

Present Pain Intensity Scale

Comparison of PPI Scale ratings during the experimental course show a reduction in pain associated with oral mucositis consistent with reductions observed in CTC Stomatitis Scale scores (see Figure 10). A decrease in pain ratings during the experimental course, compared to the baseline course was observed in 5 of the 6 subjects. Subjects 1 and 6 reported an absence of oral pain during the experimental course, whereas a rating of 4 was given for the baseline course. Subject 2 lacked oral pain during the experimental course but gave a rating of 2 during the baseline course. Subjects 3 and 4 had a rating of 2 during the experimental course, a reduction from their baseline score of 4. Finally, subject 5 showed no change in PPI Scale scores during baseline and experimental courses, a pattern consistent with her CTC scores.

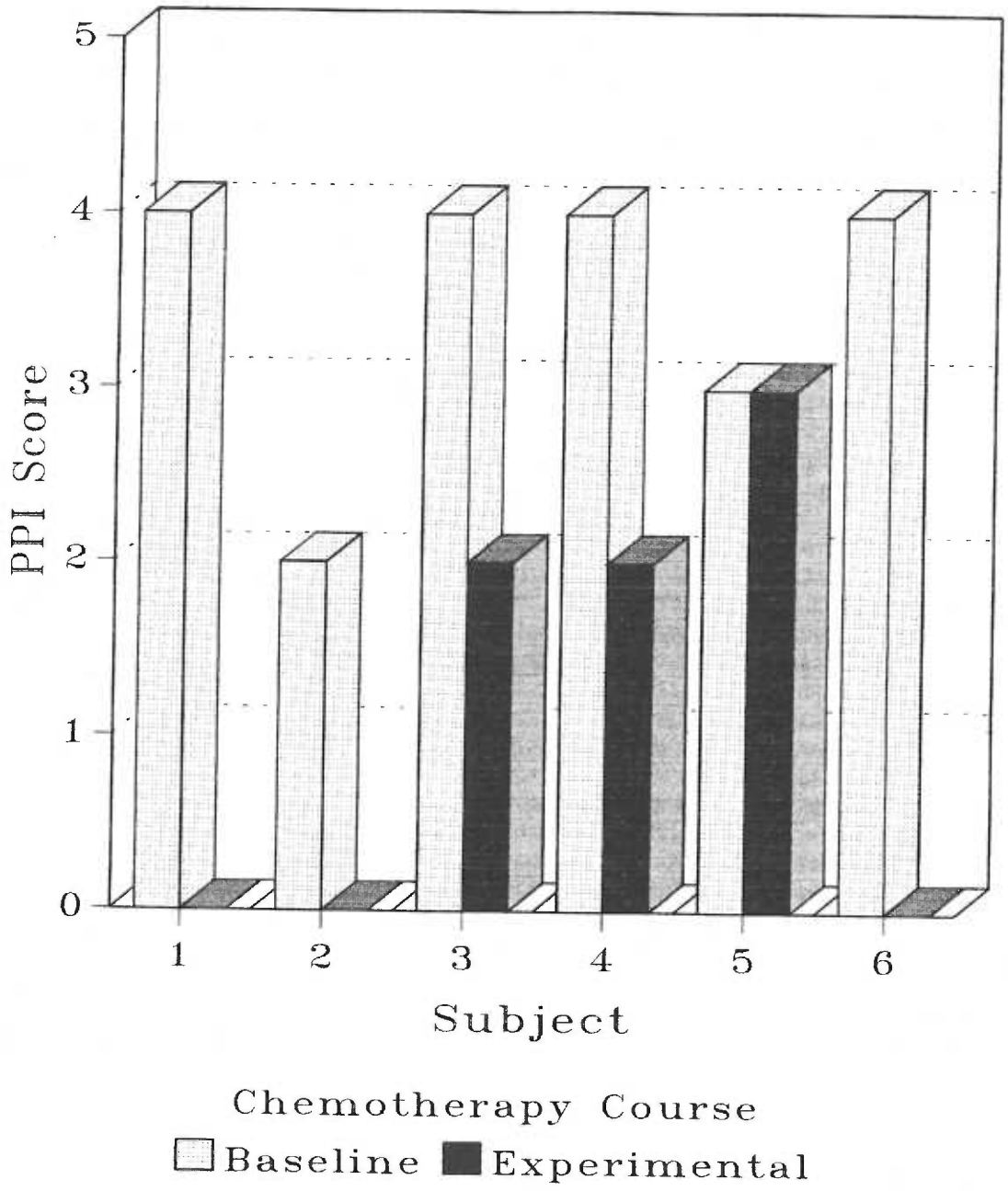

Figure 10. Comparison of worst PPI Scale scores during baseline and experimental courses of chemotherapy in the six study subjects.

Tolerance of Oral Cryotherapy

Subjects were asked to use the PPI Scale to rate pain associated with oral cryotherapy prior to, during, and immediately following each oral cryotherapy treatment. The scores for subjects 1, 2, and 3 are shown in Figure 11 and Figure 12 displays scores for subjects 4, 5, and 6. All subjects reported no oral pain prior to initiating oral cooling. Ratings after 5 to 9 minutes of oral cryotherapy ranged from 0 (no pain) to 2 (discomforting) with a median of 1 (mild). Post-cryotherapy ratings ranged from 0 to 1 with a median of 0.5. Thus, oral cryotherapy was well tolerated. Side effects were limited to mild nausea in three subjects, complaints of feeling "cold" in three subjects, and a "bad taste" from the oral ice bags or melting ice in two subjects. Since nausea and taste changes are commonly associated with 5-FU therapy, these side effects may be partially or entirely secondary to chemotherapy. None of the subjects reported oral pain persisting following cryotherapy, headache, dental complications, popsicle panniculitis, aphthous ulcers, or lip ulceration.

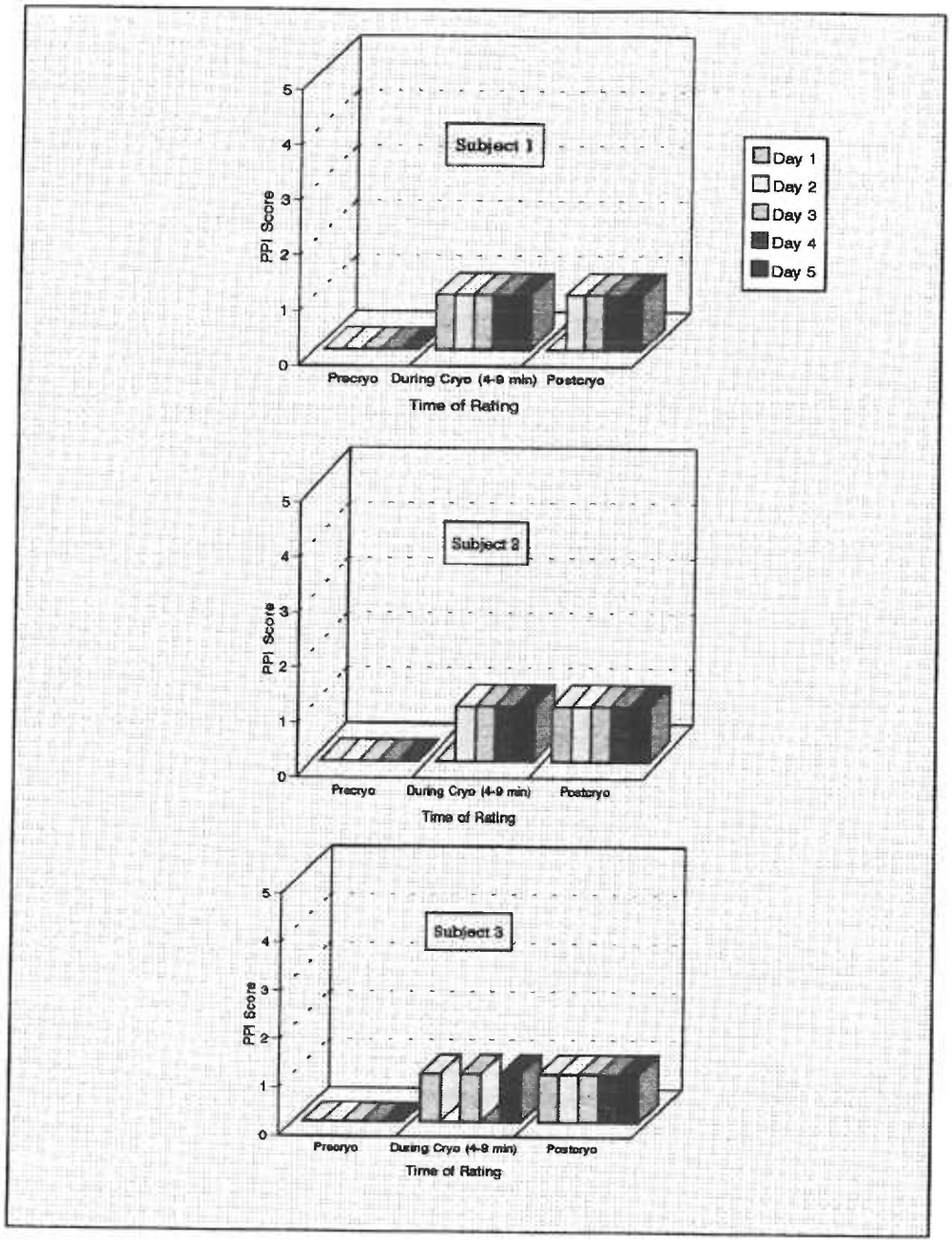

Figure 11. PPI Scale scores before, during, and immediately following oral cryotherapy in Subjects 1, 2, and 3. PPI Scale rating: 0 = no pain; 1 = mild; 2 = discomforting; 3 = distressing; 4 = horrible; 5 = excruciating.

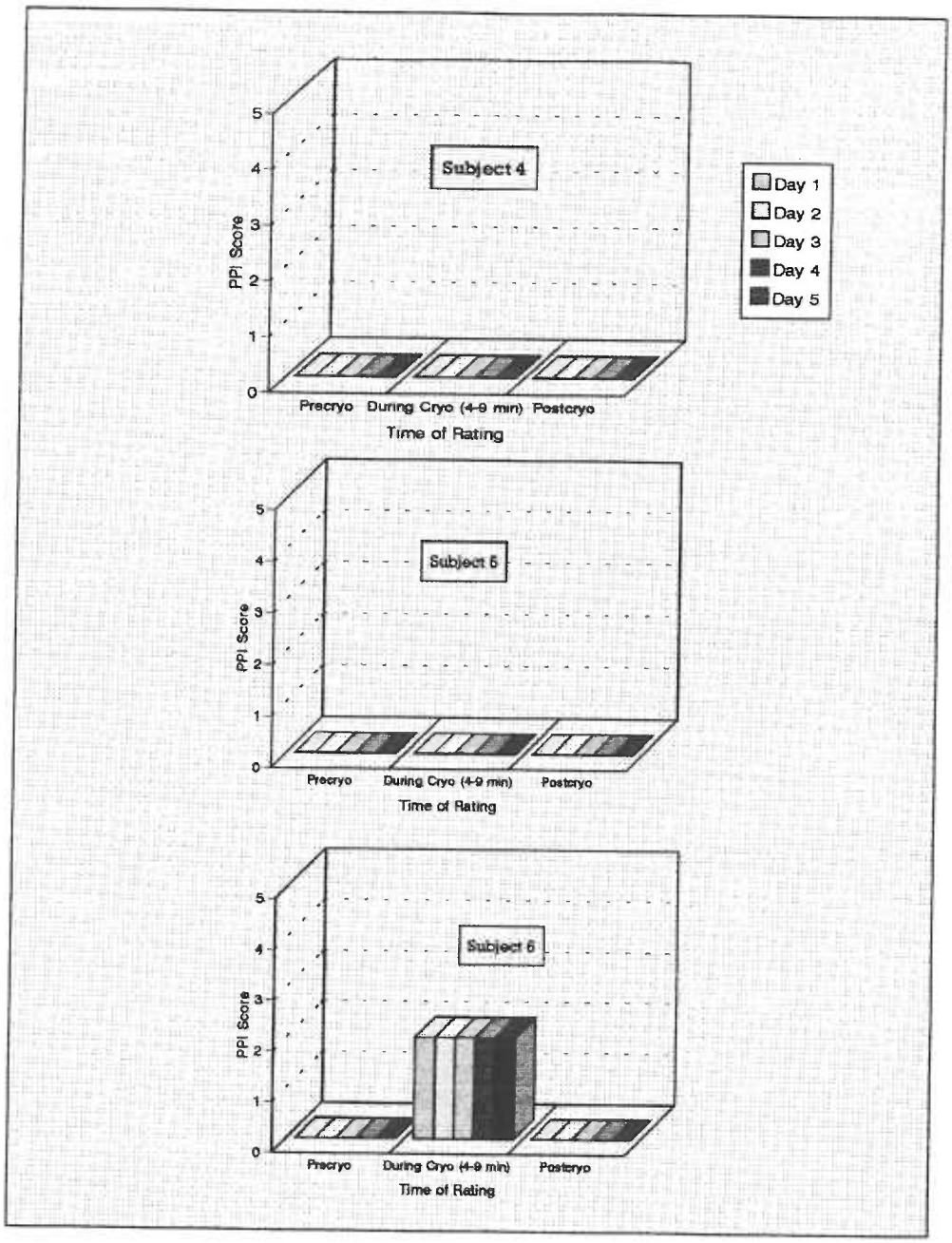

Figure 12. PPI Scale scores before, during, and immediately following oral cryotherapy in Subjects 4, 5, and 6. PPI Scale rating: 0 = no pain; 1 = mild; 2 = discomforting; 3 = distressing; 4 = horrible; 5 = excruciating.

CHAPTER V

DISCUSSION

Efficacy of Oral Cryotherapy

Combination chemotherapy with 5-FU/LV is the most promising treatment to date for advanced colon cancer. From the patient's standpoint, however, 5-FU/LV may be a double-edged sword. The hope for extended survival is often tempered by the suffering caused by chemotherapy induced oral mucositis. This study tested a simple procedure, oral cooling with an ice bag, designed to reduce the incidence and severity of oral mucositis associated with 5-FU/LV therapy. Five of the six subjects demonstrated a clinically significant benefit with the use of oral cryotherapy. Oral ulceration was absent in four of the six subjects when oral cooling was used, while all subjects had oral ulcers during the baseline course when oral cooling was not used. In the subjects who had oral ulcers during the experimental course, one demonstrated only a few small, painless ulcers and the second "thought she felt an ulcer" but was unavailable for objective assessment.

Oral pain markedly decreased in 5 subjects during the experimental course. Three of the six subjects reported no oral pain during the experimental course, while all six subjects reported oral pain related to mucositis during the baseline course. Two subjects had lower pain scores when oral cooling was used. Even the single subject who lacked measurable improvement in oral mucositis and pain scores asserted that oral cryotherapy was helpful.

Oral Cryotherapy as a Nursing Intervention

Oral cryotherapy administered with an oral ice bag was a simple and inexpensive treatment. Administration was uncomplicated, and subjects were able to perform the procedure with little assistance from the investigator or nursing staff. Preparation of 8 to 10 oral ice bags necessary for one daily treatment could be accomplished in 10 minutes. The average cost of materials for one daily treatment was approximately 20 cents.

A common complaint associated with oral cryotherapy was the inconvenience of remaining at the clinic for 25 minutes following 5-FU injection. Three subjects would have preferred to leave the clinic immediately following chemotherapy, while the remaining three stated they did not feel inconvenienced. However, one of the latter group needed to remain at the clinic to receive additional intravenous hydration which required one to two hours.

Extra time is required to prepare oral cooling devices. Providing the patient with a cup of crushed ice for oral cryotherapy, as suggested by Mahood et al. (1991), is certainly more expeditious. In this study, three subjects felt that crushed ice alone would be too cold for them to tolerate. The insulation provided by the polyurethane bag was considered helpful by these subjects, allowing them to undergo oral cooling for the prescribed time period. The method employed in this study was well tolerated, even in subjects with extensive dental work or severe periodontal disease. In this study, the use of oral ice bags was beneficial in subjects who had experienced moderate (CTC grade 2) or severe (CTC grades 3 and 4) mucositis following their

Since oral mucositis is not a universally associated with 5-FU/LV, it is not appropriate to expose all patients to the discomfort and inconvenience of oral cryotherapy. It is questionable whether oral cryotherapy should be used during the first course of chemotherapy, even though this has been recommended in two national clinical trials (Fisher, 1991; Haller, McDonald, Mayer, & Zalcberg, 1988). Approximately 50% to 60% of patients receiving 5-FU/LV are likely to develop oral mucositis, and it is this subset that may benefit from oral cryotherapy.

Measurement of Oral Mucositis

Use of the Common Toxicity Criteria Stomatitis Scale

The CTC Stomatitis Scale combines objective observations such as oral redness, ulceration, and ability to eat with subjective reports of oral pain. Oral intake is the major factor which differentiates CTC grades 2, 3, and 4. The CTC Stomatitis Scale lacks sensitivity regarding the degree of oral mucositis present. For example, a patient with one painful ulcer will have an identical rating to a patient with widespread ulceration, as long as both are able to eat. Many patients with painful mucositis use topical viscous xylocaine to temporarily numb painful oral tissues, thereby allowing oral intake. During the baseline course, two subjects in the study sample stated they could eat only after application of viscous xylocaine. Use of viscous xylocaine may have reduced the CTC rating from 3 (painful erythema, edema, or ulcers and cannot eat) to 2 (painful erythema, edema, or ulcers but can eat). Other variables such as motivation and social support can influence oral intake during chemotherapy (Szeluga, Groenwald, & Sullivan, 1990). Three subjects in the study sample explained they

forced food down because they were aware of the importance of adequate nutritional intake during chemotherapy.

The CTC Stomatitis Scale was a practical instrument in this study due to its common use in clinical oncology practice. Physicians performing the baseline ratings had extensive experience with the CTC. Moreover, the descriptive categories were easy to rate and mutually exclusive. The information needed to assign a score could be quickly obtained when examining a patient. Finally, CTC Stomatitis Scale scores provided a common language for rating oral mucositis that is used by research organizations and clinicians throughout the country.

Use of the Oral Assessment Guide

The OAG is designed to rate different parts of the oropharyngeal cavity by observation combined with the patient's voice character and ability to swallow. Since oral mucositis is frequently accompanied by pharyngeal pain and ulceration, the OAG attempts to encompass these variables in addition to assessment of oral tissues. The total OAG score reflects the summed scores of the eight categories. As oral mucositis increases in severity, the OAG score increases. One disadvantage to using a summed score is that severe disruption in one area, for example a blistered or cracked tongue (OAG of 10) would not appear to be as significant as minor changes in several categories, such as mild pain on swallowing, dry lips, localized plaque on teeth, and slightly reddened mucous membranes (OAG = 12). In this case, the higher tongue rating is somewhat obscured in the total summed score while the presence of mild changes in several areas appear to reflect a higher degree of oral mucositis.

changes in several areas appear to reflect a higher degree of oral mucositis.

Elevation of the OAG score is not necessarily specific to oral mucositis. Pre-existing periodontal disease or poor dental hygiene lead to a higher score on the gingival and tooth ratings, respectively. The lip category may not be related to oral mucositis. A rating of 2 is given to dry or cracked lips. Obviously, other clinical conditions such as chapped lips or cheilitis would be rated as 2 on the OAG. In addition, the OAG score does not always correlate with the clinical severity of oral mucositis. For example, the mucous membrane category gives reddened or coated mucous membranes a score of 2, whereas ulcerations are scored as 3. Yet, in clinical practice, one or two small ulcers may reflect mild mucositis, while generalized redness or coated mucous membranes can be associated with severe oral pain, infection, and disruption in oral intake. Ratings for the lips may not accurately represent the actual severity of oral mucositis. Ulcerated lips are rated as 3 on the OAG. A patient with a small herpetic ulcer would be rated as 3; however, the presence of painful cracked lips which limit oral intake would receive the lower OAG rating of 2.

The eight category OAG is not based entirely on objective assessment, but includes subjective pain ratings in the categories of swallow and voice as well. Ratings of the remaining six categories, on the other hand, are strictly based on observation and pain is not included in scores of the lips, tongue, mucous membranes, gingiva, and teeth (the saliva category would not apply). Inclusion of pain in the swallow and voice categories provides an indirect measure of mucosal disruption in an

anatomic area which is not easily accessible by oral assessment with a tongue blade and mirror. In addition to rating oral mucositis, the OAG attempts to encompass functional impairment in swallowing and speech which can be affected by severe chemotherapy induced pharyngitis.

The OAG has been used in nursing studies to describe the degree of disruption present in oral condition and function in association with cancer chemotherapy toxicity. This scale gives a rating for different parts of the oral cavity, however, it may not allow fine discrimination between the clinical assessment of mild and moderate mucositis. One advantage of the OAG over other oral assessment scales is the pictorial guide which includes a photograph depicting an example of each rating for all 8 categories. The OAG provides specific information on all parts of the oral cavity and the pharynx, whereas the CTC Stomatitis Scale focuses primarily on the oral cavity. Since pharyngitis often accompanies oral mucositis, the inclusion of this category in the OAG contributes to evaluation of the entire spectrum of oral mucositis.

Use of the Present Pain Intensity Scale

Subjects experienced little difficulty in using the PPI Scale to rate their oral pain. However, several subjects reported their score fell between two ratings. For example, subjects stated, "The pain is not really discomforting, I guess it's mild." "It was between a 2 and a 3." Categorizing pain based on a list of adjectives, such as those included in the PPI Scale, requires the patient to make a choice which may not accurately describe their pain experience (McGuire, 1988). Moreover, retrospective ratings obtained for the baseline course may have been different if the subject was

asked to mark the PPI Scale while they were actually experiencing the most severe oral pain during that course. Despite these disadvantages, the PPI Scale could be scored quickly and easily, even when a subject had an oral ice bag in place. Thus, the PPI Scale provided a simple method for each patient to report perceived pain related to oral mucositis and the oral cryotherapy treatment.

In this study, the PPI Scale contributed valuable information regarding the patient's perception of oral pain. Unfortunately, PPI Scale scores range from 0 to 5 and may not detect subtle changes in perceived pain. A scale with a range of 1 to 10 may be more sensitive and offers more choices for the subject (McGuire, 1988). However, the subjects in this study used the verbal descriptors rather than numbers to rate their oral pain intensity. The PPI Scale was a useful adjunct to the CTC Stomatitis Scale and the OAG for measuring oral mucositis. The combination of these three instruments provided a comprehensive picture of the subject's oral condition, including oral mucosal and dental variables, pharyngeal variables, ability to eat, and pain related to oral mucositis.

Recommendations for Future Research

Findings from this study support the use of oral cryotherapy to reduce or prevent oral mucositis in patients receiving 5-FU/LV for the treatment of colon cancer and suggest a practical and inexpensive method for carrying it out. Control or prevention of oral mucositis can facilitate administration of full doses of 5-FU/LV, thus maximizing therapeutic benefit of chemotherapy. The small sample size of the study precluded application of inferential statistics to detect a difference in oral mucositis

sample would provide data which can be statistically analyzed to evaluate the benefit of oral cooling with ice bags in patients who have experienced oral mucositis associated with 5-FU/LV therapy.

Questions relating to the optimal administration of oral cryotherapy remain. One group of investigators is testing different approaches for the timing (duration of cooling prior and after 5-FU injection) of oral cryotherapy with ice chips (M. Rothenberg, personal communication, January 27, 1993). Comparison of tolerance and efficacy of oral ice bags, as used in this study, versus oral cryotherapy with ice chips would help elucidate the optimal method for cryotherapy delivery. Laboratory studies of buccal mucosal blood flow during oral cooling, analogous to laser-Doppler flow studies of scalp hypothermia performed by Hillen et al., (1990), would add to the theoretical basis for oral cryotherapy.

Testing of oral cryotherapy is needed to determine its efficacy in patients receiving 5-FU or 5-FU/LV for treatment of malignancies other than colon cancer. Oral cryotherapy may be useful in other malignancies such as rectal and anal cancer, where 5-FU is an integral part of therapy. In addition, oral cooling should be evaluated when 5-FU/LV is combined with other treatments such as radiation therapy or biologic therapy.

Patients with colon cancer represent a small subset of the estimated 400,000 patients who develop chemotherapy induced oral mucositis annually. Severe mucosal toxicity also is commonly associated with treatment of head and neck cancer, lymphatic cancer, hematopoietic malignancies, and bone marrow transplantation.

However, agents utilized in treatment of these malignancies do not possess the short half life of 5-FU and temporary oral cooling, as used in this study, would probably have little or no benefit. Additional study is needed to test novel interventions designed to reduce oral mucositis. Interventions that interfere with mucosal cell uptake of chemotherapy may prove beneficial in patients receiving drugs with long half-lives, such as doxorubicin.

Valid and reliable oral assessment tools which encompass all manifestations of oral mucositis will enhance systematic measurement of this toxicity. Validity and reliability data are available for tools such as Beck's Oral Exam Guide and the OAG. However, further investigation is needed to evaluate the use of these tools in the clinical setting (Beck, 1992; Eilers, et al., 1988). One of the primary considerations in selecting an oral assessment tool is choosing an instrument which provides a quantitative rating of mucositis severity while contributing qualitative information such patterns of ulceration and inflammation. Unfortunately, an instrument which provides extremely detailed information could be useful in the research setting but would be too complex and time consuming for general use in the clinical setting (S. L. Beck, personal communication, April 24, 1993). The OAG is probably suitable to both areas since it provides specific numerical data necessary for scientific investigation but is simple enough to use in the outpatient clinical setting.

This study demonstrated that oral cryotherapy reduced or prevented oral mucositis in 5 of 6 subjects undergoing 5-FU/LV therapy. Half of the subjects were able to continue with full doses of chemotherapy. In patients receiving adjuvant therapy, full

continue with full doses of chemotherapy. In patients receiving adjuvant therapy, full doses may translate into a greater chance of cure. Patients with advanced disease may receive more effective palliative therapy, thus enjoying extended months of quality survival. Administration of oral cryotherapy is a simple procedure which can improve tolerance of 5-FU/LV therapy by reducing one of the most common toxicities, oral mucositis. Oral cryotherapy is an effective new weapon in the nurse's armamentarium of supportive care strategies in cancer. Controlling toxic effects of effective antineoplastic therapies will assist in maximizing quantity as well as quality of life in patients living with cancer.

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APPENDIX A
DATA COLLECTION PROTOCOL

Identification and Enrollment

1. A letter was sent to all oncologists practicing in the clinic which described the study, its purpose, procedures, and the name and telephone number of the investigator conducting the study (see Appendix I).
2. Review out chemotherapy records and interview oncologists to identify all patients currently on a 5-day schedule of 5-FU/LV who have experienced oral mucositis.
3. Review patient records to determine eligibility.
   a. At least 18 years of age.
   b. Receiving 5-FU/LV chemotherapy for either adjuvant or palliative treatment of colon cancer.
   c. Minimum 5-FU dose of 370 mg/m^2 administered with a minimum leucovorin dose of 20 mg/m^2 on a 5-day schedule that is repeated every 28 days. Patients who have had a temporary dose reduction below this level are eligible if they continue to demonstrate oral mucositis despite a dose reduction.
   d. Evidence of oral mucositis during a previous course of chemotherapy.
   e. No concurrent radiation therapy
   f. No brain metastases.
4. Notify oncologist of each eligible and obtain his/her approval to invite the patient to participate. Determine if oncologist wishes to introduce study or if he would like investigator to do so.
   a. If oncologist wishes to introduce study, provide Summary Sheet (see Appendix K) explaining study prior to visit.
   b. If the oncologist does not wish to introduce the study prepare to do so at the earliest time convenient to the patient. The most appropriate time will probably be at the next scheduled clinic visit. However, if the patient is not scheduled until day 1 of the next treatment course, it may be necessary for the investigator to contact the patient by telephone to set up an appointment to discuss the study prior to the next course. It is feasible to review study procedures over the telephone then mail the consent form to the patient. However, the patient must sign the consent form at the clinic using the procedure listed below (#5-6).
5. The following procedure will be used for introducing the study and obtaining informed consent: Check with the oncologist prior to the patient's visit to determine when it will be convenient to discuss the study (the time may be concurrent with the oncologist's visit or immediately following). When meeting the patient, introduce yourself, explain your affiliation with the study, and purpose of your visit. Tell him/her the title of the study, name of investigator and that the study is approved by the Oregon Health Sciences University and his/her oncologist. Then explain the study. For example, "Hello, I am

_____ a graduate student at the Oregon Health Sciences University School of Nursing. I am conducting a study of mouth soreness which is experienced by patients who are receiving 5-FU and leucovorin chemotherapy for colon cancer. I understand you have had this side effect from your chemotherapy. I am testing a treatment that uses a plastic bag filled with crushed ice to cool the mouth and possibly reduce the mouth soreness that people often get after their chemotherapy. Similar treatments using crushed ice alone have been tested and have shown some benefit. The treatment in this study may be more comfortable and possibly helpful in reducing mouth soreness caused by the chemotherapy drugs you are receiving. The treatment is called oral cryotherapy and it is given here in the clinic when you receive your chemotherapy. When you start a new chemotherapy course, cryotherapy would begin 10 minutes before the chemotherapy is given and continue for 25 minutes after the injection. I will give you an ice bag designed to fit inside your mouth. We will leave the bag in your mouth until it thaws, then replace it with a new one. We will continue doing this during the 5-FU injection and for 25 minutes afterward. This consent form explains how we do the oral cooling treatment."

6. Give the patient a consent form and tell him/her you will allow time for reading it and will answer any questions regarding the contents of the form. Also ask, "If you would like any help or you would like me to read the form to you, I would be happy to do so." This will enable patients with poor eyesight or poor literacy skills to complete the informed consent process. Once the form has been read, all questions have been answered to the patient's satisfaction, and the patient is interested in participating in the study, ask the him/her to sign the signature page. The investigator will sign and date the consent form below the patient's (subject's) signature.

Background Data Collection

1. Assign a sequential study ID number to each eligible subject.
2. Record the subject's age at last birthday (on face sheet of chart).
3. Record the date and type of surgical procedure in which diagnosis was determined (on operative report or in oncology consultation).
4. Record the treatment intent of chemotherapy as curative or palliative (in oncology consultation).
5. Record the amount of weight loss the subject experienced from date of diagnosis (if available) or treatment start date (in oncology consultation, progress notes, or calculate based on first weight recorded after diagnosis and present weight).
6. Record number of 5-FU/LV treatment courses completed (on physician's flowsheet or chemotherapy flowsheet).
7. Record the dose of 5-FU/m^2 administered during the previous course.
8. Record the dose of LV/m^2 administered during the previous course.
9. Note worst Common Toxicity Criteria mucositis grade and date documented at the

previous chemotherapy course (usually day 10 to 12). This will be baseline assessment 1.

10. Review all progress notes and physical exams since chemotherapy began to determine the most severe mucositis grade (Common Toxicity Criteria) documented by the oncologist. If this was not the most recent course, record the course #, date course started, date mucositis documented, dose of 5-FU/m^2 administered and the Common Toxicity Criteria mucositis grade during that course.
11. Note if the subject has had a previous diagnosis of cancer (in oncology consultation). Document the type of cancer.
12. If the subject has a history of cancer, indicate if chemotherapy, radiation therapy, and/or biologics have been given in the past to treat this cancer.
13. Record the clinic site where the subject is being treated.
14. Record OAG and Oral Pain Score if obtained previously.

Interview

1. Record background information obtained from subject interview. Begin by determining smoking status. Record the subject's status as a smoker or non-smoker. A subject will be considered a smoker if at least 1 cigarette has been smoked in the past month. If the subject smokes, ask how many packs per day, on the average, are smoked and how many years he/she has smoked. Multiply the packs per day times the number of years smoked to determine the pack/year smoking history of the subject. Record this value.
2. Ask the subject if he/she wears either partial or full dentures. Mark the appropriate box.
3. Ask the subject if he/she has gum disease or is receiving treatment for a dental condition. If yes, indicate "yes" for periodontal disease."
4. Ask the subject if mouth soreness was present during the previous chemotherapy course. If the answer is yes, ask if soreness interfered with eating. If yes, ask if the subject was able to eat solid foods. If no, ask if intake was limited to liquids. Mark the appropriate box.
5. Ask the subject if any area of the mouth is particularly sensitive to hot or cold at this time. Record comments on line provided on form.
6. Obtain a retrospective rating of oral pain during the previous chemotherapy course by asking the subject to complete the Present Pain Intensity Scale. Tell the subject that "this question rates any pain you may have in your mouth or teeth. I will be asking you to mark this scale several times during the study. Now I would like you to think about how your mouth felt when you were having mouth soreness after your last chemotherapy treatment." Read the instructions at the top of the page to the subject. Then provide the subject with a pencil and ask him/her to "circle the number next to the word that best describes the worst amount of mouth pain you felt at that time."

Schedule Initiation of the Oral Cryotherapy Treatment

1. Set up appointment for initiation of cryotherapy treatment to coincide with day 1 of chemotherapy course.
   a. Provide the subject with a clinic appointment card noting that the oral cryotherapy treatment will begin with the next chemotherapy cycle.
   b. Notify chemotherapy nurses that the subject will be participating in oral cryotherapy protocol. Clarify with nurses that investigator or an assistant will administer the oral cryotherapy while chemotherapy nurses will administer the 5-FU/LV according to physician's orders and usual nursing procedures.
   c. Notify oncologist via form letter (see Appendix J) that the subject will be initiating oral cryotherapy protocol with the next treatment course. Complete the letter by including the dates of cryotherapy treatment and the dates of planned follow-up assessments.

Assemble Equipment and Supplies

1. Forms and scales
   Oral Assessment Guide (OAG)
   Common Toxicity Criteria (CTC) Stomatitis Scale
   Present Pain Intensity (PPI) Scale (3 copies)
   Oral Assessment article (Schweiger, Schweiger, & Lang, 1980).
   Forms booklet containing:
      Oral assessment form
      Oral cryotherapy data form
      Oral cryotherapy procedure form

2. Oral assessment supplies
   Tongue blade
   Tissues
   1- 2 x 2 inch gauze sponge
   Penlight or flashlight
   Disposable dental mirror
   1 pr. latex procedure gloves

3. Oral cryotherapy supplies (for each procedure).
   9 oral cooling devices (leave in ice chest or freezer until needed)
   Disposable paper barrier or towel
   2 small plastic containers
   Tissues
   Emesis basin
   2 pairs latex procedure gloves
   Stopwatch

Oral Assessment - Day 1

1. Prior to initiation of chemotherapy course (most likely on a Monday) the baseline # 2 oral assessment will be performed. Assessment will be done immediately following oncologist's exam.
2. Bring forms booklet and supplies for oral assessment to examination room.
3. Explain to the subject that an inspection of the mouth, called an oral exam, will be done. For example, state that, "I will be looking at your teeth, tongue, gums, and inside your cheeks. You probably won't have any pain during the exam. If you do, please let me know. I will be writing down some of the things I see after the exam."
4. Prior to initiation of the exam, ask the subject to complete the PPI Scale. Remind the subject that "this is the scale which rates any discomfort you may have in your mouth or teeth. I will be asking you to mark this scale three times today; now, during the oral cryotherapy, and just after the oral cryotherapy is finished." Read the instructions at the top of the page to the subject. Then provide the subject with a pencil and ask him/her to "circle the number next to the word that best describes how your mouth feels right now." Also ask the subject, "Tell me, does anything bother you about your mouth right now?" If so, ask, "Please explain what bothers you." Record comments on the oral assessment form.
4. Prepare to begin the oral exam. Follow the oral assessment technique adapted from Schweiger, Schweiger, and Lang (1980). Refer to the pictures illustrating technique if necessary prior to the exam.
   a. Wash hands and don gloves prior to beginning the exam.
   b. Lips: Instruct subject to open mouth to semifullness; visually inspect lips from commissure to commissure.
   c. Anterior buccal mucosa: Instruct subject to relax mouth; draw lip away from teeth and inspect visually from the vermillion border to the inner mucosal surface.
   d. Anterior gingiva and teeth: Instruct subject to relax mouth and occlude teeth; pull lips back to visually inspect mucosal surface and teeth; use of a tongue blade facilitates retraction from more thorough examination.

   e. Buccal mucosa, wall of cheeks, posterior teeth: Instruct subject to open mouth to semifullness; use a penlight, tongue blade, and gloved hand to inspect by palpation and visualization. To palpate, a gloved finger is run along the wall of the buccal cavity while the thumb is placed outside the cheek opposing the finger. Visually inspect teeth while examining buccal mucosa.
   f. Tongue: Instruct subject to stick out tongue; inspect visually and by palpation. Grasp the tongue with gauze sponge and pull it forward to inspect visually and by palpation the dorsum, lateral borders, and base. Perform gently.

g. Lingual gingiva, floor of mouth: Instruct subject to place the tip of the tongue against roof of mouth to visualize the ventral surface of the tongue, the floor of the mouth and the frenulum attaching the tongue to the mouth. Use dental mirror to inspect lower lingual gingiva.
h. Palate, upper posterior gingiva, uvula: Instruct subject to open mouth wide and depress middle of tongue with tongue blade. Use dental mirror to visualize upper lingual gingiva.
i. Swallow: Ask the subject to swallow a small amount of water. Observe for nonverbal signs of discomfort and ask the subject if any discomfort is felt with swallowing.
j. Tell the subject you are finished with the examination and he/she can now proceed to the chemotherapy area where you will begin the cryotherapy treatment. Remove gloves and discard them, wash hands, and record findings immediately on the Oral Assessment Guide scale and mark the corresponding Common Toxicity Criteria mucositis grade.

Oral Cryotherapy Procedure.

1. Check to see the subject is comfortably seated in the chemotherapy administration area.
2. Assemble oral cryotherapy supplies.
   a. Remove container of oral ice bags from the freezer and place on table in the chemotherapy area.
   b. Place forms booklet, oral pain scale, pen, and clipboard in chemotherapy administration area.

3. Begin the oral cryotherapy treatment
   a. If the subject wears full or partial dentures, ask him/her to remove them and place them in one of the plastic cups prior to beginning the procedure.
   b. Minute 0: Have the subject place an oral ice bag in his/her mouth. The bag should fit behind the front teeth and extend past the molars laterally to the buccal mucosa. The subject may alter the position of the bag for comfort by grasping the tied end. When the bag has been adjusted satisfactorily for comfort, ask the subject to bite down three times on the bag.
   c. Minute 1: Ask the subject if water is starting to leak slowly from the ice bag. If not, have him/her bite down on to release more water.
   d. Instruct the subject to swish the ice water leaking from the ice bag thoroughly around oral cavity then swallow as it accumulates.
   e. Minute 4: Ask the subject to mark the PPI Scale to "describe any pain you feel in your mouth or teeth right now."
   f. Minute 5: Check the oral ice bag to make sure some crushed ice remains. When frozen material no longer remains, immediately replace the ice bag with another frozen one. Continue checking the device every 3 to 5 minutes and replace as necessary.

g. Notify chemotherapy nurse when minute 10 will be reached so 5-FU injection can be given precisely at this time.
h. Between minute 5 and minute 8: Leucovorin will be injected over 1 minute by chemotherapy nurse. (NOTE: subjects enrolled on the NSABP C-05 protocol will receive leucovorin via 30 minute infusion one hour prior to 5-FU. In this case, oral cryotherapy will still begin 10 minutes prior to 5-FU injection).
i. Minute 10: 5-FU will be injected by chemotherapy nurse. Record time.
j. Continue checking the oral cooling device every 3 to 5 minutes to determine if frozen material remains. If greater than 30 seconds elapses when no cooling device is present in mouth, note the amount of time this occurred in seconds and record in the comments section of oral cryotherapy form. Continue the procedure until exactly 25 minutes have elapsed since completion of 5-FU injection. Remove oral ice bag with gloved hand or have subject remove it and place in plastic container. Record time. Offer tissues to subject.
k. Place disposable materials in garbage receptacle. Wash hands.
l. Ask the subject to mark the PPI Scale again to "describe any pain you feel in your mouth or teeth right now."
m. Offer subject a cold liquid such as water or juice.
n. Ask the subject to describe any discomfort experienced by the procedure and record comments on Oral Cryotherapy form.
o. Record any deviations from the oral cryotherapy protocol not previously noted.
p. Record any other pertinent comments or suggestions made by the subject.

4. Repeat the above oral cryotherapy procedure on days 2 through 5.

Oral Assessment - Day 5

1. When the subject arrives at the clinic for day 5 chemotherapy, check with the medical assistant to determine which exam room would be available to perform the oral exam.
2. Greet the subject and ask him/her to sit down in the exam room so the oral exam can be done before proceeding to the chemotherapy area.
3. Ask the subject how he/she is feeling and offer to answer any questions regarding the oral cryotherapy treatment.
4. Prior to initiation of the exam, ask the subject to complete the Oral Pain Rating Scale. Ask the subject if he/she would like the instructions read again. If so read them, then provide the subject with a pencil and ask him/her to "circle the number next to the word that best describes the amount of mouth pain you feel right now." Also ask the subject, "Tell me, does anything bother you about your mouth right now?" If so, ask, "Please explain what bothers you." Record comments on the oral assessment form.
5. Conduct the oral exam as described in 4 a-j of Baseline Assessment #2. Then

proceed with the oral cryotherapy procedure. Rate findings of oral exam with CTC and OAG.

6. After oral cryotherapy on day 5, the subject will have an appointment made for the next clinic visit. This appointment will be on day 10, day 15, or day 29 (day 1 of next course). The procedure for arranging oral exams during these days will be as follows:
   a. If subject has a clinic appointment on day 10 and 29: note on appointment card that an oral exam will be done at the clinic on days 10 and 29. Provide an appointment card for day 15 indicating that the investigator will come to the subject's home to perform the oral exam on day 15. Arrange a satisfactory time with the subject for the home visit.
   b. If subject has clinic appointment on day 29 only: note on appointment card that an oral exam will be done at the clinic on day 29 (day 1 of next course). Provide an appointment card for days 10 and 15 indicating that the investigator will come to the subject's home to perform the oral exam on those dates. Arrange a satisfactory time with the subject for the home visits.

Oral Assessment - Day 10 to 12

1. Since the subject will not be receiving chemotherapy on day 10, this exam may be performed in his/her home. An appointment will be scheduled prior to day 10.

2. If the subject is scheduled to come into the clinic, the oral exam will be conducted immediately following the oncologist's visit. The investigator will accompany the oncologist during his/her exam.
3. Prior to initiation of the exam, ask the subject to complete the PPI Scale. Ask if he/she would like the instructions read again. If so read them, then provide the subject with a pencil and ask him/her to "circle the number next to the word that best describes the amount of mouth pain you feel right now." Also ask the subject, "Tell me, does anything bother you about your mouth right now?" If so, ask, "Please explain what bothers you." Record comments on the oral assessment form.
4. Conduct the oral exam as described in 4a-j of Baseline Assessment #2. Extreme care will be necessary when palpating oral structures and using instruments as painful mucositis may be present. Rate findings of oral exam with CTC and OAG.

Oral Assessment - Day 15

1. Since the subject will not be receiving chemotherapy on day 15, this exam may be performed in the subject's home. An appointment will be scheduled prior to day 10.
2. If the subject is scheduled to come into the clinic, the oral exam will be conducted immediately following the oncologist's visit. The investigator will

accompany the oncologist during his/her exam.

3. Ask the subject to complete the PPI Scale. Also ask the subject, "Tell me, does anything bother you about your mouth right now?" If so, ask, "Please explain what bothers you." Record comments on the oral assessment form.
4. Conduct the oral exam as described in 4 a-j. Extreme care will be necessary when palpating oral structures and using instruments as painful mucositis may be present. Rate findings of the oral exam with the CTC and OAG.
5. Remind the subject that the investigator will perform the final oral exam when he/she returns to the clinic on day 29 and that any questions about the cryotherapy treatment will be answered at that time.

Assessments, Study Completion, Day 29

1. The investigator will be present at the physician's office when the subject returns for an examination prior to the next chemotherapy course.
   a. Call the physician's office the week prior to the scheduled appointment to confirm the date and time of the subject's appointment.
   b. Notify the physician that you plan to be present during the visit.
   c. Arrive 10 minutes prior to the appointment to accommodate any unplanned scheduling changes and assure it will be possible to meet with the subject during the scheduled physician examination.
2. During the physician visit, write down any comments the subject makes regarding mucositis, oral discomfort, or subjective experiences with the oral cryotherapy procedure.
3. Ask the subject to complete the PPI Scale. Also ask the subject, "Tell me, does anything bother you about your mouth right now?" If so, ask, "Please explain what bothers you." Record comments on the oral assessment form.
4. Inform the subject that the oral cryotherapy study has been completed. If the subject wishes to continue using oral cryotherapy for the prevention of mucositis, inform the physician and the nurses responsible for administering chemotherapy. Check to be certain the chemotherapy nurses have a copy of the cryotherapy procedure and necessary supplies to continue the treatments. Clarify with the subject and chemotherapy nurses that conduct of the treatment will be assumed by clinic staff.

ORAL CRYOTHERAPY STUDY CALENDAR

5-FU/Leucovorin Chemotherapy

		Baseline	Oral Cryotherapy							Post Cryotherapy Assessment
	VARIABLES	Day -23----> -1	Day 1	Day 2	Day 3	Day 4	Day 5	Day 10-12	Day 15	Day 29
INDEPENDENT	Oral Cryotherapy		X	X	X	X	X			
DEPENDENT	CTC Stomatitis Scale	X@	X				X	X	X	X
	Oral Assessmt. Guide	X*	X				X	X	X	X
	Oral Pain (PPI Scale)	X**	X	X	X	X	X	X	X	X
BACKGROUND	Personal Variables	X								
	Treatment Variables	X	X							

Comments:

@ MD rating if investigator rating not available.

* Investigator rating if available.

** Retropective patient report.

APPENDIX B

Stomatitis Scale of the Common Toxicity Criteria

GRADE				
0	1	2	3	4
None	Painless ulcers, erythema, or mild soreness	Painful erythema edema, or ulcers, but can eat	Painful erythema edema or ulcers, and cannot eat	Requires parenteral or enteral support

Note. From "Guidelines for Reporting Adverse Drug Reactions" by the National Cancer Institute, 1989, U. S. Department of Health and Human Services.

Oral Assessment Guide*

Developed by
the University of Nebraska
Medical Center

Category	Voice	Swallow	Lips	Tongue	Saliva	Mucous membranes	Gingiva	Teeth, Dentures, or denture bearing area
Tools for Assessment	Auditory assessment	Observation	Visual/palpatory	Visual/palpatory	Tongue blade	Visual assessment	Tongue blade and visual assessment	Visual assessment
Methods of Measurement	Converse with patient	Ask patient to swallow To test gag reflex, gently place blade on back of tongue and depress	Observe and feel tissue	Feel and observe appearance of tissue	Insert blade into mouth, touching the center of the tongue and the floor of the mouth	Observe appearance of tissue	Gently press tissue with tip of blade	Observe appearance of teeth or denture bearing area
1 *Numerical and descriptive rating*	 Normal	 Normal swallow	 Smooth and pink and moist	 Pink and moist and papillae present	 Watery	 Pink and moist	 Pink and stippled and firm	 Clean and no debris
2	 Deeper or raspy	 Some pain on swallow	 Dry or cracked	 Coated or loss of papillae with shiny appearance with or without redness	 Thick or ropy	 Reddened or coated (increased whiteness) without ulcerations	 Edematous with or without redness	 Plaque or debris in localized areas (between teeth if present)
3	 Difficulty talking or painful	 Unable to swallow	 Ulcerated or bleeding	 Blistered or cracked	 Absent	 Ulcerations with or without bleeding	 Spontaneous bleeding or bleeding with pressure	 Plaque or debris generalized along gum line or denture bearing area

* J.Ellers, RN, MSN et al 2-84 Rev 5-84, 4-85, 11-85

Photographs courtesy of Simon W. Rosenberg, DMD, Memorial Sloan-Kettering Cancer Center

Special thanks to the personnel of the University of Nebraska Medical Center and to Simon W. Rosenberg, DMD, Memorial Sloan-Kettering Cancer Center

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APPENDIX D

Present Pain Intensity Scale For Oral Pain

EXAMPLE

Please circle the number which best describes the amount of pain you are feeling in your mouth.

0	no pain
1	mild
2	discomforting
3	distressing
4	horrible
5	excruciating

Note. From "The McGill Pain Questionnaire: Major Properties and Scoring Methods, by R. Melzack, 1975, Pain, 1, p. 277-299.

APPENDIX E

Background Data Collection Form

ID # _____ Age _____ Date of diagnosis _____

Height _____ Weight _____ BSA _____

Surgery ☐ Segmental Resection ☐ Hemicolectomy ☐ Biopsy only

Treatmnt ☐ Curative ☐ Palliative

Wt. loss ☐ No ☐ Yes amount: _____

Chemo courses ☐ # Previous courses ☐ 5-FU dose previous course ☐ LV dose previous course

Mucositis ☐ CTC Grade previous course ☐ Most severe CTC grade ☐ Course # of most severe ☐ Date course started ☐ Date documented ☐ 5-FU dose administered

Previous cancer ☐ No ☐ Yes type: _____

Previous cancer tx ☐ No ☐ Yes, chemotherapy ☐ Yes, radiation ☐ Yes, biologics

Concomitant medications: _____

_____

Clinic ☐ Main office ☐ NW office ☐ Other

Smoker ☐ No ☐ Yes ☐ # Pack yrs.

Dentures ☐ No ☐ Partial ☐ Full

Periodontal Disease ☐ No ☐ Yes

Prev. Mouth Soreness ☐ No ☐ Yes ☐ Ate solid food ☐ Liquids only

Temp . sensitivity ☐ No ☐ Yes

Previous OAG score ☐

PPI Score ☐ Retrospective

Comments: _____

Date form completed _____

APPENDIX F

Oral Assessment Record

ID # _____

VARIABLES	SCORES	DATE	COMMENTS
Baseline Assessment #1			
CTC mucositis grade (0-4)			
PPI Scale (if obtained)			
OAG score (if obtained)			
Baseline Assessment #2			
OAG Baseline #2			
CTC Baseline #2			
PPI Scale			
Oral Assessment Day 5			
OAG Score			
CTC Score			
PPI Scale			
Oral Assessment Day 10 to 12			
OAG Score			
CTC Score			
PPI Scale			
Oral Assessment Day 15			
OAG Score			
CTC Score			
PPI Scale			
End of Course Assessment Day 29			
OAG Score			
CTC Score			
PPI Scale			

Day 29 patient comments regarding oral cryotherapy treatment:

APPENDIX G

Oral Cryotherapy Form

ID # _____ **Date** _____ **Chemotherapy day** _____

5FU dose _____ **LV dose** _____ **Protocol # (if appl.)** _____

Time	Event	Comments
hr:min		
:	Begin oral cryotherapy	
:	Administration of PPI Scale	
:	LV injected (# min if given before cryotx)	
:	5-FU injection begun	
:	5-FU injection completed	
:	Completion of oral cryotherapy	
:	Administration of PPI Scale	

Variances from oral cryotherapy protocol (cite reasons below).

Check	
	Elapsed interval > one minute without cryotx
	Oral cryotherapy discontinued before minute 35
	Oral cryotherapy continued past minute 36
	Other (describe)

Additional comments from patient or nursing staff:

APPENDIX H

January 24, 1992

John R. Smith, M. D.
500 E. Main Street
Portland, OR 97201

Dear Dr. Smith:

I am conducting a study to test the efficacy of an oral cooling procedure for the prevention or reduction of oral mucositis in patients receiving 5-fluorouracil and leucovorin for treatment of colon cancer. As you know, oral mucositis is a common toxicity associated with this treatment regimen. Since there are no proven methods to prevent mucositis, physicians are often limited to prescribing oral rinse solutions which provide only temporary relief from oral pain while the patient's ability to maintain adequate oral intake may be markedly compromised. A study by Mahood et al. (1991) suggests that cooling the oral cavity with ice immediately prior to 5-FU and for 25 minutes thereafter reduces the severity of oral mucositis. I have modified the procedure in order to improve patient tolerance and possibly improve its effectiveness.

Candidates for the study must have experienced mucositis during a prior course of 5-fluorouracil and leucovorin prescribed on a 5-day schedule and repeated every 28 days. I will administer the oral cryotherapy in your office during chemotherapy administration. I will also evaluate patients at defined intervals following the 5-day chemotherapy treatment to determine the degree of mucositis which develops and compare the results to prior chemotherapy courses. Approximately 10 to 30 patients will be included in the study.

I am conducting this study as a requirement for the master's degree in Nursing at the Oregon Health Sciences University. The study has been approved by the university's institutional review board and confidentiality of patient data will be assured in accordance with federal regulations. Should you have a patient who may benefit from the proposed oral cryotherapy treatment or if you desire more information about this study, please contact me at 280-4458 or on display pager 299-5105.

Thank you for your consideration.

Sincerely,

Lisa K. Trif, R. N., O. C. N.

How can I find out more about MOCT?

Should you have a patient who may benefit from the proposed oral cryotherapy treatment or if you desire more information about this study, please contact Lisa Trif, R.N., B.S.N., O.C.N. at 280-4458 or on display pager 299-5105.

This study has been reviewed and approved by the Committee on Human Research of the *Oregon Health Sciences University.* Its conduct is encouraged by physician investigators and staff of the *Columbia River Oncology Program.*

MODIFIED ORAL CRYOTHERAPY TREATMENT (MOCT)

A NURSING RESEARCH STUDY FOR PATIENTS WITH ORAL MUCOSITIS

Who is at risk for oral mucositis?

Oral mucositis is a common toxicity associated with several cancer chemotherapy agents. This toxicity is frequently seen in patients undergoing 5-FU-based chemotherapy for colon cancer. The popular combination, 5-FU and leucovorin, is associated with a 30-80% incidence of oral mucositis. Since there are no proven methods to prevent mucositis, treatment is often limited to prescribing oral rinse solutions which provide only temporary relief from oral pain while the patient's ability to maintain adequate oral intake may be markedly compromised. Moreover, severe mucositis often necessitates dose reductions which may compromise the therapeutic efficacy of 5-FU and leucovorin.

What is Modified Oral Cryotherapy (MOCT)?

This purpose of this study is to test the effects of a new oral cryotherapy procedure for the prevention or reduction of oral mucositis in patients receiving 5-fluorouracil and leucovorin for treatment of colon cancer. An earlier study by Mahood et al.[1] suggests that cooling the oral cavity with crushed ice immediately prior to 5-FU and for 25 minutes thereafter reduces the severity of oral mucositis. Oral cryotherapy probably reduces mucositis through local vasoconstriction which decreases delivery of 5-FU to sensitive oral mucosal cells. The cooling procedure has been modified in this study in order to improve patient tolerance and possibly enhance its effectiveness.

Mahood, J. J, Doss, A. M., Loprinzi, C. L., et al. (1991). Inhibition of fluorouracil-induced stomatitis by oral cryotherapy. Journal of Clinical Oncology, 2, 449-452.

Who is eligible for the MOCT study?

Candidates for the study must have experienced mucositis during a prior course of 5-fluorouracil and leucovorin. Patients who have demonstrated oral mucositis despite use of "crushed ice" oral cryotherapy are eligible if their planned 5-FU dosage is ≥ 370 mg/m^2. Those receiving adjuvant or palliative chemotherapy are eligible if they are willing to provide informed consent and are able to cooperate in the MOCT procedure.

How is MOCT administered?

Oral cryotherapy will be administered by the nurse investigator in the clinic or chemotherapy area during administration of 5-FU. Patients will begin cooling the oral cavity 10 minutes prior to injection of 5-FU. MOCT will continue for 25 minutes after 5-FU. The nurse investigator will also evaluate patients at defined intervals following the 5-day chemotherapy treatment to determine the degree of mucositis which develops and compare the results to prior chemotherapy courses. If the patient benefits and wishes to continue MOCT with subsequent courses, chemotherapy nurses will be instructed on how to administer MOCT upon request.

APPENDIX J

February 10, 1992

John R. Smith, M. D.
500 E. Main Street
Portland, OR 97201

RE: Mrs. Mary L. Jones

Dear Dr. Smith:

I understand Mrs. Jones is under your care for the treatment of her colon cancer. She has consented to participate in my study, "Effectiveness of Oral Cryotherapy in the Reduction or Prevention of Chemotherapy-Induced Oral Mucositis." As you may recall from my letter of January 6, 1992, I am conducting this study to determine if oral cryotherapy can reduce oral mucositis experienced by patients receiving 5-fluorouracil and leucovorin. Since Mrs. Jones developed oral mucositis during her last chemotherapy course, she is interested in receiving oral cryotherapy in an attempt to decrease the oral pain she anticipates will occur following her treatment.

I will provide the supplies and conduct the entire oral cryotherapy procedure in your office. Furthermore, I will perform oral examinations and interview the patient at specific intervals. Oral cryotherapy will be administered in the chemotherapy area, while an exam room will be used for oral assessments and interviews. There are no requirements for additional blood work or physical examinations, hence, the study will not create additional costs for the patient. If the patient is not scheduled to return to the clinic for follow-up assessments required for the study, I will make arrangements to visit her home to conduct these assessments.

I have enclosed a study summary and the study calendar which indicates when Mrs. Jones will receive the oral cryotherapy and assessments. Mrs. Jones has received a study calendar in addition to her copy of the consent form. I will keep you informed regarding Mrs. Jones' response to oral cryotherapy and any effects it has on the development of oral mucositis.

Thank you for allowing me to offer this study to your patients.

Sincerely,

Lisa K. Trif, R. N., O. C. N.

APPENDIX K

STUDY SUMMARY

Effectiveness of Oral Cryotherapy in the Reduction or Prevention of Chemotherapy-Induced Oral Mucositis

Master's Research Project
Lisa K. Trif
Graduate Student, Master's Program
Oregon Health Sciences University School of Nursing

Rationale

Oral mucositis is characterized by inflammation and ulceration of oral mucosal tissues. Approximately 40% of patients receiving chemotherapeutic agents for the treatment of cancer develop primary oral mucositis or secondary oral complications as a result of mucositis, including impaired nutritional intake, periodontal disease, and increased risk of life-threatening infection. One study has shown that oral cooling with ice chips, termed oral cryotherapy, may reduce the severity of oral mucositis associated with the chemotherapy regimen, 5-fluorouracil/leucovorin (5-FU/LV). Hypothetically, oral cryotherapy causes vasoconstriction in oral tissues, thereby reducing exposure of the oral mucosa to the toxic effects of 5-FU. Additionally, local cooling may retard cellular processes and reduce cellular uptake of the drug. This study will seek to conceptually replicate results of the prior study while using a slight modification of the oral cryotherapy treatment.

Purpose

To determine whether oral cryotherapy will reduce the incidence and severity of oral mucositis in patients receiving combination 5-FU/LV chemotherapy for colon cancer.

Patient Selection Criteria

1. Patients, ages 18 or older, with a diagnosis of colon cancer who are receiving a 5-day regimen of 5-FU/LV which is repeated every 28 days, are potentially eligible. Patients receiving 5-FU/LV on NSABP protocol C-05 are eligible.

2. All patients must have demonstrated evidence of oral mucositis during a previous course of chemotherapy.

3. Treatment intent may be curative (adjuvant) or palliative.

4. Those receiving concurrent radiation therapy will be excluded due to effects which may intensify mucositis by other cytotoxic mechanisms.

5. Patients with brain metastases will be excluded due to a relatively short estimated survival and the possibility of cognitive changes which may influence the ability to obtain informed consent.

Procedure

Initial data collection will be done by review of the patient's clinic record. Information which will be collected includes: operative data, chemotherapy data, treatment-related toxicity (specifically oral mucositis), weight loss, previous cancer history, and concomitant medications. The oral cryotherapy procedure will be performed during chemotherapy administration in the physician's office. Prior to beginning oral cryotherapy, the principal investigator will perform an oral assessment and administer a single-item questionnaire which rates oral pain.

Oral cryotherapy will be administered as follows. Ten minutes prior to 5-FU injection, the patient will place a polyurethane bag filled with about 3 tablespoons of ice in his/her mouth. Oral cryotherapy will continue during 5-FU injection and for 25 minutes following the injection. Patient tolerance of oral cryotherapy will be evaluated during and immediately following each oral cryotherapy treatment.

Oral examinations will performed prestudy during an episode of mucositis (if this is not possible, the physician's rating of oral mucositis by the NCI Common Toxicity Criteria will be used). Subsequent examinations will be done at baseline (Day 1 of chemotherapy), and on days 5, 10, 15 and 29 following chemotherapy. The scores indicating the worst degree of oral mucositis and oral pain obtained from both the prestudy chemotherapy course, and the oral cryotherapy course, will be compared to determine if the experimental treatment is associated with a reduction in the incidence or severity of oral mucositis.

APPENDIX L

July 13, 1992

OREGON HEALTH SCIENCES UNIVERSITY
CONSENT FORM

TITLE: EFFECTIVENESS OF ORAL CRYOTHERAPY IN THE REDUCTION OR PREVENTION OF CHEMOTHERAPY INDUCED ORAL MUCOSITIS

INVESTIGATOR: Lisa K. Trif, R.N., B.S.N., O.C.N.
Graduate Student
School of Nursing
(503) 280-4458

FACULTY ADVISOR: Roberta S. Erickson, Ph.D., R.N.
(503) 494-7839

PURPOSE: You are invited to participate in a clinical study designed to evaluate a new treatment for mouth soreness, also called "mucositis," which often occurs several days after receiving certain chemotherapy drugs. Your physician has recommended the drugs
5-fluorouracil and leucovorin (5-FU/LV) for treatment of your colon cancer. Since at least half of all patients receiving these drugs experience some mouth soreness, researchers are trying to find ways to reduce this uncomfortable side effect. The purpose of this research project is to learn if a procedure which cools the mouth during the chemotherapy treatment will help reduce the development of mouth soreness. The cooling procedure, called "oral cryotherapy," is believed to temporarily reduce blood flow to areas of the mouth where soreness usually develops. Reducing the blood flow immediately before, during, and after injection of the chemotherapy can decrease the amount of drug entering sensitive cells in the mouth and possibly reduce mouth soreness or prevent it from occurring. If you have experienced oral mucositis despite the use of oral cryotherapy with ice chips, you can participate in this study which uses a different method of oral cooling.

PROCEDURES: If you agree to participate in this study, you will have an examination of your mouth and teeth (oral exam) before beginning the 5-day chemotherapy treatment. You will be asked some questions about yourself, including your smoking history, dental condition, and the amount of mouth soreness you had with the last chemotherapy treatment. If you have used oral cryotherapy with ice chips, you will also be asked to describe your experience with this procedure. This interview will take about 10 to 15 minutes to complete.

Persons who have undergone oral cryotherapy with ice chips will be asked to have their interviews tape recorded. If you do not wish to have the interview tape recorded, you may still participate in the study.

To help describe the study group, information from your clinic record about your age, weight, previous surgery, previous chemotherapy, and blood counts also will be collected. The total duration of the study will be 4 weeks.

The oral cooling procedure will be done on days 1 through 5 when you receive chemotherapy during this 4-week course. Oral cooling will start 10 minutes before the 5-FU chemotherapy is given, continue during the chemotherapy injection, and for 25 minutes afterward. The procedure will be done with a frozen oral cooling device (a plastic pouch filled with ice). The oral cooling device fits inside your mouth to cool your cheeks, gums, tongue, and the roof of your mouth. After placing the device inside your mouth, you will bite down on it three or four times to allow ice water to slowly leak into your mouth as the ice thaws. The ice water will be swished around to cool your cheeks for a few seconds then you will swallow it. If you wear dentures, they will be removed before the procedure. Then the investigator will make tiny holes in the device before placing it in your mouth so ice water can leak out slowly as it thaws.

You will be asked to tell the investigator if the oral cooling device has thawed and it will be checked every 5 minutes to see if some ice remains. If the oral cooling device thaws before the procedure is finished, it will be replaced with a new frozen one. The oral cooling procedure will continue until exactly 25 minutes after the 5-FU injection. After oral cooling is finished, you will be asked to rate any discomfort you experienced.

On day 5 of the 5-FU/LV treatment, you will have another oral exam before your last oral cooling treatment. The oral exam will then be repeated on days 10, 14, and 29 of the 4-week chemotherapy course. If you are not scheduled to come in to the clinic on days 10 and 14 of the chemotherapy course, the investigator will arrange to visit your home to perform the oral exam. When you return to the clinic for your next course of chemotherapy on day 29, you will have another oral exam and you will be asked about any mouth soreness you had during the past 3 weeks.

The oral cryotherapy treatment has been approved by your physician and he/she will be notified of your participation in this study. The investigator will answer any questions regarding this treatment and its side effects of any other treatment for mouth soreness available to you now or during your participation in the study.

RISKS AND DISCOMFORTS: We cannot and do not guarantee that you will benefit if you take part in this study. The oral cooling procedure may even have harmful effects. Although this treatment has been tested previously, it is possible that you may have a side effect which has not yet been reported. Very little risk is predicted for oral cooling, however. You may feel some temporary discomfort including toothache, headache, irritation of the tongue, or pain in the cheeks or tongue due to the cold temperature. Oral pain or discomfort is expected when the cooling device is initially placed in the mouth. This discomfort usually decreases as your mouth cools. If you are prone to develop canker sores, these may occur several hours to days after oral cooling. The canker sores may or may not be caused as a result of the oral cooling. The device is designed to be large enough to prevent choking or gagging and you will be observed closely for these reactions. There is a slight risk that teeth with existing cracks or those in poor condition could develop a crack or further damage from the procedure. However, dental cracking has never been reported from this oral cooling procedure and is considered unlikely. There are reports in children of an irritation of the cheek caused by prolonged contact with frozen foods such as popsicles and ice cream. This condition clears up without treatment in several days and has not been reported in adults. Some patients have experienced nausea, although this may be due to the chemotherapy drugs rather than oral cooling.

BENEFITS: If effective, this treatment may prevent or reduce the amount of mouth soreness that you experience during the 3-week interval between your chemotherapy courses. Since severe mouth soreness usually requires a reduction of the amount of chemotherapy given, this
side effect could prevent your receiving the most effective doses of anti-cancer drugs. If oral cooling reduces the severity of mouth soreness, your physician may not need to decrease your chemotherapy and you may be able to receive more effective doses. Another benefit is that you will have the opportunity to participate in a study in which the knowledge gained may help you and others receiving 5-FU/LV chemotherapy.

ALTERNATIVE TREATMENTS: Alternative treatments for mouth soreness occurring with chemotherapy include medications to reduce pain and infection once mouth soreness has started. There are no standard treatments used to prevent mouth soreness although some research centers are using crushed ice alone. Other treatments are being tested but remain experimental at this time.

GENERAL INFORMATION: Your participation in this study is voluntary. You may refuse to participate, or you may withdraw from this study at any time without affecting your relationship with your physician or treatment at this facility. You have the right at any time, upon request, to be told about how the oral cooling procedure is affecting you. You may also ask that any other person be given this information and

a copy of this form. If any new information about this treatment develops which will affect your case, your doctor or the investigator will tell you.

CONFIDENTIALITY: Any information specifically about you obtained from this study will be kept strictly confidential and never identified in any report or publication unless you sign a release. Study results may be published with the assurance that the information will remain anonymous and/or disguised so that you cannot be identified. The data will be kept indefinitely and may be used in future related research. Authorized representatives of the Oregon Health Sciences University may examine your records, and there will be no breach of confidentiality. Neither your name nor identity will be used for publication or publicity purposes.

COSTS: Supplies for oral cooling and oral exam will be provided through the research study. Additional bloodwork, physician examinations, and procedures are not a part of this study. Costs of any of medical care requested by your physician will be your responsibility and will not be covered by this study. In addition, you will not be paid for being in the study.

LIABILITY: Because the investigator is a graduate student at Oregon Health Sciences University, the following statement applies: Oregon Health Sciences University, as an agency of the State, is covered by the State Liability Fund. If you suffer any injury from the research project, compensation would be available to you only if you establish that the injury occurred through the fault of the University, its officers, or employees. If you have further questions, please call Dr. Michael Baird at (503) 494-8014.

VOLUNTARY CONSENT: You have read the preceding or it has been read to you and you understand its contents. Any questions that you have pertaining to the study have been or will be answered by Lisa Trif, R.N., B.S.N., O.C.N., who can be reached at (503) 280-4458. A copy of this consent form will be given to you.

Your signature below means that you have freely agreed to participate in this study and that the conditions stated in this consent form are appropriate and acceptable to you.

_____ _____

Date Patient's Signature

_____ _____

Date Investigator's Signature