Assessing the Effectiveness of Dead Sea Products as Prophylactic Agents for Acute Radiochemotherapy-Induced Skin and Mucosal Toxicity in Patients with Head and Neck Cancers: A Phase 2 study

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Abstract

Background: Mucositis and dermatitis are frequently encountered in patients treated with radiochemotherapy. Dead Sea products that contain minerals and other properties have proven effective in treating various skin diseases.

Objectives: To evaluate the effectiveness of Dead Sea products in reducing acute radiochemotherapy-induced side effects in patients with head and neck cancer.

Methods: In this phase 2 study we compared the outcomes in 24 treated patients and 30 conventionally treated patients matched for age, tumor site, and type of treatment. The Dead Sea products comprised a mouthwash solution (Lenom®) and a skin cream (Solaris®) used three times daily for 1 week before, during, and up to 2 weeks after completion of radiotherapy. Mucositis and dermatitis were evaluated using common toxicity criteria.

Results: Thirteen treated patients (54%) had grade 1-2 and none had 3-4 mucositis, while 17 controls (57%) had grade 1-2 and 4 (13%) had grade 3-4 mucositis. Thirteen treated patients (54%) had grade 1-2 dermatitis; there was no instance of grade 3-4 dermatitis, while 11 patients in the control group (37%) had grade 1-2 and 5 (17%) had grade 3-4 dermatitis. More patients in the control arm needed a break than did patients in the treatment arm ($P = 0.034$).

Conclusions: The two Dead Sea products tested decreased skin and mucosal toxicity in head and neck cancer patients receiving radiochemotherapy.

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Radiation therapy alone or combined with chemotherapy, given as a primary treatment or postoperatively, has a high cure rate in patients with localized head and neck cancer. The associated side effects of radiation therapy include injury to the skin and mucositis [1,2]. The inflammatory process ranges from mild redness to severe ulceration and can lead to local pain, the inability to tolerate food or fluid, and the development of opportunistic infections. Interruption in the administration of treatment is quite often indicated, and this delay may compromise the therapeutic efficacy [3].

Multiple approaches for minimizing these debilitating complications have been evaluated in a number of clinical studies [4-9]. Spielberger et al. [7] reported that palifermin, a human keratinocyte growth factor, is effective in reducing grade IV mucositis in patients undergoing stem cell transplantation. El-Sayed and co-workers [8] evaluated the ability of an antimicrobial lozenge to decrease mucositis in head and neck cancer patients but found that approach to be ineffective. Szumacher et al. [9] failed to show any usefulness of the cream Biafine® to treat skin irritation in breast cancer patients. Other studies showed no clear-cut benefit in treating radiation-induced damage to the skin or mucosa

Minerals and muds from the Dead Sea (balneotherapy) are effective in treating various dermatological conditions, such as psoriasis and atopic dermatitis [10,11]. The mechanisms have not been fully elucidated and probably involve chemical and immunomodulatory effects. The purpose of the present study was to examine the effectiveness of two Dead Sea products, a moisturizing cream (Solaris®) and a mouthwash solution (Lenom®), in minimizing skin and mucosal toxicity associated with radiochemotherapy to head and neck tumors .

Patients and Methods

Patients

Twenty-four consecutive patients with head and neck tumors (oral cavity, oropharynx, nasopharynx, larynx, salivary glands, etc.) were randomly recruited for this study and gave their signed consent to undergo treatment with Dead Sea products. They were matched by age, tumor site and type of treatment to 30 patients assigned to conventional measures who served as the control group. The characteristics of the patients in both groups are presented in Table 1. The study was approved by the local ethics committee.

Radiation therapy

The irradiation was delivered using 6 MV photon and 6-12 MeV electron beams. The irradiation field encompassed the tumor site and the regional lymph nodes when indicated. The total irradiation dose ranged from 56 to 70 Gy (mean 65 Gy) in the treatment group and from 50 to 75 Gy (mean 64 Gy) in the controls. The average (median) duration of treatment was 7.14 weeks (range 5–12, mean 7 weeks) in the control group, and 7.48 weeks (range 6–11, mean 7 weeks) in the treated group. The dose per fraction in all patients was 1.8–2.0 Gy, given once daily five times a week [Table 1].

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Table 1. Patient characteristics and treatment parameters

	Control arm	Treatment arm
No. of patients	30	24
Age (yrs), median (range)	60.4 (22–83)	66.1 (31–86)
Tumor site		
Oral cavity	5	5
Oropharynx	3	1
Nasopharynx	1	4
Larynx	13	9
Salivary glands	3	4
Others	3	1
Radiation therapy		
Primary treatment	16	10
Postoperative treatment	14	14
Total dose (Gy), median (range)	64 (50–75)	65 (56–70)
Dose/fraction (Gy)	1.8–2.0	1.8–2.0
Chemotherapy	9	12
Radiation therapy (wks) (range)	7.14 (5–12)	7.48 (6–11)
Mean	7	7
Chemotherapy (peri-irradiation)	9	12
Average cycles (range)	6.4 (3–10)	9.6 (4–17)
Mean cycles	6	9

Chemotherapy

Chemotherapy, consisting of carboplatin (AUC-2) or cisplatin (40 mg/m^2) once weekly, was started 1–2 weeks prior to the initiation of radiation therapy and stopped 1–2 weeks after completion of the course of radiation. Chemotherapy was administered to 12 patients treated with Dead Sea products who received a mean of nine courses and to 9 patients in the control group who received a mean of six courses [Table 1].

The Dead Sea products

A mouthwash solution (Lenom®) and a moisturizing cream (Solaris®) were the two Dead Sea products used in this study. The treated patients were requested to use both the mouthwash and the skin cream three times daily starting 1 week before, during, and up to 2 weeks after the completion of radiotherapy. The controls were treated with baking soda mixed with water or salty water for mucositis, and allovera or Biafine® creams for skin irritation.

The active ingredients in the hydrating cream are: isopropyl, witch hazel extract (*Hamamelis virginiana*), carrot seed oil (*Daucus carota-sativa*), jojoba seed oil (*Simmondsia chinensis*), chamomile extract (*Anthemis nobilis*), rosemary oil (*Rosmarinus officinalis*), lavender oil (*Lavandula angustifolia*), sea salt, *Aloe barbadensis* gel, Madonna lily (*Lilium candidum*), tocopherol, lecithin, isopropyl myristate, Dead Sea salt, and thyme oil (*Thymus vulgaris*).

The active ingredients in the mouthwash are: Dead Sea salt, chamomile extract (*Anthemis nobilis*), thyme oil (*Thymus vulgaris*), lemon peel oil (*Citrus medica limonum*), Clary sage oil (*Salvia sclarea*) and peppermint oil (*Salvia sclare*)

Toxicity criteria

All patients were followed for toxicity evaluation once a week for up to 3 weeks following completion of irradiation and 1–2 weeks after termination of chemotherapy. The toxicity grading was based on common toxicity criteria version 2.0 (12) [Table 2]. The overall treatment time was documented in all patients and treatment breaks of more than 3 days due to acute toxicity were recorded.

Statistical analysis

The Fisher exact test was used to compare between the two groups.

Results

Three of the 27 patients in the treatment arm were excluded: 2 because of progressive disease at the start of the treatment and 1 due to early termination of treatment (the patient's health management organization covered the radiotherapy costs at another medical center).

Of the 24 remaining Dead Sea products-treated patients, 13 (54%) developed grade I-II mucositis, none had grade III-IV [Table 3]. Thirteen (54%) had grade I-II dermatitis, and none had grade III-IV. None of these patients reported any discomfort attributed to Dead Sea products.

Seventeen of the 30 controls (57%) had grade I-II mucositis and 4 (13%) had grade III-IV mucositis. Eleven controls (37%) had grade I-II dermatitis and 5 (17%) had grade III-IV dermatitis. None of these differences between the groups reached statistical significance [Table 3].

As expected, the therapeutic side effects were more frequent among the patients who received chemo- and radiotherapy than those who underwent radiotherapy alone. Chemoradiotherapy resulted in side effects in all 9 patients in the control group and in 9 of 12 patients in the study group.

Three of the patients treated with Dead Sea products (12.5%)

Table 2. Common toxicity criteria (version 2.0): acute radiation morbidity criteria

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
Radiation-induced mucositis	Erythema of the mucosa	Patchy pseudo-membranous reaction	Confluent pseudomembranous reaction (contiguous patches generally > 1.5 cm in diameter) fibrinous mucositis; may include severe pain requiring narcotic	Necrosis or deep ulceration
Radiation-induced dermatitis	Faint erythema or dry desquamation	Moderate to brisk erythema, patchy moist desquamation confined to skin folds and creases; moderate edema	Confluent, moist desquamation > 1.5 cm diameter other than skin folds; pitting edema	Skin necrosis or ulceration of full-thickness dermis

Table 3. Comparison between radiochemotherapy-induced acute toxicity in the treatment and control arms

	Control arm (n=30)	Treatment arm (n=24)	*P**
Mucositis			
Grade I	11	9	
Grade II	6	4	
Total	17 (57%)	13 (54%)	1.000
Grade III	3	0	
Grade IV	1	0	
Total	4 (13%)	0	0.120
Dermatitis			
Grade I	4	13	
Grade II	7	0	
Total	11 (37%)	13 (54%)	0.272
Grade III	4	0	
Grade IV	1	0	
Total	5 (17%)	0	0.058
Treatment break (> 3 days)			
No. of patients (%)	12 (40%)	3 (12.5%)	0.034
Mean duration (days) (range)	15.1 (5–33)	15.0 (3–21)	

* Fisher's exact test

required a treatment break (> 3 days) and the mean duration of their breaks was 15 days (range 3–21). Twelve controls (40%) required a treatment break, mean duration 15.1 days (range 3–31) [Table 3]. A comparison between the two groups (3/24 versus 12/30) revealed that this difference was statistically significant ($P = 0.034$).

Discussion

Balneotherapy of the Dead Sea has proven effective in treating various skin disorders, such as psoriasis and atopic dermatitis, although the mechanism is yet undetermined. Matz et al. [10] claimed that balneotherapy evokes chemical, thermal, mechanical and immunomodulary effects. Halevy and colleagues [11] conducted a double-blind controlled study to evaluate the role of trace elements in patients treated with Dead Sea salt. The control group was treated with common table salt. The results of these investigations showed that Dead Sea salt significantly decreased the mean serum level of manganese and lithium in the treated group as a whole and that the change was prominent in the responding patients. Dead Sea products are commercially available in Israel as well as in other countries. Among the non-medical products are the popular cream Solaris® and a mouthwash solution (Lenom®), both claimed by the manufacturer to have a radiation-protection effect. Several *in vivo* and clinical studies from countries of the former Soviet Union have demonstrated the safety and possible effectiveness of salts and minerals in treating radiation-induced toxicity. It has been suggested that absorption through the skin or mucosa of trace elements present in Dead Sea water may affect the immune system. The fact that sulfur spa baths have been used successfully in immunomediated afflictions such as contact dermatitis, psoriasis and atopic dermatitis has led to the speculation that sulfurous mineral waters could play a role in immunoregulation of the skin. The benefit resulting from the application of mineral waters to the skin could be related to the modifications of functional subsets of T lymphocytes, the increased or decreased synthesis and/or release of different cytokines in the skin, and elution of pro-inflammatory mediators. The Dead Sea has a salt content of about 320 g/L, of which potassium chloride, magnesium chloride, calcium chloride and sodium chloride (with their respective bromides) are the major components, comprising 98% of the salts on a dry weight basis.

The average mineral salt content is as follows: sodium 1.70%, potassium 1.30%, calcium 20.40%, magnesium 4.90%, chloride 7.80%, sulfate 7.80%, and carbonate 23.20%. Compared to an ocean, the Dead Sea is richer in its proportions of calcium, magnesium, potassium and bromide, and lower in its proportions of sodium, sulfate and carbonate. The salts and minerals are present in a total concentration of 33%, in contrast to a total concentration of only 3% in the ocean. Some thermal water is able to induce a reduction in degranulation of cutaneous basophils in atopic patients. Other thermal water seems to exhibit a suppressive activity on the cytokine (production of Langerhans cells) and an irreversible decrease of ATPase-positive epidermal Langerhans cells following treatment with salt from the Dead Sea in both murine ear skin and in humans.

In the current study, we evaluated the effects on patients with head and neck cancer who were receiving radiochemotherapy. The acute dermatitis rate was 54% in both the Dead Sea product-treated and untreated group; no grade III-IV toxicity was detected in the treated group but was present in five non-treated patients ($P = 0.058$). Radiochemotherapy-related mucositis developed in 70% of the non-treated patients and in 54% of the treated group, with grade III-IV toxicity appearing in 4/30 non-treated and 0/24 treated patients (P = NS). The difference in the results between the two evaluated therapeutic side effects might stem, at least partially, from patient compliance: gargling with a mouthwash is not as convenient as applying skin cream.

In addition to acute toxicity to the skin and mucosa, we evaluated the number of patients who needed a break from the treatment. Only 3 of the 24 patients in the treatment arm had a treatment break while 12 of the 30 non-treated patients needed to interrupt therapy ($P = 0.034$). Thus, all three parameters (dermatitis, mucositis, treatment break) that were evaluated in this study favored the use of Dead Sea products in patients undergoing radiochemotherapy. Since our armamentarium to treat mucositis [4,5] and dermatitis is limited, such an approach should be evaluated further in prospective randomized phase 3 studies.

In conclusion, the two Dead Sea products that we tested – the moisturizing cream Solaris® and a mouthwash solution Lenom® – decreased skin and mucosal toxicity in patients with head and neck cancer receiving radiochemotherapy. Additional prospective randomized studies are warranted.

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