Review Article

Supportive Cryotherapy: A Review From Head to Toe

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Abstract

Context. Conventional chemotherapy leads to multiple adverse mucocutaneous complications such as oral mucositis, alopecia, ocular toxicity, and onycholysis. Limited pharmacologic interventions are available for preventing these clinical problems.

Objectives. This study aimed to critically review the role of cryotherapy (regional hypothermia) for alleviating these adverse symptoms.

Methods. A narrative review was performed, with an emphasis on randomized controlled trials. A comprehensive search using PubMed, Ovid, Embase, and MEDLINE® was completed. References of all cited articles also were reviewed. Data from the review were composed of articles published between 1970 and May 2013.

Results. Available evidence suggests that regional hypothermia decreases the burden of chemotherapy-related oral mucositis, alopecia, ocular toxicity, and onycholysis. The major limitations of studies include the absence of blinded control groups and variable clinical end points.

Conclusion. Regional hypothermia decreases the burden of these four chemotherapy-induced complications and is well tolerated. More research is needed to determine what subgroups of cancer patients are most likely to respond to different types of regional hypothermia, the ideal duration of cooling needed, and further improve the ease of use of the cooling devices. J Pain Symptom Manage 2014;47:1100–1115.

Key Words

Cryotherapy, regional hypothermia, mucositis, alopecia, onycholysis

Introduction

Conventional chemotherapy leads to adverse mucocutaneous complications such as oral mucositis (OM), alopecia, onycholysis, and 5-fluorouracil (5FU)-related ocular toxicity. Despite extensive research, limited pharmacologic

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interventions are available for preventing these clinical problems. Cryotherapy uses the basic principle that cold-induced vasoconstriction can limit the local effects of certain cytotoxic therapies. This review critically appraises the role of cryotherapy in supportive oncology, focusing on the prevention of these four chemotherapy-induced complications.

Oral Mucositis

OM causes oropharyngeal pain and can prevent adequate nutritional intake. Beyond causing significant pain and suffering,[1] it is associated with increased hospitalizations, the need for total parenteral nutrition, and septicemia.[2,3] As such, this complication leads to significant resource utilization and is a major economic burden.[4]

Pathogenesis of OM

The pathogenesis of chemotherapy-induced mucositis is complex and yet to be fully understood. Although previously believed to be a nonspecific effect of chemotherapy on rapidly dividing cells of the mucosal tract, the pathobiology of mucositis has more recently been described as a sequence of five biological stages. These include initiation, upregulation and message generation (primary damage response), signaling and amplification, ulceration, and healing.[5] Despite a better understanding of the pathogenesis of mucositis, multiple pharmacologic agents, posited to act at different stages of this sequence, have failed to show consistent benefits in randomized controlled trials (RCTs).[6–9] For example, glutamine, an amino acid necessary for cell mitosis, could theoretically decrease OM; however, its use has been poorly supported in adequately powered and well-designed RCTs.[10] Other agents, such as palifermin, that interact at multiple stages in this sequence have proven to be beneficial in well-designed RCTs but are only a U.S. Food and Drug Administration-approved preventative agent in certain patients undergoing autologous hematopoietic stem cell transplantation (HSCT).[11]

Cryotherapy and OM

The mechanism of oral cryotherapy, placing ice chips in the mouth during chemotherapy infusion for the prevention of OM, is, at least hypothetically, understood. When developed, it was assumed that such a maneuver would decrease the temperature of the oral cavity. A recent study of 12 healthy patients confirmed that crushed ice in the oral cavity leads to a mean difference of $\approx 13^{\circ}C$ in the oral cavity tissues.[12] Hypothermia leads to vasoconstriction, and the resultant reduction in blood flow is posited to decrease the local effects of concentrated levels of cytotoxic drugs in the cooled area.

Since 1991, more than 20 controlled and uncontrolled trials have assessed the efficacy of oral cryotherapy for the prevention of OM (Tables 1 and 2). Almost all trials studied its effectiveness in patients receiving chemotherapeutics with a short serum half-life, such as bolus 5FU and high-dose melphalan. Mahood et al.[13] were the first to observe that cryotherapy reduced 5FU-induced OM by $\sim 50\%$. In a confirmatory analysis, 84 patients were randomized to either oral cryotherapy or control, and a similar reduction in the mean OM toxicity score was observed.[14] Following the results of these pivotal trials, French and Italian researchers found cryotherapy effective in reducing OM in patients undergoing conditioning regimens containing high-dose melphalan.[15,16] However, one of the limitations of these early trials was that they did not assess for pretreatment oral health. Although the optimal regimen of oral care remains to be determined,[17] maintaining adequate oral hygiene before and after chemotherapy and radiation appears to reduce the incidence and severity of OM.[18,19]

Beyond reducing the incidence of OM in patients receiving such chemotherapy, further trials have demonstrated the effectiveness of cryotherapy in reducing the duration of OM, its effect with different chemotherapeutic regimens, utility with other prophylactic agents, and the optimal duration of cryotherapy itself.

In 2005, 60 patients with solid tumors receiving varying combinations of etoposide, cisplatin, vinblastine, and mitomycin were randomized to cryotherapy or standard treatment.[20] The patients allocated to cryotherapy had less mucositis and a shorter mean duration of OM (seven vs. 12 days). The shortened course of OM also was observed in other trials, most averaging a reduction of approximately four days.[13,21]

Table 1
Studies of Oral Cryotherapy in Solid Malignancies

Reference	Year	Randomized	Number in Intervention/ Control Group	Type of Cryotherapy	Duration of Cryotherapy	Chemo Regimen	Mucositis Staging	Intervention Group	Control Group
Mahood et al.[13]	1991	Yes	50/45	Ice chips	5 Minutes before 5FU and then for 30 minutes	5FU/LV	Mean patient and physician judged mucositis grading (0–4), mean score	Patient: 1.1 Physician: 0.9	2.4 1.9
Rocke et al.[30]	1993	Yes	89/89[a]	Ice chips	5 Minutes before 5FU and then for 30 or 60 minutes	5FU/LV	Mean patient and physician judged mucositis grading (0–4), mean score	Patient: 30 minutes: 0.73 60 minutes: 1 Physician: 30 minutes: 0.58 60 minutes: 0.79	
Cascinu et al.[14]	1994	Yes	44/40	Ice chips	5 Minutes before 5FU and then for 30 minutes	5FU/LV ± etoposide or interferon	Combined patient and physician judged mucositis grading (0–4), mean score	0.59	1.1
Dreicer et al.[25]	1997	No	37/—	Ice chips	30 Minutes before edetrexate infusion	Edatrexate	ECOG grade, Grades 3–4	38%	
Gandara et al.[26]	1997	No	23/—	Ice chips	5 Minutes before, during, and 15 minutes after edetrexate infusion	Edatrexate + carboplatin	Not specified, Grade 3	13%	
Edelman et al.[22]	1998	No	46/—	Ice chips	5 Minutes before, during, and 15 minutes after edetrexate infusion	Edatrexate + carboplatin	CTC, Grades 1–4	Grades 1–2: 59% Grades 3–4: 15%	
Hudes et al.[109]	1999	No	27/—	Ice chips	5 Minutes before 5FU and then for 30 minutes	5FU/LV + interferon	CTC, Grades 3–4	36%	
Yokomizo et al.[29]	2004	No	20/32	Allopurinol ice balls	Before 5FU infusion and at two, four, and six hours until melted	5FU/LV	CTC, Grades 1–4	Grades 1–2: 15% Grades 3–4: 0%	41% 6%
Karagozoglu and Filiz Ulusoy[20]	2005	Yes	30/30	Smooth ice cubes	5 Minutes before chemo until all infusions complete	Etoposide, cisplatin, mitomycin, vinblastine	Patient and physician judged mucositis grading (0–4), Grades 1–4	Patient: 37% Physician: 10%	90% 50%
Nikoletti et al.[31]	2005	Yes	67/67/67[b]	Plain ice or flavored ice	5 Minutes before and during, until 20 minutes after 5FU	5FU ± LV	Oral Assessment Guide, OR[c]	None vs. plain: 3.26 None vs. flavored: 3.5 Plain vs. flavored: 1.07	

Baydar et al.[110]	2005	Yes	45/54[d]	Ice chips	Start of infusion until 10 minutes after 5FU	5FU/LV	WHO, Grades 1–3	7% (only Grade 1)	39% (Grades 1–3)
Papadeas et al.[32]	2007	Yes	36/40	Crushed ice	5 Minutes before and during, until 30 minutes after 5FU	5FU/LV	Patient and physician judged mucositis grading (0–4); Grade 3	Patient: 17% Physician: 11%	23% 13%
Sorensen et al.[21]	2008	Yes	70/64/63[e]	Crushed ice	10 Minutes before 5FU and then for 35 minutes	5FU/LV	CTC, Grade 3	Cryotherapy: 10% Chlorhexidine: 11%	32%
Katranci et al.[111]	2012	Yes	30/30	Crushed ice	5 Minutes before, during, and up to 15 minutes after 5FU	5FU/LV	WHO, Grade 3	3%	20%

5FU = 5-fluorouracil; LV = leucovorin; ECOG = Eastern Cooperative Oncology Group; CTC = Common Toxicity Criteria; OR = odds ratio; WHO = World Health Organization.
[a]Patients were randomized to either 30 or 60 minutes of oral cryotherapy.
[b]All the 67 patients were randomized sequentially in a crossover design during three cycles of therapy to flavored ice, plain ice, and no ice.
[c]Reported by authors only as OR as odds of symptoms increasing vs. not increasing.
[d]Forty patients in total; patients were randomized to either cryotherapy ($n = 45$) or standard care ($n = 54$) initially and then crossed over at next cycle.
[e]Arms A/B/C are chlorhexidine/normal saline/cryotherapy, respectively.

Edatrexate, an analogue of methotrexate with a short serum half-life, has been used with marginal success in regimens for both solid and liquid tumors, with the major dose-limiting side effects being OM and myelosuppression. In a phase I trial of 46 patients receiving edatrexate plus carboplatin in advanced solid tumors, only 15% had Grade 3/4 OM with the use of cryotherapy,[22] less OM than was seen in trials not using cryotherapy.[23,24] Two other trials found mixed results with cryotherapy in patients receiving edatrexate.[25,26]

Although allopurinol mouthwashes alone do not consistently appear to prevent OM,[10,27,28] its role combined with cryotherapy (i.e., allopurinol ice balls) was shown to be promising in a Japanese trial.[29] In contrast to all previous trials, the patients were administered allopurinol ice balls during the infusion and at two, four, and six hours after infusion. To address whether a longer duration of cryotherapy in patients receiving 5FU is needed, 178 patients were randomized to either 30 or 60 minutes of cooling, and no difference was observed between groups, supporting that 30 minutes was adequate.[30]

Five more recent trials also have reported a clear benefit of oral cryotherapy over standard care alone in patients receiving 5FU. The earliest of these studies found that both flavored and plain ice cryotherapy reduced mucositis compared to control; however, no preference for flavored ice was observed.[31] Patients receiving flavored ice were more likely to complain of nausea, oral sensitivity, and headaches. Papadeas et al.[32] confirmed the persistent benefit of oral cryotherapy over three cycles of chemotherapy. In the largest RCT to date, oral cryotherapy and chlorhexidine each significantly decreased the incidence of Grade 3 OM over normal saline.[21] Compliance rates were the highest for the cryotherapy arm; however, this arm was associated with more headaches than the other arms (21% vs. 14%).

In patients undergoing melphalan-containing conditioning regimens, initial reports suggested the benefit of oral cryotherapy in nonrandomized studies as described previously.[15,16] Since then, three nonrandomized and three randomized studies have shown significant benefit for OM with the use of oral cryotherapy in this patient population (Table 2).[15,16,33–38] To address the optimal duration of cryotherapy in patients

Table 2
Studies of Oral Cryotherapy in Hematological Malignancies

Reference	Year	Randomized	Number in Intervention/ Control Group	Type of Cryotherapy	Duration of Cryotherapy	Chemo Regimen	Mucositis Staging	Intervention Group	Control Group
Dumontet et al.[15]	1994	No	22/—	Ice chips + cold water	5 Minutes before melphalan and continued for 30 minutes	Mel or BEAM ± TBI	WHO, Grades 3–4	TBI: 86% No TBI: 33%	
Meloni et al.[16]	1996	No	18/—	Ice popsicles	5 Minutes before, during, and after melphalan infusion	Mel or BEAM	WHO, Grade 4	6%	
Aisa et al.[33]	2005	No	18/7 (Historical control)	Ice chips + cold water	15 Minutes before and during, until 90 minutes after melphalan infusion	Mel + Flu ± Other[b]	CTC, Grades 2–3	11%	86%
Mori et al.[36]	2006	No	17/18[a]	Ice chips + cold water	15 Minutes before and during, until 60 or 90 minutes after melphalan infusion	Mel + Flu ± Other[b]	CTC, Grades 2–3	60 Minutes: 11.8% 120 minutes: 11.1%	—
Lilleby et al.[35]	2006	Yes	21/20	Ice chips	30 Minutes before and during, until six hours after infusion	Mel	CTC, Grades 3–4	14%	74%
Svanberg et al.[37]	2007	Yes	39/39	Ice chips or ice water	During infusion of chemotherapy	Variable	Modified Oral Mucositis Assessment score[c]	Autologous = 1.6 Allogeneic = 3.7	4.3 11.6
Gori et al.[39]	2007	Yes	62/60	Ice chips	At least 60 minutes once methotrexate infusion started	Methotrexate	CTC, Grades 3–4	47%	53%
Bhatt et al.[34]	2010	No	12/13 (Historical cohort)	Ice chips	30 Minutes before until infusion complete	Mel	CTC, Grade 3	17%	38%
Svanberg et al.[38]	2010	Yes	39/39	Ice chips or cold water	During infusion of chemotherapy	Variable	WHO, Grades 3–4	36%	62%

Mel = melphalan; BEAM = carmustine, etoposide, cytarabine, and melphalan; TBI = total body irradiation; WHO = World Health Organization; Flu = fludarabine; CTC = Common Toxicity Criteria.
[a]Study compared two different total durations of oral cryotherapy: 60 minutes ($n = 17$) and 120 minutes ($n = 18$).
[b]Other included total body irradiation vs. craniospinal irradiation vs. high-dose cytarabine.
[c]Based on modified Oral Mucositis Assessment Score, autologous group ($n = 62$) index ranged 0–5 and allogeneic group ($n = 16$) index ranged 0–16.

receiving melphalan, a study found that a total duration of cryotherapy for 60 minutes compared with 120 minutes improved tolerability without decreasing efficacy.[36] Other studies in patients undergoing HSCT have shown that oral cryotherapy also reduces opioid use[37] and decreases the need for parenteral nutrition.[38]

Despite the above positive data, a large randomized multicenter study found no significant difference between cryotherapy compared with standard therapy in patients receiving low-dose methotrexate after allogeneic HSCT (47% vs. 53%).[39] Although the researchers found that peak methotrexate plasma levels occur within 30 minutes of infusion, the elimination half-life and methotrexate by-products likely decreased the efficacy compared with studies involving melphalan and 5FU. Given the large number of positive studies and virtual lack of negative studies (except for the study noted above), it is reasonable to consider a potential publication bias. However, it is unlikely that there is more of a publication bias in this setting vs. other settings with multiple positive studies.

Adverse Effects of Cryotherapy for OM

Most patients tolerate oral cryotherapy without serious issues. The most common adverse effects reported include headaches, nausea, and chills. Some patients note a subsequent aversion to ice as it can bring back memories of other chemotherapy-induced toxicities such as dysgeusia. A recent report found no serious adverse effects such as an increased relapse rate in hematological cancers over a five-year period.[40]

Chemotherapy-Induced Alopecia

Chemotherapy-induced alopecia (CIA) is a common and distressing adverse effect of cancer treatment that can negatively impact quality of life.[41–43] The incidence and severity of alopecia is dependent on the route, dose, and schedule of the cytotoxic drugs used.[44] Hair loss generally occurs two to four weeks after the initiation of chemotherapy, and regrowth occurs three to six months after cessation of therapy, although irreversible hair loss does rarely occur.[45,46] Therapy to prevent the occurrence of alopecia is desired as it is a feared complication of cancer treatment, and nearly 10% of women would consider refusing chemotherapy because of it.[47–50]

Pathogenesis of CIA

The pathophysiology of CIA is complex and not fully understood. Much of the understanding has been gleaned from studies involving newborn rats, the C57BL/6 mouse model, and more recently an adult rat model.[51–53] Two broad mechanisms are felt to be responsible for hair loss: thinning of the hair shaft leading to breakage and inhibition of dividing hair matrix cells resulting in hair separation from the bulb (anagen effluvium). Both processes are related, in part, to the capacity of cytotoxic therapy to impair mitotic activity and induce apoptosis. The molecular mechanisms of chemotherapy-induced apoptosis continue to be elucidated, and activation of p53 plays a critical role in the devolvement of CIA.[54]

Delivery of scalp hypothermia (i.e., cryotherapy) can occur in the form of an ice turban, gel cap, cool cap, or a thermocirculator. It involves physically decreasing the amount of cytotoxic drug that is delivered to the scalp. It is theorized that scalp hypothermia triggers vasoconstriction of local blood vessels, thereby limiting temperature-dependent absorption of cytotoxic therapy and reducing local tissue metabolism by the hair follicle.[55,56]

Cryotherapy and CIA

In the 1970s, scalp hypothermia was initially reported to improve alopecia in patients receiving doxorubicin.[57–59] Since then, there have been more than 50 nonrandomized and seven randomized studies evaluating its efficacy in diverse patient populations; patients with breast cancer remain the most studied group. A comprehensive review, published in 2005, concluded that most findings were positive, with an average success rate before and after 1995 of 56% and 73%, respectively (most often based on the World Health Organization alopecia grading criteria and less frequently on the need for a wig or a head cover).[60] Six of the seven randomized trials ($N = 233$) published to date were positive, and of these, five occurred in the 1970s and 1980s,[58,61–64] whereas only two were more recent.[65,66] Although the chemotherapy regimens used in these earlier studies differed from more recent studies, other methodological variables including scalp

cooling technique, postinfusion cooling times, duration of chemotherapy infusion, and eligibility criteria make comparisons between studies difficult.

Since the review published in 2005,[60] there have been nine studies evaluating the efficacy of scalp hypothermia (one systematic review and eight nonrandomized studies) (Table 3). The systematic review only included three of the older randomized controlled studies because of methodological issues and tentatively recommended the use of scalp hypothermia.[67] In 2009, a study involving breast cancer patients found that scalp hypothermia significantly reduced the need for a wig or a head cover compared with control.[68] Scalp hypothermia was felt to be burdensome in a minority of the group (33%), with a common concern being that scalp cooling will fail to prevent hair loss. In a separate analysis by the authors, successfully cooled patients had an improved feeling of well-being; however, patients who were unsuccessfully cooled reported the highest degree of distress.[43]

In another study of 64 patients, primarily with breast cancer, 83% of patients using a scalp cooling gel cap reported Grade 0/1 alopecia, and only 17% had Grade 3 alopecia.[69] Most patients did not report any side effects (57%), and tolerable side effects were reported by 30%. Only four patients discontinued the use of the scalp cooling gel cap because the process was too unpleasant or cold.

In 2011, Karger et al.[70] completed a study of 63 patients with various cancers and compared the scalp cooling group with a control group; they found greater benefit earlier in the course of therapy, suggesting a component of cumulative toxicity from chemotherapy leading to less benefit from scalp cooling during subsequent cycles. The authors did not mention any significant adverse effects of therapy.

The largest cohort ever studied, comprising 1411 patients from the Dutch Scalp Cooling Registry, found that the overall use of head covering (wig or other) was 50% within the entire cohort but varied from 5 to 10% with low-dose docetaxel or paclitaxel to more than 90% of patients receiving combination regimens.[71] Higher chemotherapy doses, shorter infusion times, non-Western European hair, female gender, and older age were associated with a higher use of head covers. Median pre- and postinfusion cooling times were significantly longer than the reported pre- and postinfusion times in the more recent studies. A subsequent study by the same authors found that a shorter postinfusion cooling time was as effective as a longer postinfusion cooling time (45 vs. 90 minutes).[72]

A recent prospective cohort study, available only in abstract form, found that scalp hypothermia significantly reduced alopecia compared with a control group.[73] Compared with hairstylist assessments, patient-reported assessments suggested a greater degree of benefit, highlighting the significance of patient expectations in this study. Adverse effects and quality-of-life measurements are yet to be published.

The most recent study comparing the Paxman cooling system with another cold cap (manufacturer not specified) found a significant decrease in alopecia in patients receiving either form of scalp hypothermia.[74] Importantly, a shorter postinfusion cooling time (45 vs. 90 minutes) was again found to be effective.

Adverse Effects of Scalp Hypothermia

Most patients tolerate scalp hypothermia well; however, a few may find it too cumbersome, lengthy, or intolerable. Although uncommon, adverse effects include headaches,[68,75] extreme coldness,[69,76] or a heavy sensation.[69] Rare side effects include nausea, dizziness, or anxiety.[76,77]

Risk of Scalp Metastases and Influence of Drug Metabolism

Two case reports of scalp metastases associated with scalp hypothermia in patients with hematological malignancies have been reported.[78,79] Although similar concerns have been raised in patients with solid tumors, more recent evidence suggests that this risk is minimal. The incidence of scalp metastases was 0.45% in one large retrospective study (two of 442 patients).[80] The incidence of scalp metastases in another retrospective cohort was similar in patients undergoing scalp hypothermia or not (1.1% vs. 1.2%).[81] The large Dutch registry of 1411 patients has yet to observe a scalp metastasis within its entire cohort.[71] Given the lack of supporting data to suggest safety in patients with hematological malignancies and the aforementioned case reports, scalp hypothermia is not recommended for this population.

Table 3
Recent Studies of Scalp Hypothermia

Reference	Year	Randomized	Number in Intervention/ Control Group	Cooling Method	Chemo Regimen	Hair Loss Grading	Intervention Group	Control Group
Mols et al.[68]	2009	No	98/168	Paxman system	AC, FEC, FAC, DAC	No wig required	52%	3%
Auvinen et al.[69]	2010	No	64/—	Gel cap	A, D, D + FEC, FEC	Modified CTC[a]		
						Grade 1	69%	—
						Grade 2	17%	
Kargar et al.[70]	2011	No	31/32	Penguin Cap	D, ABVD, BEP, CHOP	WHO, Grade 3 or 4		
						Week 2	23%	61%
						Week 6	50%	75%
van den Hurk et al.[71]	2012	No (registry)	1411/—	Various	Various	No wig required	50%	—
van den Hurk et al.[72]	2012	No[b]	53/15	Paxman system	D	No wig required		27%
						90 Minutes PICT	79%	
						45 Minutes PICT	95%	
Lemieux et al.[112]	2012	No	110/26	Penguin Cap or Dignicap	Various	Success per:[c]		
						Hairstylist	34%	9%
						Patient	49%	4%
van den Hurk et al.[113]	2013	No	160/86	Paxman system	Various	WHO		
						Grade 2	50%	7%
						Grade 3	30%	91%
Betticher et al.[74]	2013	No	128/71/39[d]	Paxman system or cold cap	D as weekly or Q 3 weekly ± other chemotherapy	WHO Grade 3 or 4		
						Paxman		
						D Q 3 week	23%	74%
						D Q weekly	7%	17%
						Cold cap		
						D Q 3 week	27%	
						D Q weekly	8%	

AC = adriamycin and cyclophosphamide; FEC = 5-fluorouracil, epirubicin, and cyclophosphamide; FAC = 5-fluorouracil, adriamycin, and cyclophosphamide; DAC = docetaxel, adriamycin, and cyclophosphamide; A = adriamycin; D = docetaxel; CTC = Common Toxicity Criteria; ABVD = adriamycin, bleomycin, vinblastine, and dacarbazine; BEP = bleomycin, etoposide, and cisplatin; CHOP = cyclophosphamide, adriamycin, and vincristine plus prednisolone; WHO = World Health Organization; Q = every/.

[a]Modified CTC were used: Grade 0 = no hair loss, Grade 1 = thinning of hair, and Grade 2 = patchy or major hair loss or complete alopecia.

[b]The study was an observational study followed by randomization if the initial phase of study suggested significant benefit.

[c]Success was defined as moderate, little, or no hair loss.

[d]Study compared three groups: Paxman system = 128, cold cap = 71, and control = 39.

Initial reports of severe alopecia in patients with liver insufficiency treated with doxorubicin despite scalp hypothermia suggest the influence of drug metabolism as a predictor of scalp hypothermia failure.[82,83] More recent studies also suggest that liver insufficiency could lead to higher rates of alopecia despite scalp hypothermia.[60]

Chemotherapy-Induced Onycholysis

A variety of changes to the nail can occur because of chemotherapy including onycholysis (detachment or loosening of the nail from the nail bed). Beyond esthetic disfigurement, onycholysis can be painful, increase the chance of superimposed infection, and delay chemotherapy administration.[84] It is most commonly associated with taxanes including docetaxel and paclitaxel, but its occurrence because of other chemotherapeutic agents can occur. The incidence of taxane-induced onycholysis is variable (5%–30%) depending on the specific taxane used (the risk with docetaxel is greater than that with paclitaxel) and the dosing schedule.[85,86]

Pathogenesis of Chemotherapy-Induced Onycholysis

Although the etiology of chemotherapy-induced onycholysis remains to be elucidated, direct cytotoxic, vascular, and neurogenic mechanisms have been postulated. A thin nail bed epithelium is responsible for supporting the adhesion of the nail plate to the nail bed. Chemotherapy-related cytotoxic injury to this epithelium could contribute to the development of onycholysis.[84,87] A neurogenic mechanism was first proposed based on the sparing of toxicity in the paretic hand of a patient who had docetaxel-induced onycholysis in the other three extremities.[88] The authors hypothesized two particular neurogenic mechanisms: the first is related to persistent neurogenic inflammation from taxane-induced *stimulation* of cutaneous nociceptive C-fibers and the second is related to taxane-induced release of proinflammatory mediators that promote *maintenance* of nociceptive primary afferent stimulus (peripheral sensitization).

Cryotherapy and Chemotherapy-Induced Onycholysis

Similar to scalp hypothermia and oral cryotherapy, the suspected mechanism of regional hypothermia in the prevention of onycholysis is likely related to local vasoconstriction leading to reduced levels of cytotoxic drug to the nail bed and matrix. Based on the efficacy of cryotherapy for alopecia and mucositis, multiple studies evaluating regional hypothermia for prevention of nail toxicity have been completed (Table 4). Scotte et al.[89] reported a case-control trial of 45 patients, using an Elasto-Gel frozen glove with the patient's left hand used as a control, for the prevention of docetaxel-induced onycholysis and skin toxicity. Nail toxicity was significantly less in the frozen glove-protected hand. Most patients were satisfied with treatment. However, 11% withdrew because of cold intolerance. The same authors conducted a similarly designed matched case-control trial using a frozen sock and found significantly less docetaxel-induced onycholysis and skin toxicity in the protected foot.[90] Only one patient was dissatisfied with the treatment because of cold intolerance. Two further studies, each reported in abstract form, found similar benefits with frozen glove therapy, with no serious adverse effects reported except discomfort.[91,92]

To evaluate the ideal duration and degree of cooling necessary to prevent nail toxicity and maintain comfort, Ishiguro et al.[93] compared a standard frozen glove worn for 90 minutes with a glove worn for 60 minutes. At five months, patients in the 60 minutes group had a similar degree of nail toxicity with less discomfort, suggesting that the shorter duration intervention worked as well as the more intense treatment. Docetaxel exposure over the study period did not correlate with nail toxicity.

Despite the aforementioned positive studies, a recent study of 55 patients receiving either taxane were treated with frozen gloves and socks on all extremities and were compared with a similar cohort; no statistical difference was observed in nail toxicity between groups.[94] Possible explanations for the lack of effect observed include the variety of chemotherapy regimens used in both groups and, more importantly, the differences among individuals, as opposed to each individual being their own control (i.e., using one side to compare with the other).

Adverse Effects of Extremity Hypothermia

The major adverse effect observed in clinical studies includes discomfort related to the

Table 4
Studies of Regional Hypothermia for the Prevention of Onycholysis

Reference	Year	Number in Intervention/ Control Group[a]	Chemo Regimen	Nail Toxicity Scale	Intervention Group[b]	Control Group
Scotte et al.[89]	2005	45	Docetaxel 75 mg/m^2 ± other chemotherapy	CTC, Grade 1 or 2	27%	51%
Scotte et al.[90]	2008	50 (foot)	Docetaxel 70–100 mg/m^2 ± other chemotherapy	CTC, Grade 1 or 2	0%	21%
Sakurai et al.[92]	2009	70/52[c]	Docetaxel 75 mg/m^2 ± other chemotherapy	CTC		
				Grade 1	54%	74%
				Grade 2 or 3	4%	18%
Hayashi et al.[91]	2009	52[d]	Docetaxel 75 mg/m^2 + cyclophosphamide	CTC, Grade 1 or 2	19%	37%
Ishiguro et al.[93]	2012	23[e]	Docetaxel ≥ 40 mg/m^2 ± other chemotherapy	CTC, Grade 1 or 2		
				−25°C to −30°C for 90 minutes	0%	
				−10°C to −20°C for 60 minutes	0%	
Can et al.[94]	2012	55/145[f]	Docetaxel or paclitaxel (variable dose) ± other chemotherapy	CTC, Grade 1, 2, or 3		
				Paclitaxel Q 7 days	56%	43%
				Paclitaxel Q 21 days	50%	53%
				Docetaxel Q 21 days	38%	50%

CTC = Common Toxicity Criteria.
[a]All studies, unless indicated otherwise, used one hand as the control and the other as the intervention.
[b]All studies, unless indicated otherwise, used a frozen glove at −25°C to −30°C for a duration of 90 minutes: 15 minutes before, during, and 15 minutes after the infusion of docetaxel.
[c]Both hands in intervention group were provided with frozen gloves; control group did not receive any intervention.
[d]Frozen glove was worn for 15 minutes before, during, and 30 minutes after the infusion of docetaxel.
[e]One hand received standard frozen glove and other received frozen glove at −10°C to −20°C for 60 minutes (see text).
[f]Intervention group received frozen gloves and socks on all extremities; control group received neither.

degree of cooling and the duration of use. A minority of studied patients (≈2%–10%) stopped the intervention because of discomfort. One case report described frostbite occurring in the fingers of a man who used frozen gloves (cooled to −25°C to −30°C and worn for 90 minutes) during one cycle of docetaxel therapy, which improved with supportive care and subsequent avoidance of frozen gloves.[95]

5FU-Related Ocular Toxicity

Many types of ocular toxicity related to anticancer treatments have been described in patients receiving cytotoxic[96] and targeted therapy.[97] Ocular toxicities related to 5FU can be divided into complications of the ocular surface, ocular adnexa, or the lacrimal system. Based on 210 patients, receiving a variety of chemotherapy agents, unpleasant ocular symptoms were reported by ≈40% of patients receiving 5FU-containing regimens compared with ≈20% of patients receiving non-5FU-containing regimens, suggesting a strong association of 5FU exposure with ocular toxicity.[98] The most frequent adverse symptoms included tearing (27%), blurred vision (11%), ocular irritation with pain (6%), and eyelid dermatitis (6%).[99] 5FU-related ocular symptoms generally occur within 11–17 days of the infusion and last for 10–15 days.[98] Although not life threatening, these adverse symptoms can cause suffering and delay chemotherapy administration.

Pathogenesis of 5FU-Related Ocular Toxicity

Damage of the conjunctiva, cornea, and the eyelid margin within days to weeks of 5FU administration is likely related to the cytotoxic effect on the rapidly proliferating cellular elements of these ocular surfaces. Two proposed mechanisms for the etiology of tearing, the most common adverse effect, have been suggested. One theory postulates a reflex phenomenon as a result of direct cytotoxic irritation of the ocular surface.[100] As drug levels are detectable in tears of patients receiving 5FU, the second theory proposes irritation of the lacrimal gland leading to hypersecretion.[101] Concentrations of 5FU in tears, in a small series of 12 patients, were not found to be associated with adverse symptoms[98] but were associated with symptoms in another series of 13 patients.[102] More prolonged administration of 5FU (more than three months) can lead to chronic inflammation of the lacrimal system and has been associated with punctal–canalicular stenosis that can rarely result in permanent excessive lacrimation requiring surgical correction.[103]

Cryotherapy and 5FU-Related Ocular Toxicity

In 1990, an initial report of eight patients receiving cyclophosphamide, methotrexate, and 5FU, who had ocular toxicity on a previous cycle of cyclophosphamide, methotrexate, and 5FU, were treated with ice packs over their eyes for a total of 30 minutes before and during the 5FU infusion. The majority had a decrease in adverse ocular symptoms during the next month.[98] The postulated mechanism is likely similar to that of cryotherapy for other indications, in that regional hypothermia induces constriction of the blood vessels around the eye resulting in reduced cytotoxic effect during peak 5FU serum concentration. Based on these pilot data, a randomized crossover trial was conducted in 62 patients who had previously complained of ocular toxicity and were undergoing additional 5FU therapy.[104] Ice packs were provided five minutes before bolus 5FU infusion and continued for a total of 30 minutes. Mean total ocular toxicity score was reduced in patients receiving ocular ice therapy (20 vs. 29 U, $P = 0.056$). Although generally well tolerated, unpleasant side effects, such as "feeling cold," "sore sinuses," and headaches occurred in 22% of patients.

Conclusions for Supportive Cryotherapy

Most studies addressing the use of supportive cryotherapy have shown benefit in preventing OM, alopecia, onycholysis, and 5FU-related ocular toxicity. The major limitations of these studies are the variability of study design and the lack of blinding. The latter issue is not technically feasible, given the nature of the intervention. Although the ideal technique for providing supportive cryotherapy for each of these issues remains to be elucidated, a few conclusions can be made.

Oral cryotherapy has demonstrated a reduction in incidence, severity, and duration of OM (by approximately 50% compared with

standard care) in multiple controlled studies involving patients with a variety of cancers receiving bolus 5FU and conditioning regimens containing melphalan. Its role with other cytotoxic regimens such as edatrexate is promising. However, it would not be expected to be effective with chemotherapeutics with longer half-lives. In patients receiving bolus 5FU, crushed ice should be given five minutes before infusion and be continued for at least 30 minutes. Based on available evidence, the duration of cryotherapy in patients receiving melphalan-containing conditioning regimens can be increased to 60 minutes, if tolerated. A recent systematic review[105] and the most recent Multinational Association of Supportive Care in Cancer OM guidelines[106] support these recommendations. Areas of potential further research include the role of oral cryotherapy with other chemotherapy regimens, its efficacy in pediatric populations, and comparisons with promising pharmacological interventions used for OM.

Scalp hypothermia reduces the burden of CIA. Its role has largely been studied in patients with breast cancer; however, significant distress related to alopecia in male cancer patients warrants further investigation in this population.[107,108] Although the ideal technique for cooling has yet to be elucidated, recent reports have yielded promising data regarding the optimal degree of cooling necessary[55] and the duration of postinfusion cooling.[72,74] Further studies comparing different cooling techniques are needed. Finding more user-friendly means of providing effective scalp hypothermia would be helpful. As research progresses, formal guidelines regarding the role of cryotherapy for alopecia will be warranted.

Although nail toxicity is not life threatening, onycholysis can be disfiguring, painful, and delay chemotherapy administration. Most clinical data support that regional hypothermia of the hands and feet decreases the incidence of onycholysis, with minimal discomfort. It appears to be most consistently effective in patients receiving one hour infusions of docetaxel. A single trial reported similar benefit with a more tolerable regimen (glove cooled to −10°C to −20°C and worn for 60 minutes compared with −25°C to −30°C for 90 minutes).[93]

Cryotherapy also appears to be an effective and tolerable intervention for short-term ocular toxicity related to bolus 5FU infusions. Many current chemotherapy regimens, however, use continuous infusions of 5FU, and cryotherapy would likely not provide benefit for these patients. Although largely of historical significance, ocular ice therapy further supports the role of regional hypothermia for certain chemotherapy-induced complications.

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