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ORIGINAL ARTICLE

Topical amitriptyline, ketamine, and lidocaine in neuropathic pain caused by radiation skin reaction: a pilot study

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Abstract
Purpose The purpose of this study is to assess the effect of topical amitriptyline, ketamine, and lidocaine (AKL) on alleviation of neuropathic pain from radiation dermatitis and the feasibility of a randomized trial.
Materials and methods Eligible subjects had radiation dermatitis with dry or moist desquamation with neuropathic pain and were intolerant or allergic to standard intervention. AKL was applied to painful sites three times a day daily until 2 weeks post-radiotherapy. Subjects were monitored every 2–5 days during radiotherapy and at 2 and 6 weeks after completion of radiotherapy. The University of Washington Neuropathic Pain Scale was used to grade the neuropathic pain before and after use of the interventional gel. Compliance was assessed by asking subjects at each visit how frequently they were using the interventional gel.
Results Over a 14-month period, 16 subjects met eligibility criteria. Eighty-two percent of subjects used the AKL as directed. Five subjects (32%) reported fatigue, and three subjects (19%) reported site irritation from the interventional gel. AKL was shown to significantly reduce ($p<0.05$) pain intensity, sharpness, burning, sensitivity, itchiness, unpleasantness, deepness, and surfaceness levels on a short-term basis (i.e., between pre-treatment and 30 min post-treatment). AKL was shown to significantly reduce ($p<0.05$) burning levels on a long-term basis (i.e., between pre-treatment and 2 weeks post-treatment).
Conclusions AKL was a safe intervention to use with minimal toxicity and good compliance. It significantly reduced several measures of neuropathic pain associated with radiation dermatitis. A larger-scale study would require recruitment from multiple centers.

Keywords Radiation dermatitis · Neuropathic pain · Topical amitriptyline · Ketamine · Lidocaine

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Radiation dermatitis and pain

During radical radiotherapy, the basal layer of the epidermis is damaged as early as 10–14 days after dosing and is characterized by a reactive pink hue without epidermal changes, most likely mediated by cytokines and other inflammatory mediators [1]. Radical radiotherapy repeatedly impairs cell division within the basal layer, and so the degree to which a skin reaction develops is dependent on the survival of actively proliferating basal cells in the epidermis. Basal cell loss begins once the radiation dose reaches 20–25 Gy [2]. In practice, skin reactions tend to become visible 2–3 weeks after the start of a course of radical radiotherapy, reaching a peak at or within 1 week of completion of radiotherapy. The majority will have healed within 4 weeks of completion of treatment after epidermal regeneration occurs [2]. The first visible skin change is generalized erythema. When injury occurs to sebaceous glands and hair follicles, dry desquamation appears with epilation, scaling,

and dyspigmentation. Often, pruritis or pain is present [1]. Subsequently, after 4–5 weeks of radiotherapy or at least 40 Gy, focal loss of epidermis results in moist desquamation, which is characterized by epidermal breakage, fibrinous exudates, and often considerable pain [1].

Very few research studies have documented the incidence or addressed the management of pain associated with radiation dermatitis [2].

The incidence of moist desquamation can be as high as 21% in patients with breast cancer treated with intensity-modulated radiotherapy [4] and 38% in patients treated with conventional radiotherapy [6]. Patients with anal canal tumors or some types of gynecological tumors undergoing radiotherapy and chemotherapy experience close to 100% incidence of dermatitis, often grade 3 or 4 [1]. Standard treatment of painful radiation skin reactions such as moist desquamation consists of saline or tap water soaks, silver sulfadiazine, and oral analgesics [3]. However, sometimes the pain is not alleviated by these standard interventions, patients are allergic to sulfa, or patients are intolerant to oral analgesics such as opioids. Often, the pain associated with moist desquamation has neuropathic qualities, such as deep and intense burning, or is associated with hypersensitivity to non-painful stimuli (allodynia).

Use of topical amitriptyline, ketamine, and lidocaine for neuropathic pain

Inflammatory nerve injury produced by radiotherapy can produce alterations in the excitability of peripheral nerves and in the expression of neurotransmitters and ion channels in these nerves [8]. Peripheral pain signaling in conditions of pain related to inflammation involve the actions of a complex array of chemical mediators that interact to produce a more pronounced activation of the sensory nerve terminal[8], which may require multiple agents for optimal pain relief. Modulation of these peripheral processes with localized topical agents may be appropriate for relief of pain [8].

Controlled clinical trials have demonstrated efficacy for topical amitriptyline (2%), ketamine (1%) [9–13], and lidocaine (5%) [13] used separately in neuropathic pain. Lynch et al. [9, 10] demonstrated that use of a combination of topical amitriptyline and ketamine was safe and effective at reducing nonmalignant neuropathic pain. Minimal adverse events were reported, and there were no serious medication-related adverse events. Topical amitriptyline and ketamine block the same sodium and potassium channels and block excitatory mediators at peripheral sensory nerve endings [8]. Lidocaine (5%) is currently the only medication approved by the US Food and Drug Administration for the treatment of post-herpetic neuropathic pain. Lidocaine exerts its effect by blocking the sodium channels of peripheral sensory afferent neurons [11–13]. Only anecdotal experience exists for the use of all three products in combination topically.

Pleuronic lecithin organogel (PLO gel) is an organic base that is used as a vehicle for the absorption of medications through the skin. It contains no active ingredients or metals that can react with radiation therapy.

The purpose of this pilot study was to assess the compliance and baseline effects of the use of topical amitriptyline, ketamine, and lidocaine (AKL) combined in PLO gel on neuropathic pain related to radiation dermatitis and to determine the feasibility of a randomized trial assessing the efficacy of the gel.

Methods and materials

Study population

Subjects were eligible for the study if they were treated with radiotherapy and developed neuropathic pain from radiation dermatitis causing dry or moist desquamation. Eligible subjects were identified by physicians or radiotherapy nurses when they came for weekly review and management of their toxicity during radiation treatment or up to 2 weeks after the completion of radiotherapy. Subjects had to be at least 18 years of age and provide written informed consent. Eligible subjects were allergic to, intolerant of, or not receiving pain control from standard interventions. Standard interventions included education regarding skin care during radiotherapy treatment, topical application of water or saline gauze soaks and sulfadiazine cream to areas of moist and dry desquamation, and use of oral analgesics. Potential subjects scored their pain at the start of the standard interventions using the University of Washington Neuropathic Pain Score (UWNPS) [7] and then again 2 days after the start of the standard interventions. If there was no decrease in the pain score, then they were eligible for this trial. Subjects were ineligible if they were allergic to the interventional gel, were on MAO inhibitors, had other sources of neuropathic pain, had pain more severe than the radiation dermatitis, or had untreated major depression.

Study design

This was a prospective, single-arm, cohort pilot study carried out at the BC Cancer Agency, Vancouver Island Centre. The primary objectives of the study were to determine compliance and baseline effects of using the AKL gel for neuropathic pain from radiation dermatitis in

subjects resistant to standard treatment and to assess the potential accrual rate for a larger randomized study testing the efficacy of the AKL gel.

Study intervention

After consenting to the study, at the initial visit, 4 cc of interventional gel was applied to the most painful areas by study nursing staff. Subjects were instructed to use the AKL gel three times daily from the initial visit until 2 weeks after the completion of radiotherapy. Verbal and written instructions were given to the subjects. Subjects were asked to stop the AKL gel if they developed grade 3 toxicity or greater.

Study assessment

The UWNPS is a validated tool consisting of 10 questions grading various characteristics of the pain on an ordinal integer scale from 0 to 10 (except for question 8, which is scored on a nominal scale of 1, 2, or 3; Table 1), as reported by the subject. Subjects scored the UWNPS themselves with written instructions on each sheet. The Skin Toxicity Assessment Tool (STAT) (Fig. 1) is a validated tool assessing risk factors for radiation dermatitis, the type of radiation dermatitis, and patient-reported symptoms.

The STAT was chosen because it is a validated tool that integrated the objective skin assessments with the subjective symptoms of the patients including pain. It consisted of three components. The first component assessed patient and treatment characteristics, which may influence the incidence and severity of radiation dermatitis. The second component included objective scoring of the levels of skin reactions: intact skin, mild erythema, brisk erythema, dry desquamation, moist desquamation, exudates, and other as present or not present. The area of skin involvement was also to be recorded in this section. However, due to time constraints in this study, this was not done. Berthelet et al. [5] also reported poor compliance in reporting the dimensions for involved skin reactions due to time requirement. The third component documented patient-reported symptoms including pain from 0 to 10 on a Visual Analogue Scale, and presence of burning, pulling, or tenderness.

At baseline, a physician performed a history and physical exam to document dynamic allodynia or pinprick hyperalgesia. A radiotherapy nurse then assessed the subject using UWNPS and STAT [5]. Informed consent was then obtained if the subject was eligible.

The nurse or doctor graded the STAT at baseline, weekly during radiotherapy, and 2 and 6 weeks post-radiation. UWNPS score was assessed at baseline, 30 min after application of AKL gel, every 2–5 days during the course of radiotherapy, and at 2 and 6 weeks after the completion of radiotherapy. Toxicity from the AKL gel was assessed at baseline and every visit. Data collected included fatigue, skin irritation, rash other than desquamation, acne, allergic reaction, or any other side effect. At each visit, subjects were asked to report how often, i.e., how many days and how many times per day, they were using the gel to assess compliance. Six weeks after completion of radiotherapy, subjects were asked to assess how convenient the use of the AKL gel was using a Likert 5-point rating scale.

Table 1 University of washing neuropathic pain scale

Questions	Characteristics	Scale
1	Intensity	0–10
2	Sharpness	0–10
3	Burning	0–10
4	Dullness	0–10
5	Coldness	0–10
6	Sensitivity	0–10
7	Itchiness	0–10
8	Periodicity	1, 2, 3
9	Unpleasantness	0–10
10a	Deepness	0–10
10b	Surfaceness	0–10

All scales are ordinal (except question 8) and rated such that 0 represent no pain and 10 represents the most or highest level of the characteristic of pain. The scale for question 8 is nominal and ranked on an integer scale of 1, 2, and 3. A ranking of 1 represents "pain all of the time and occasional flare-ups some of the time"; a ranking of 2 represents "single type of pain all the time"; and a ranking of 3 represents "single type of pain only sometimes"

Statistical method

To investigate the potential efficacy of AKL gel, repeated measures data were analyzed using the Wilcoxon signed rank sum test for short term efficacy, i.e., comparison of pain scores pre-AKL intervention with 30-min post-AKL intervention and Friedman rank sum tests for long-term efficacy, i.e., comparison of pain scores pre-AKL intervention with scores during and 2-week post-radiotherapy treatment ending. Originally, the sample size of 20 was chosen to provide 90% confidence of determining a major complication, including sedation, with a 10% or higher probability of occurrence. Due to the prolonged time and economic restrictions, the study was closed after 17 were accrued.

This study was approved by the UBC/BC Cancer Agency Research Ethics Board.

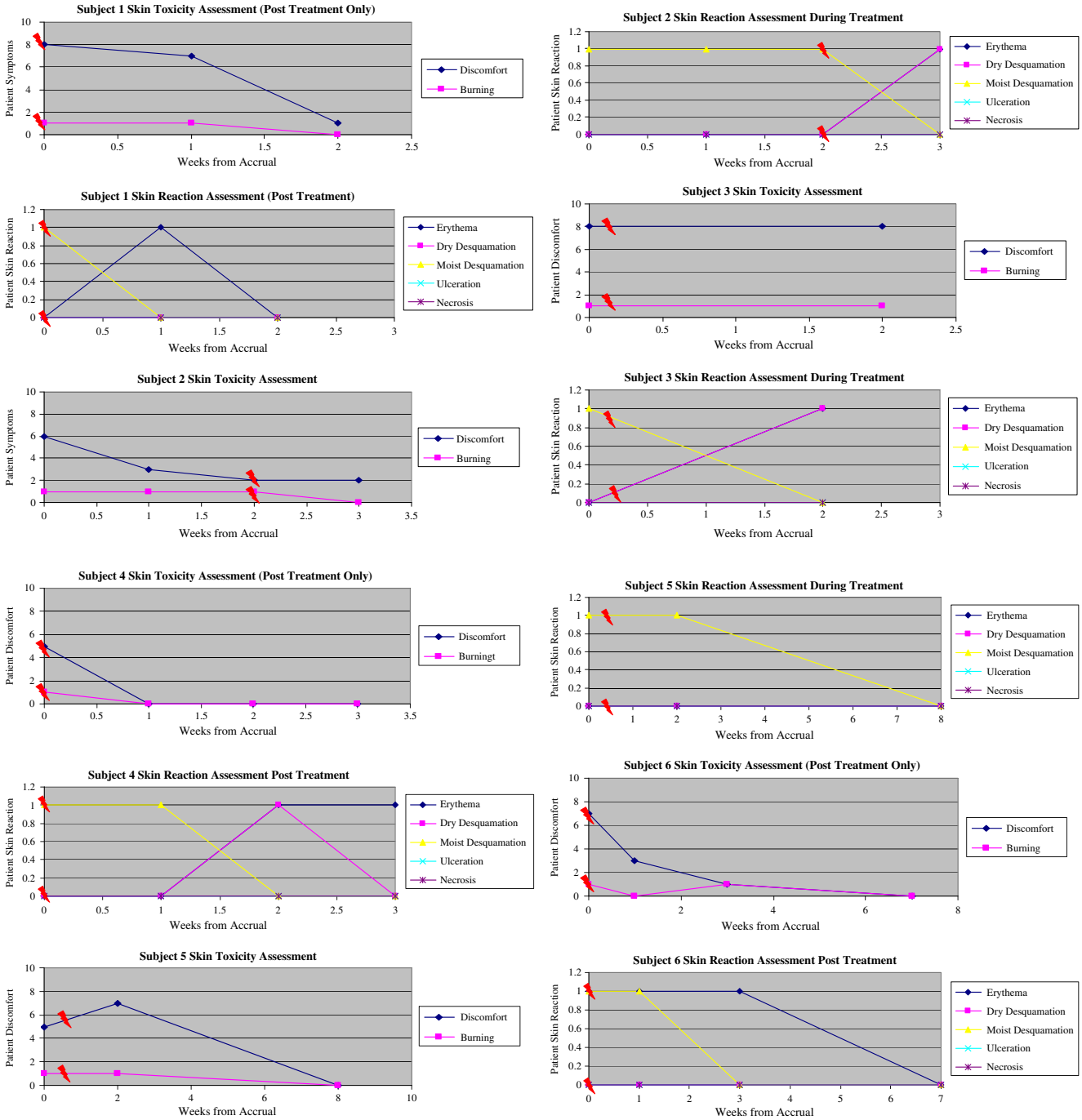

Fig. 1 Skin toxicity assessment tool results over time. *Red lightning bolts* represent the end of radiation therapy

Results

Participation rate

Seventeen subjects were identified as being potentially eligible over a 14-month period, and all of the subjects offered participation in the trial consented to enroll. Clinical characteristics of the study cohort are shown in Table 2. The most common sites of radiotherapy were breast, pelvis, and head and neck. One patient withdrew from the study early because her neuropathic skin reaction was thought to be caused by chemotherapy as the dermatitis resolved as soon as the chemotherapy was stopped.

Skin Toxicity Assessment Tool

Subjects 7, 8, and 17 showed resolution of burning, with an average decrease of 4 points in pain score, at

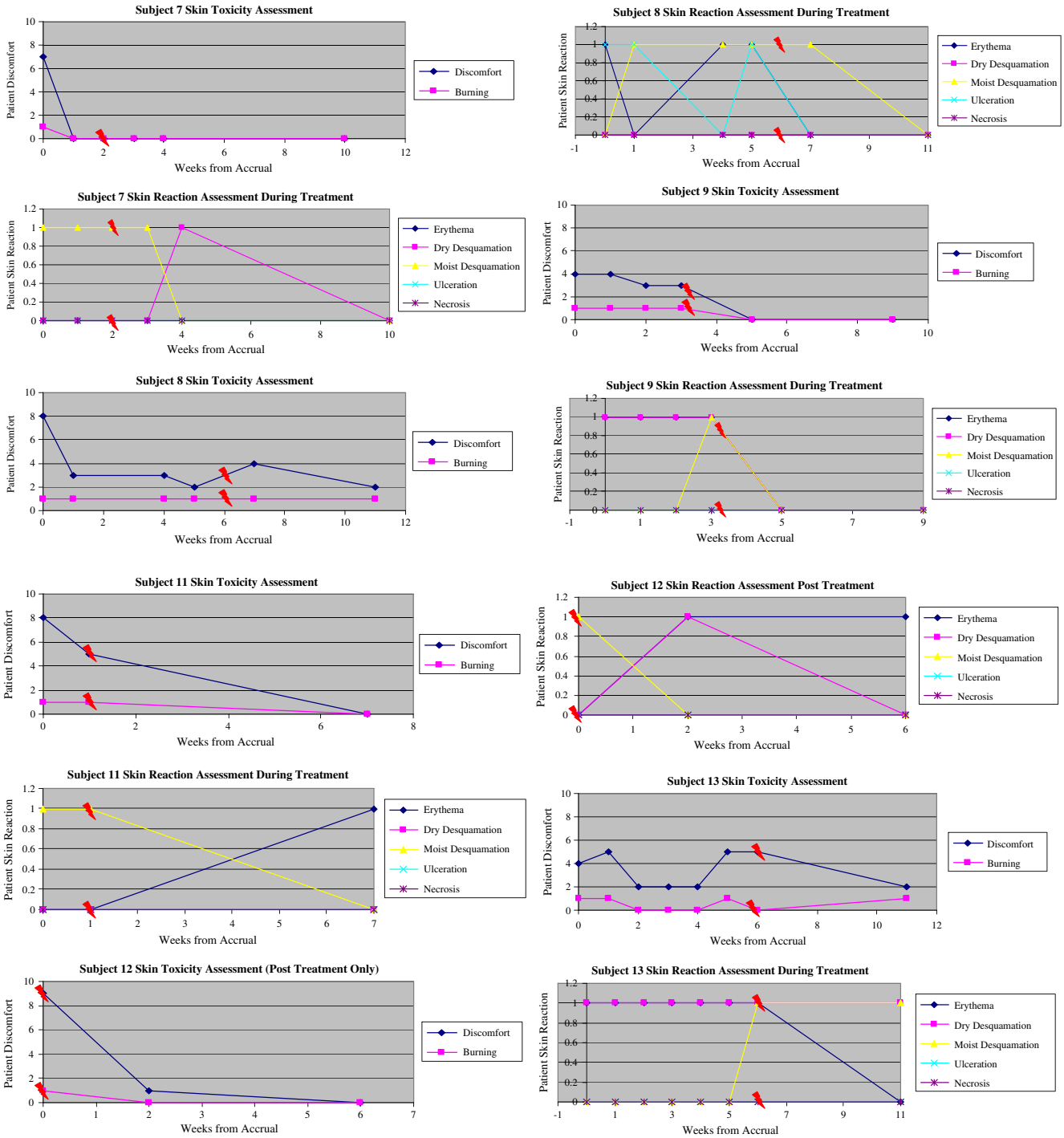

Fig. 1 (continued)

least 3 weeks before resolution of the moist desquamation (Fig. 1). Subject 8 developed progression of vulvar tumors, including ulcerating lesions, while on treatment and required larger doses of opioids and lidocaine spray, which may have confounded the results; however, she was the only subject on opioids. Most other subjects were intolerant to opioids. Subject 9 showed decrease in pain and burn score, 1 week before resolution of tumor necrosis. Subject 2 experienced a 4-point decrease in pain score 1 week prior to resolution of moist desquamation. Subject 13 initially experienced a decrease in pain score of 3 points during the dry desquamation phase of the dermatitis, with slight worsening of scores as the skin reaction progressed to moist desquamation, but eventual

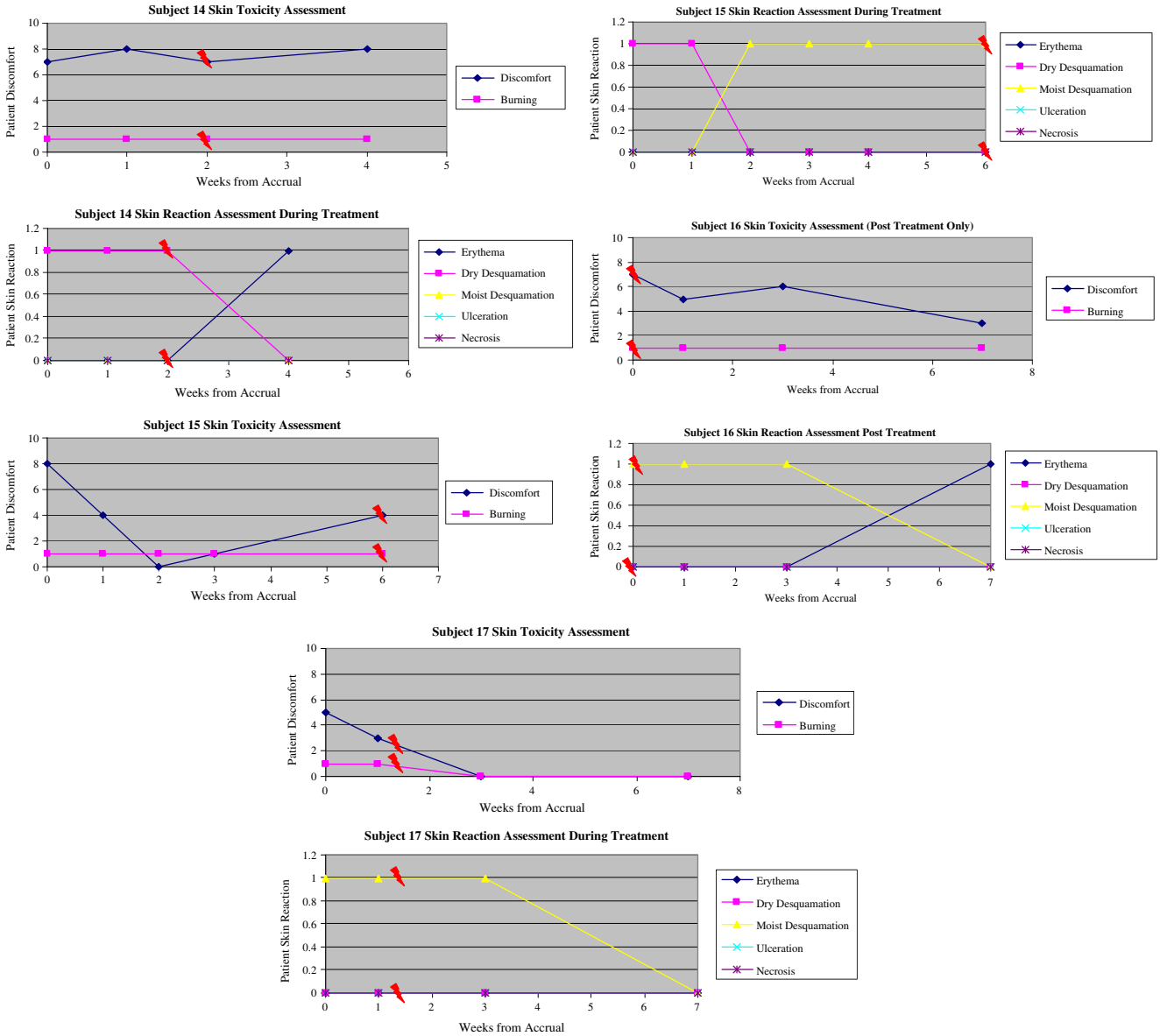

Fig. 1 (continued)

decrease in pain and burn score with the AKL gel despite persistence of moist desquamation.

Subjects 3 and 14 showed no change in pain or burning, and subject 6 showed a 1-point increase in burn with a decrease in pain score despite resolution of moist desquamation. Subjects 15 and 16 showed initial decrease in pain scores but then an increase in pain scores with persistent moist desquamation as radiotherapy progressed. Subject 16 eventually showed decrease in pain scores once radiotherapy stopped and moist desquamation resolved.

Risk factors for radiation dermatitis

One might expect increasing pain scores to correlate with increasing areas of involvement with moist desquamation as radiotherapy doses escalated. Subjects 15 and 16 may have demonstrated this. Unfortunately, the area of moist desquamation was not recorded. Extrinsic factors identified to influence risk and severity of radiation dermatitis include radiotherapy total dose, dose-fractionation regimen, use of electron beams, and beam energy [2].

All subjects were treated using six or 18 MV photon treatments. Two (13%) of the subjects received electron boost. Subject 6 received 12 MeV for five fractions to breast and continued to have pain score decrease throughout the radiation with application of AKL gel, despite the electron boost. However, subject 5 initially had a decrease in her pain score during radiotherapy with application of AKL gel, then increase in her pain

score 2 weeks post-radiotherapy, which could have been secondary to her 16 fractions of 6 MeV to her entire chest wall. She also had a 1-cm custom bolus over her chest wall.

There is evidence that chemotherapy can worsen the severity of radiation dermatitis [1, 2]. Nineteen percent (3/16) of the subjects were on concomitant chemotherapy. All had anal canal tumors. No doubt, those three subjects scored the highest baseline pain scores above 8/10 with moist desquamation. However, they also demonstrated marked decrease (on average from 9/10 to2/10) in pain scores with use of AKL gel as opposed to other subjects who were not on concurrent chemotherapy.

In general, moist areas of the body or those that contain skin folds, for example, under the breast, axilla, head and neck, perineum, and groins [2] are at risk for more severe skin reactions. As expected, eligible subjects in this study all had moist or dry desquamation in these primary sites as shown in Table 2. Eighty-eight percent of the subjects were female. This was expected given that 50% of all subjects were breast cancer subjects, and of the remaining sites, 25% were male and 75% female. Sex has not been identified in the literature as an intrinsic risk factor for radiation skin reactions. General skin condition, nutritional status, age, general health, comorbid disease, and ethnicity are among the other intrinsic factors identified [2]. All subjects in this study were white Caucasians that are typical of the demographics of this cancer center. They all were also radical cases that had to have an Eastern Cooperative Oncology Group performance status of 0–2 and were generally healthy. Average age was 60 years (Table 2).

Adverse events

Thirty-two percent (5/16) of subjects reported fatigue generally grade 1. Nineteen percent (3/16) of the subjects reported skin irritation grades 1–2, immediately after applying the interventional gel but were able to continue to use the gel.

Compliance

Eighty-two percent (13/16) reported using the AKL gel daily, three times a day as prescribed. One patient on oral amitriptyline 100–125 mg daily became so much sedated that she only applied it every other day one to two times a day and stopped at the end of radiotherapy. One subject had difficulty with wound dressing changes and could only apply twice a day but used it daily. One subject had such severe pain that she had to stop radiotherapy for 1 week and did not apply the gel during this time because it was ineffective. She subsequently developed progression of her cancer and tumor pain while on radiotherapy and died. She required oral narcotics and lidocaine spray.

Convenience rating

Average convenience rating for application of the interventional gel was 4 out of 5 on Likert convenience rating scale, i.e., most thought it was easy to apply.

University of Washington neuropathic pain scale efficacy

Subjects reported significant reductions in all scores of the UWNPS scale ($p<0.05$) except dullness and coldness of pain 30 min post-treatment compared to prior to treatment on the first day of application (Table 3). In the short term, pain initially characterized primarily as *background pain with flare-ups* (question 8 UWNPS) was later characterized in a similar manner or as a *single type of pain some of the time.*

Subjects reported significant reductions in the levels of burning ($p<0.05$), 2 weeks post-treatment compared to prior to treatment. Furthermore, there was a trend to reductions in pain scores between pre-treatment and 2 weeks post-treatment for pain intensity, sharpness, unpleasantness, and surfaceness (Fig. 2). In the long term, the AKL gel was not shown to significantly reduce the dullness, coldness, sensitivity, itchiness, or the deepness of pain. In the long term, pain initially characterized primarily as *background*

Table 2 Patient and treatment characteristics ($N=16$)

Variable	Number of subjects	Percent/range
Mean age, years	60	Range, 43–80
Sex: female/male	14:2	88:12%
Anatomic site of treatment		
Breast site	8	50%
Pelvic site (anus/gyne)	7	44%
Head and neck site	1	6%
Mean dose/fractionation Radiotherapy	50.6 Gy/27 fractions	Range, 44–70 Gy/20–35 fractions
Electron boost	2	13%
Concurrent chemotherapy	4	25%

Table 3 Median differences in UWNPS score questions at baseline and 30 min after AKL gel application: question 8 was not included in this analysis since the data were nominal

Question	Estimated median difference	Confidence Interval	*p* value
1. Intensity	2.99	(2.00, 3.99)	0.00067
2. Sharpness	4.00	(2.99, 5.49)	0.00161
3. Burning	3.99	(2.50, 4.99)	0.00106
4. Dullness	1.49	(−1.00, 2.00)	0.25080
5. Coldness	−0.50	(−2.49, 2.99)	0.78926
6. Sensitivity	3.49	(2.00, 5.50)	0.00884
7. Itchiness			
9. Unpleasantness	3.49	(2.49, 4.49)	0.00069
10a. Deepness	3.00	(1.99, 4.99)	0.00764
10b. Surfaceness	4.49	(3.00, 5.49)	0.00069

pain with flare-ups (question 8 UWNPS) was later characterized primarily as a *single type of pain some of the time.*

When looking at absolute values of pain reductions (Fig. 2), 12 of the 16 patients (75%) reported reductions of burning pain to levels below 4/10 (pain which can be ignored) from baseline during and up to 2 weeks post-radiation. It is often a goal for pain physicians to relieve pain to 4 and below to allow subjects to be more functional, sleep, or have more general well-being [19]. The range of absolute pain reductions fell from 0 to 9 points with 11/16 (69%) having 2 or more point reductions in pain.

Discussion

As expected in the normal sequence of radiation dermatitis skin healing, subjects with moist desquamation, over time, showed resolution to dry desquamation or erythema once radiotherapy ended. Subsequently, one would expect pain scores to decrease with this resolution sequence of healing over time. Within 4 weeks post-radiotherapy, most skin reactions will have completely healed [2].

All subjects showed decrease in all pain scores and burning presence once resolution of desquamation occurred, at 2 weeks post-radiotherapy. The sense of "burning" was significantly reduced with AKL gel intervention in the short and long term

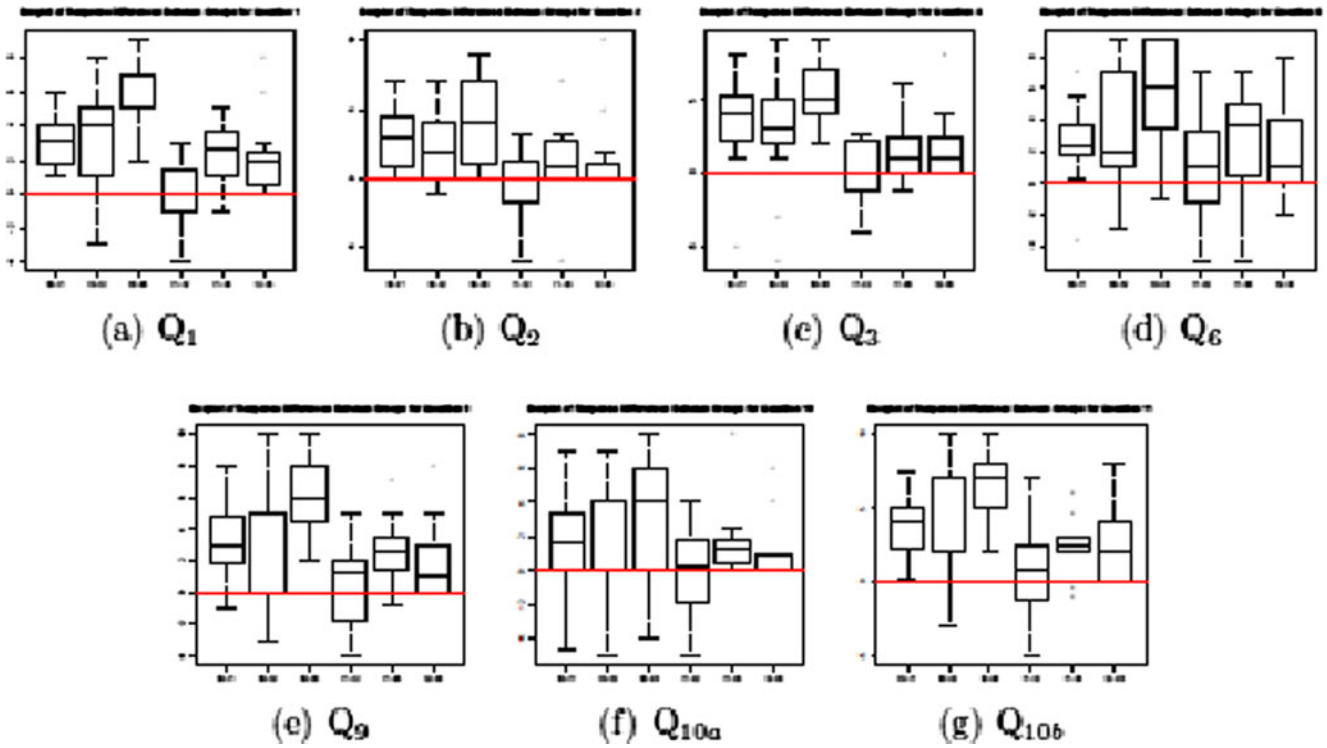

Fig. 2 Within each plot, six differences are illustrated. Specifically, *from left to right*, each box represents the difference between the distributions at time period pre-treatment and during, pre-treatment and 2 weeks post-treatment, pre-treatment and 6 weeks post-treatment, during and 2 weeks post-treatment, during and 6 weeks post-treatment, and 2 weeks post-treatment and 6 weeks post-treatment. For example, the second box from each plot shows the following differences between pre-treatment and 2 week post-treatment: the AKL gel was shown to significantly reduce ($p<0.05$) the levels of burning (box c, question 3), on a long-term basis (i.e., between pre-treatment and 2 weeks post-treatment). Furthermore, results suggest that there may be an improvement (i.e., pain reduction) between pre-treatment and 2 weeks post-treatment for pain intensity (box a, Q1), sharpness(box b, Q2), unpleasantness(box e,Q9), and surfaceness (box 6, Q10 b)

(i.e., 2 weeks post-radiotherapy). The general pain and "burn" scores for each subject are shown in Fig. 1. This figure also shows the evolution of the skin reactions over time

Berthelet et al. [5] validated the STAT to assess breast cancer patients with radiation dermatitis. It has not been validated in any other sites to date. Fifty percent of the subjects in this trial were from breast sites.

The eligibility criteria to use AKL gel as an adjunctive treatment (when standard intervention failed or was not appropriate) may have slowed accrual but showed that, even in this treatment-resistant population, the AKL gel can be effective. With the low toxicity, moderate compliance and high convenience rating results in this study with AKL gel, future randomized studies of AKL gel compared to standard intervention should be undertaken.

Data from this study showed that the AKL gel may be effective in alleviating pain in subjects who are resistant to standard treatments such as opioids. Jensen et al. [7] failed to demonstrate significant reduction in burning, pain when comparing opioids to placebo in their validation of the neuropathic pain score over 6 weeks. AKL gel did significantly reduce burning pain in the short and long term in this study. Opioids are known to have inhibitory influences on sensory nerve endings [8], which would explain their well-known efficacy of reducing overall pain. Burning pain, however, is influenced more by excitatory influences at the nerve ending with the release of chemical mediators or stimulation of ion channels that are blocked by drugs such as amitriptyline, ketaime, and lidocaine [8]. This may explain the efficacy of AKL gels to reduce burning pain. Similar to this trial, Jensen et al. [7] also failed to demonstrate significant reduction in cold, itchy, or sensitive pain with opioids compared to placebo. The mechanisms for these qualities of pain need to be further researched.

A recent systematic review of the literature [14] identified trials that investigated products for the prophylaxis and management of acute radiation dermatitis. Thirty-nine studies met the pre-defined criteria (published abstracts of clinical trials between 2000 and 2008 that reported a method of grading skin reaction and had statistically evaluated the skin reaction as primary or secondary outcome to the intervention). Thirty-three were categorized as prophylactic trials and six as management trials. Only 13 of the trials specifically addressed the relief of pain from radiation dermatitis. Heggie et al. [15] demonstrated significant pain reduction (p=0.03) with prophylactic aqueous cream compared to aloe vera cream. Pommier et al. [16] demonstrated that prophylactic calendula ointment compared to biafine cream resulted in lower average maximum pain scores (p=0.03). Vavassis et al. [17] demonstrated in a management clinical trial of radiation dermatitis that, subjectively, silver-leaf dressing was superior for 67% patients compared to silver sulfadiazine. Mak et al. [18] demonstrated in a randomized controlled management trial that gentian violet compared to moist hydrocolloid dressing resulted in significantly lower severity of pain (p=0.012) and frequency of pain (p=0.03). However, gentian violet treatment received significantly lower ratings for dressing comfort and aesthetic acceptance. Most of the trials in the systematic review addressed only overall pain on a visual analogue score or in a quality of life inventory without addressing qualities of pain. None of the trials distinguished management of type of pain, namely, neuropathic pain. The systematic review of literature [14] concluded that evidence is insufficient to support the use of one particular agent for the prevention and management of acute radiation-induced dermatitis.

The primary goal of this pilot study was to assess the feasibility from participation rate for future larger randomized study to assess the efficacy of AKL gel for neuropathic pain caused by radiation dermatitis. This study showed that in a cancer center, in which 3,500 patients are seen with a new diagnosis of cancer on a yearly basis, 16 subjects were accrued during the 14-month study time period. To achieve a rate for a good accrual to a larger randomized study, multiple centers would have to be included.

Conclusion

This pilot study of pain management using AKL gel for radiation dermatitis warrants further investigation in a phase III multicenter randomized controlled trial. With future phase III randomized controlled trials, evidence-based guidelines can be developed with the hope of standardizing the approach across centers and improving the prevention and management of pain due to radiation dermatitis.

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