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Research Article

Treatment of Skin Lesions Induced by Cetuximab Therapy with an AcidOxidizing Solution Containing Hypochlorous Acid

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Abstract

Colorectal cancer and Head and Neck Squamous Cell Carcinoma (HNSCC) are two of the most common cancers. Patients are usually treated with Cetuximab, a chimeric monoclonal IgG1 antibody known to cause adverse skin reactions. **Objectives:** The aim of this observational study was to evaluate the use of a novel hypochlorous acid-oxidizing solution (AOS) (Nexodyn-APR Applied Pharma Research [APR] SA) in the prevention and/or treatment of skin lesion in such patients. **Method:** Patient treatment consisted of: morning - moisturising with base cream; noon - spray application of AOS on face, chest and arms, evening - moisturising with base cream. Skin was assessed at baseline, at the interim visit, and at the final visit. **Results:** Fifteen patients with chest/chest and arm/arm lesions were included. Lesions regressed by at least 90% in 93% of patients, pruritus and inflammation decreased in all, wound bed preparation and quality of life scores improved. **Conclusion:** The use of AOS in cetuximab-induced skin lesions improved the side effects of chemotherapy and allowed all patients to complete it successfully. However, this is an observational study with a limited number of patients who received only the first round of cetuximab treatment and further studies are needed to confirm these results.

Keywords: Cetuximab-Induced skin reaction; Acid-Oxidizing solution; Cancer supportive care; Skin lesion, Pruritus, Inflammation, Quality of Life

Background

According to estimates by the 2020 Global Cancer Observatory (GLOBOCAN) colorectal cancer is the third most common cancer world-wide, accounting for 10% of world-wide cancer deaths, while head and neck carcinomas represent approximately 5% of all neoplasms [1]. Epidermal growth factor receptor inhibitors (EGFRi) are the first line treatment for these cancers. Cetuximab (Merck KGaA) is a recombinant chimeric human/mouse IgG1 monoclonal antibody that targets the epidermal growth factor receptor [2]. The most common adverse reactions

associated with the use of this drug involve the skin [3]. Although the physio-pathological mechanism underlying these skin manifestations has not been fully elucidated, binding of inhibitors, such as cetuximab, to the EGFR is thought to trigger inflammatory processes and apoptotic tissue damage [4]. In addition, because the barrier function of skin cells is disrupted, the skin becomes more susceptible to bacterial infections and the development of biofilms [5].

Skin Reactions Include

- Acneiform (papulopustular) rash that usually develops on the upper trunk and face 1-2 weeks after starting the treatment
- Xerosis (up to 35% of patients)
- Pruritus (12-16% of patients)
- Skin infections

Depending on the severity, acneiform rash may lead to interruption or discontinuation of treatment [6]. Approximately 10% of patients develop severe skin reactions (>grade 2) that result in suspension and/or interruption of chemotherapy, 50% of patients worsen during treatment, and 40% suffer from discomfort. Furthermore, severe adverse skin reactions can affect the efficacy of drug treatment [7]. Prevention and/or rapid intervention are critical as skin reaction severity, response rate and survival may be correlated. Phase II trials with different tumors, have shown that patients who developed an acneiform rash survived longer than those who did not, suggesting that the rash may be a relevant surrogate for the clinical efficacy of cetuximab [8].

Current Treatments

Because few controlled trials have been performed and there are no convincing data for any particular treatment, there is no therapeutic protocol for the treatment of adverse skin manifestations of cetuximab. The Common Terminology Criteria for Adverse Events Guidelines (v4.0) and the National Comprehensive Cancer Network (NCCN) recommend treatment based on the physio-pathological mechanisms, such as topical moisturisers, emollients and antiseptics/steroids for grade 1 reactions and oral or systemic antibiotics and steroids for the more severe ones [9]. However, in patients being treated with cetuximab only, moisturizing or emollient creams are used for prevention/treatment.

Novel Management

Hypochlorous Acid (HOCl) has been shown to reduce bacterial counts in open wounds [10] and to attenuate in vivo two NF-κB-driven disease processes: acute radiation dermatitis and skin aging [11]. A novel acidoxidizing solution (AOS) (Nexodyn-APR Applied Pharma Research [APR] SA) with high-purity HClO, pH between 2.5 and 3.0 and high redox potential, generally used for wound irrigation, cleansing and hydration, has demonstrated control of bioburden and inflammation in chronic wounds [12]. The combination of low pH and high redox potential plays a role in inhibiting matrix metalloproteases, interrupting the cycle of delayed wound healing and promoting the restart of the physiological healing process.

Study

In this study, we investigated the use of AOS as an adjunct to current therapy to prevent and/or treat skin lesions in cancer patients under cetuximab treatment. This observational study was conducted between March 2017 and March 2018 at the Oncology Day Hospital of the University Hospital (AOU) City of Health and Science of Turin. Fifteen patients over 18 years of age with head and neck tumor who had developed acneiform lesions during their first three-month treatment cycle with cetuximab were included.

The dates of treatment in the hospital were recorded. Patients were instructed in the treatment regimen, which included:

- morning - hydration with base cream
- noon - spray application of AOS to face, chest and arm
- evening - hydration with base cream

The AOS is commercially available as a spray solution and its use for skin lesions is on-label. It is applied directly to the bed of the lesion on the skin around the wound, requires no compress and acts within 2 minutes. At the end of the two minutes a moistened gauze is used, if necessary, to remove fibrin, biofilm and bacterial contamination.

During the three-month period, three assessments were made and recorded: at the first visit, at the interim visit (15/30 days after the first visit, depending on the patient's health), and at the last visit.

Information collected included:

- Patient demographics at baseline
- Location and type of rash at baseline. Scores ranged from 1 to 4
- Size of the lesion (width x length)
- Peri-lesional skin (erythema, maceration, xerosis, burning, itching and inflammation, rated as mild, moderate or severe)
- Wound-Bed Preparation (WBP) score. Each parameter was assigned a score from 0 to 2; the sum of all scores could take a value between 0 (lowest or worst score) and 18 (highest or best score)
- Quality of life (assessed with QoL-EQ 5D): Mobility, personal care, usual activities, discomfort/pain, and anxiety and depression were assessed and described as no problem, a

relevant problem or problem. Perception of current condition was measured using a numerical scale - scores ranged from 0 (poor health) to 100 (best health).

Treatment safety was evaluated based on the presence or absence of manifestations such as: intolerance, wound infection or adverse events.

Results

Of the 15 patients included in the study, 66% (n=10) were male, and the average age was 60 years (range 48 – 65). Lesions were found in the chest, chest and arm, and arm in 46.6% (n=7), 33.3% (n=5) and 20% (n=3), respectively.

Wound Evolution - At baseline, lesions ranged in width from 5 cm to 22 cm, length from 10 cm to 40 cm; the smallest lesion was 5 cm x 10 cm, the largest, 22 cm x 40 cm. At the end of treatment, 93.3% (n=14) of patients had at least a 90% regression; the least regression was 88.9% (Table 1 and Figure 1).

Patient	First visit			Second visit			End of treatment			% REDUCTION OF INJURY [(Area injured at the end of treatment - area injured at the beginning of treatment) / area injured at the beginning of treatment] *100	Discontinuation of treatment with hypotonic acid solution containing hypochlorous acid (YES / NO)
	Length cm	Width cm	Injured area cm	Length cm	Width cm	Injured area cm	Length cm	Width cm	Injured area cm		
1	20	30	600.00	10	15	150	5	5	25.00	95,83	NO
2	20	40	800.00	15	30	450	5	10	50.00	93,75	NO
3	6	10	60.00	3	4	12	1	2	2.00	96,67	NO
4	21	37	777.00	19	20	380	6	9	54.00	93,05	NO
5	15	30	450.00	10	15	150	5	10	50.00	88,89	NO
6	7	9	63.00	4	5	20	2	2	4.00	92,00	NO
7	18	29	522.00	11	18	198	4	6	24.00	94,67	NO
8	22	41	902.00	10	20	200	5	11	55.00	93,75	NO
9	20	30	600.00	10	15	150	4	7	28.00	95,33	NO
10	6	11	66.00	3	5	15	1	2	2.00	96,67	NO
11	23	38	874.00	17	15	255	5	10	50.00	93,42	NO
12	21	31	651.00	12	22	264	5	5	25.00	93,33	NO
13	17	33	561.00	8	15	120	5	5	25.00	94,44	NO
14	20	29	580.00	10	19	190	5	4	20.00	92,00	NO
15	22	30	660.00	12	20	240	4	5	20.00	96,97	NO

Table 1: Lesion size reduction (%).

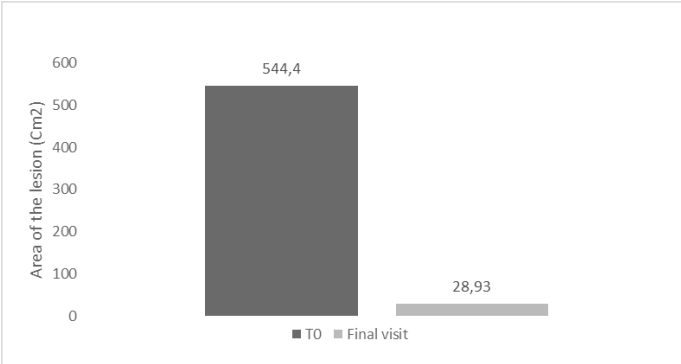

Figure 1: Lesion size reduction.

Perilesional Skin - At baseline, all patients had itchy and inflamed perilesional skin; pruritus was moderate in 60% (n=9) of patients and mild in the remaining 40% (n=6). Inflammation was moderate in 60% (n=9) and mild in the remaining 40% (n=6). Only 6.7% (n=1) had mild skin burning. At the end of treatment, no patient reported pathological symptoms.

Wound bed preparation score - 93% of patients (n=14) showed improvement at visit 2. At the end of treatment, each patient had the maximum score (Table2).

Patient	WBS Score (Modified)		
	First Visit	Second Visit	End of Department
1	14	14	18
2	15	17	18
3	16	18	18
4	16	18	18
5	14	14	18
6	14	14	18
7	14	14	18
8	15	17	18
9	16	18	18
10	14	14	18
11	15	17	18
12	15	17	18
13	15	17	18
14	14	14	18
15	16	18	18

Table 3: Wound bed preparation scores.

Quality of Life - At baseline, 46.7% (n=7) of patients reported discomfort/pain, and 33.3% (n=5) reported difficulty performing usual life activities. 100% (n=15) reported suffering from anxiety and depression. At the end of treatment, only anxiety and depression were present (Table 3).

QoL-EQ 5D	First Visit			Second Visit			End of Treatment		
	Slight	Moderate	Severe	Slight	Moderate	Severe	Slight	Moderate	Severe
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Mobility	15 (100)			15 (100)			15 (100)		
Personal care	2 (13,3)	13 (86,7)		3 (20)	12 (80)		15 (100)		
Usual activities	3 (20)	7 (46,7)	5 (33,3)	10 (67)	5 (33,3)		15 (100)		
Discomfort/ Pain	5 (33,3)	3 (20)	7 (46,7)	3 (20)	7 (46,7)	5 (33,3)	15 (100)		
Anxiety/Depression		15 (100)			15 (100)				15 (100)

Table 4: Quality of Life Assessment - QoL-EQ 5D – percentage values.

Adverse events - No adverse events occurred.

Discussion

All patients showed acneiform lesions, the most common cutaneous toxicity of cetuximab therapy. Upon treatment with AOS in combination with a base cream, the lesions gradually decreased in size, features, and associated symptomatology. Lesions remained circumscribed, peri-lesional skin intact, and itching and inflammation were reduced. All patients completed the prescribed anticancer therapy without interruption or discontinuation.

Skin infections are less likely to be a direct result of treatment, but rather a consequence of skin barrier disruption due to acneiform lesions or xerosis [13]. In this study, the antimicrobial effects of AOS in combination with the moisturizing effect of the base cream prevented skin reactions from progressing to skin infection.

Although in the patient population studied, quality of life is affected by cancer-related anxiety and depression, poor skin condition is also a factor impacting quality of life, and improved body image can certainly improve it. In a study of 459 patients with advanced cancer, 55% placed equal importance on quality of life and length of life, 27% preferred quality of life, and 18% preferred length of life [14]. Poor quality of life due to papulopustular reactions may also affect treatment adherence, leading to dose reduction and treatment discontinuation [15].

In our study, at the beginning of treatment 46.7% of patients reported discomfort/pain, 33.3% reported difficulty performing usual life activities, and 100% suffered from anxiety and depression. Although at the end of treatment only anxiety and depression were present, this did not lead to discontinuation of treatment suggesting that the improvement in the acneiform lesions led to a more general improvement.

Limitations - This was a small observational study, and its results need to be confirmed by more numerous randomized trials.

Conclusions

Our results show that AOS treatment was well tolerated, with no adverse effects or discontinuation of cetuximab therapy. No skin infection developed, suggesting that the treatment prevented further exacerbation of the existing papulopustular lesions. The AOS is easy to apply, especially in anatomical areas that are difficult to treat with alternative products, making it likely to be used by both physicians and patients.

Although further studies are needed, these preliminary results suggest that AOS is an optimal treatment strategy to aggressively treat cutaneous side effects caused by cetuximab.

Declarations

All authors contributed to the study conception and design

Conflicts of Interest/Competing Interests

The authors declare no conflicts of interests or competing interests. The authors have no financial or proprietary interests in any material discussed in this article.

Ethics approval was not required as the product was being used in the standard care of wounds in accordance with the wound care management policy Consent to participate was not necessary as this product was part of the standard wound care regimen.

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Author Contributions

Conceptualization F.C; methodology A.L. M.B and D.F investigation A.L; writing-original draft preparation, M.B; writing-review and editing M.B and D.F., supervision, F.C. All authors have read and agreed to the published version of the manuscript.

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