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Clinical report

A phase I trial of topical topitriol (calcitriol, 1,25-dihydroxyvitamin D_3) to prevent chemotherapy-induced alopecia

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This study evaluated the toxicity and efficacy of topical topitriol (calcitriol, 1,25-dihydroxyvitamin D_3) to prevent chemotherapy-induced alopecia (CIA). Patients with breast cancer scheduled to receive FAC chemotherapy (5-fluorouracil, adriamycin and cyclophosphamide) were eligible for the study. Initially, the first six patients were randomized in a double-blind fashion to have received topitriol or placebo with all subsequent patients being treated with topitriol. Topitriol cream (0.0025 or 0.005%; 25 and 50 μg/g concentration) was administered topically twice a day. Three different doses and schedules of administration were evaluated including: 500 and 1000 μg daily for 7 days prior to chemotherapy, and 2000 μg daily for 5 days prior and 5 days post-chemotherapy. Fourteen patients were treated (12 with topitriol and two with placebo) at three different dose levels. All patients developed grade 2 alopecia between day 20 and 30 after chemotherapy, demonstrating the lack of efficacy of topical topitriol on this schedule of administration to prevent CIA. Eight patients exposed to topitriol developed a toxic maculopapular dermatitis in areas exposed to the drug. In conclusion, topical topitriol at the doses and schedules evaluated in this trial was ineffective to prevent CIA and induced a local dermatitis in areas exposed to the drug.

Key words: Chemotherapy-induced alopecia, phase I Trial, vitamin D_3.

Introduction

Alopecia is one of the most distressing side-effects of anti-cancer chemotherapy.[1,2] More than 80% of patients who receive chemotherapy for breast cancer consider alopecia the most burdensome aspect of treatment and some patients refuse systemic chemo-therapy to avoid this side effect.[1,2] Various methods investigated to date to prevent chemotherapy-induced alopecia (CIA) have been cumbersome and of questionable efficacy.[3,4] Recently, the vitamin D_3 derivative 1,25-dihydroxyvitamin D_3 (topitriol) administered topically at a dose of 0.2 μg over the head and neck prevented hair loss induced in neonatal Sprague-Dawley rats by treatment with a variety of chemotherapeutic agents including etoposide, cyclophosphamide and a combination of adriamycin plus cyclophosphamide.[5] Topical topitriol has been previously evaluated in normal volunteers and doses up to 1000 μg applied to normal skin once daily for 28 days are tolerable with no clinical relevant effect on calcium metabolism. The impressive activity of topitriol in animal models to abrogate CIA together with its tolerability by topical administration in humans prompted us to initiate this dose-escalating clinical trial to assess the efficacy and safety of topical topitriol to prevent CIA.

Material and methods

Patients with stage II–IV breast cancer scheduled to receive CAF chemotherapy (cyclophosphamide 500 mg/m^2, adriamycin 50 mg/m^2 and 5-fluorouracil 500 mg/m^2 on day 1 every 21 days) for adjuvant therapy or therapy for advanced disease were eligible for the study. Patients with pre-existing scalp conditions that produced alopecia or inflammation that may have limited the applicability of topical topitriol were excluded from the study. Patients that had had previous CIA were required to have a full hair

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regrowth with normal texture and consistency before entry into study. Other exclusion criteria included known hypersensitivity to topitriol or related compounds, pre-existing hypercalcemia and hypercalciuria, or significant liver or renal dysfunction. Patients had to provide written informed consent according to institution and federal regulations. Topitriol (calcitriol; Hoffman-La Roche, Nutley, NJ) was provided in a cream containing 0.0025 or 0.005% of topitriol (25 and 50 μg/g, respectively) and was administered topically on the scalp twice a day. The drug was applied by a nurse during the first 5 days of treatment and by the patient or a family member afterwards. The cream was rubbed over the entire scalp and was maintained without washing for 8 h. Three different doses and schedules of administration were evaluated: 10 g of 0.0025% cream (500 μg of topitriol) per day for 7 days prior to chemotherapy, 20 g of 0.0025% cream (1000 μg of topitriol) per day for 7 days prior to chemotherapy, and 20 g of 0.0050% cream (2000 μg of topitriol) per day 5 days prior and post-chemotherapy. Initially patients were randomized to receive topitriol or vehicle in a 2:1 test:control fashion. After entering six patients on study, the protocol was amended so that all patients received topitriol. Alopecia was graded according to the NCI-CTC. Efficacy was evaluated prior to each course by means of clinical assessment and comparison of serial photographs. Treatment was continued until the appearance of grade 2 alopecia, adverse effects potentially attributable to the study drug or for a maximum of three courses. Patients' serum calcium and urinary calcium excretion were monitored during the study.

Results

Fourteen patients were included in the study; all of them were evaluable. There were 13 females and one male with a median age of 52 years (range: 33-75). Eight of them were receiving palliative chemotherapy for stage IV disease and six adjuvant chemotherapy for locoregional disease. Table 1 displays a summary of the results of this study. Initially, six patients were entered and randomized, four to receive topitriol and two to receive vehicle at two different dose levels (500 and 1000 μg, respectively) 7 days prior to chemotherapy. All them developed grade 2 alopecia between days 20 and 30 post-chemotherapy. In three patients, topitriol treatment resulted in the appearance of a mild maculopapular pruritic rash involving the scalp and surrounding skin exposed to topitriol. Four additional patients were treated at the 1000 μg dose level and all developed grade 2 hair loss 20-30 days after the first course of chemotherapy. Because of lack of activity in the previous dose levels, the schedule of administration was modified to expand the period of drug administration to a total of 10 days (5 days prior and 5 days post-chemotherapy) and the formulation was changed to double the concentration of topitriol (50 μg/g) to administer 2000 μg per day. Four patients were treated on this schedule and none of them preserved their hair, indicating the absolute lack of efficacy of topical topitriol to prevent CIA with these schedules and formulations. Five of the last eight patients also presented a pruritic irritative dermatitis in areas exposed to the drug that limited further dose escalation. None of the patients enrolled on this study presented systemic toxic effects potentially attributable to the study drug. Specifically, plasmatic and urinary calcium levels remained within normal limits during the study period.

Discussion

This study evaluated the feasibility and efficacy of the vitamin D derivative compound, topitriol, to prevent the development of CIA in patients with breast cancer receiving anthracycline-containing chemotherapy. The design and conduct of this trial had a strong scientific rationale based on observations made in animal models.[5] Administered topically at a dose of 0.2 μg, topitriol protected neonatal Sprague-Dawley rats from alopecia induced by etoposide, cytoxan and the combination of adriamycin plus cytoxan.[5] These results are in contrast with the observations made in

Table 1. Summary of study results

Dose level (μg)	Schedule	No. of patients	Topitriol/placebo	Alopecia	Dermatitis
500	7 days pre	3	2/1	2/1	2/0
1000	7 days pre	7	6/1	6/1	4/0
2000	5 days pre and post	4	4/0	4	2

the present study in which topitriol did not have any noticeable activity with regard to alopecia protection in human beings.

The protective effect of topitriol from CIA has been investigated in other animal models using adolescent C57BL/6 mice as opposed to neonatal rats.[6] This model has been considered to have several advantages over the rat model in this respect.[7] The mouse model studies the effects of chemotherapy on exactly defined, homogeneous, fully pigmented and mature hair follicles, which are the major targets of chemotherapy damage, as opposed to the more heterogeneous and immature type of follicle in the neonatal rat model.[6,7] Additionally, this models mimics strikingly well the histopathological changes that occur with CIA in humans.[6,7] In this model, topitriol did not prevent the development of total alopecia but, interestingly, it significantly reduced the time to hair regrowth in treated animals as compared to controls.[6] This effect is postulated to be mediated through an acceleration in the process of hair follicle repair.[6] Unfortunately, this clinical trial was designed to evaluate the activity of topitriol to prevent CIA and not to assess the rate of regrowth, making it impossible to draw any conclusion about the potential of this agent to accelerate the recovery from CIA.

Topitriol was associated with the appearance of a dermatitis in the area exposed to the agent. This effect was observed at all dose levels and limited further evaluation of topical topitriol in this setting. These data are dissimilar to observations made in normal volunteers in which doses up to 1000 μg for 28 consecutive days were not associated with cutaneous toxicity. The higher doses utilized in this trial are probably responsible for the appearance of cutaneous toxicity; however, the potential of chemotherapy to induce topitriol cutaneous toxicity could have been another factor.

In conclusion, the results of this study indicate that topitriol, at these doses, formulation and schedule of administration, produced intolerable cutaneous toxicity and was ineffective to protect patients with breast cancer treated with anthracycline-containing chemotherapy from CIA. Based on more recent and adequate animal data, additional studies should be conducted to define non-toxic formulations and to explore, in properly designed clinical trials, the potential of topitriol to accelerate recovery from CIA.

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