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Skickat via mail 3 januari 2019

Angående Upphörandeuppmaning avseende marknadsföring av Vectibix och hudvårdsprodukter

Amgen AB ("Amgen") har mottagit en upphörandeuppmaning avseende marknadsföring av Vectibix och hudvårdsprodukter från Merck AB ("Merck").

Angående punkt 1. Påsen och dess innehåll utgör inte ett tillåtet hjälpmedel och strider mot marknadsföringsreglerna:
Amgen anser inte att Påsen strider mot Kap 1, Avd 2, Art 102 och 104 samt Art 2, Avd 1, Art 11.
Påsen är ett hjälpmedel till nytta för patientomhändertagandet då Amgen vill medvetandegöra patienterna om vikten av att hantera hudbiverkningar då majoriteten av patienterna får dessa. Påsen är en del av Amgens patientstödprogram.
Påsen är avsedd att endast delas ut till patienter som får sin **första** behandling med Vectibix, ej vid nästkommande behandlingar. Således är Påsen ej avsedd för rutinmässigt tillhandahållande till patienterna.

Angående punkt 2. Påsen utgör en gåva och otillåtna incitament att rekommendera, förskriva, köpa och adminitrera läkemedel:
Amgen anser inte att Påsen strider mot Kap 1, Avd 2, Art 102 samt Art 2, Avd 1, Art 11.
Påsens innehåll är av lågt värde (under 450 kr) och marknadsmässiga priser, se bifogad dokumentation bilaga 1.
Förskrivande läkare är ej ansvarig eller involverad i utlämnadet av Påsen utan detta sköts av sjuksköterskor som administrerar det ordinerade läkemedlet. Påsen tillhandahålls patienten först när denne kommer för sin första Vectibix-behandling och är att se som ett hjälpmedel vid patientomhändertagandet.
Beställning och utlämning av Påsen sker under strikt kontrollerade former.

Angående punkt 3. Påsen med dess innehåll utgör förtäckt läkemedelsinformation och saknar minimiinformation:
Amgen anser inte att Påsen strider mot Kap 1, Avd 1, Art 5, och Kap 1, Avd 2, Art 105, och Kap 1, Avd 1, Art 17 samt Kap 1, Avd 2, Art 117.
På Påsen, som är förseglad, anges tydligt att Påsen endast är avsedd för **patienter** som får sin **första** behandling med Vectibix. Således är inte Påsen avsedd för hälso- och sjukvårdspersonal. Innuti Påsen finns en produktinformationsbroschyr avsedd för patienter som behandlas med Vectibix. Broschyren innehåller även minimiinformation.

Angående punkt 4. Marknadsföring av kosmetiska produkter med läkemedelspåståenden:
Amgen tackar för synpunkterna gällande läkemedelspåståenden av hudvårdsprodukterna i Påsen. Amgen avser att korrigera texten på informationskortet framledes samt förtydliga att andra liknande produkter kan användas vid hantering av hudreaktioner under cancerbehandling.
Att Amgen för närvarande valt La Roche-Posays hudvårdsprodukter baseras på att det finns dokumenterat vetenskapligt underlag för dessa produkters effekt på cancerpatienter, se bilaga 2 och 3.

Angående punkt 5. Uppmaning:
Amgen bestrider punkt 1-3 men kommer att justera informationen om hudvårdsprodukterna i Påsen (punkt 4).

Med vänlig hälsning

Amgen AB

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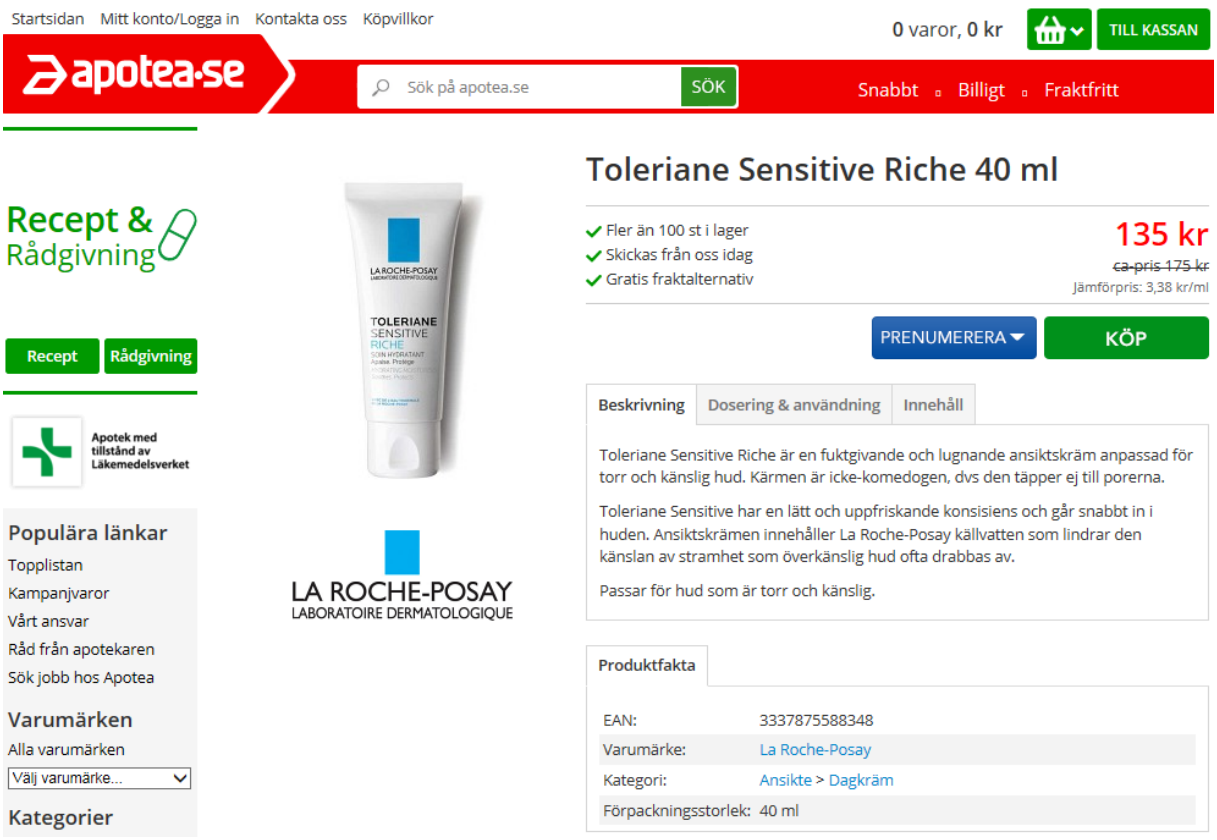
Bilaga 1. Priser från apotea.se per den 2 januari 2019
Bilaga 2. Wohlrab, J. et al. Barrier protective use of skin care to prevent chemotherapy-induced cutaneous symptoms and to maintain quality of life in patients with breast cancer. *Breast Cancer: Targets and Therapy (Dove Med Press). 2014; 6: 115–122.*
Bilaga 3. Seité, S. et al. Prevention and treatment of acute and chronic radiodermatitis. *Breast Cancer: Targets and Therapy (Dove Med Press). 2017; 9: 551–557.*

Bilaga 1. Påsens innehåll priser enligt apotea.se per den 2 januari 2019



Recept & Rådgivning

Recept Rådgivning

Apotek med tillstånd av Läkemedelsverket

Populära länkar

Topplistan
Kampanjvaror
Vårt ansvar
Råd från apotekaren
Sök jobb hos Apotea

Varumärken

Alla varumärken

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Kategorier

Allergi
Ansikte

LA ROCHE-POSAY
LABORATOIRE DERMATOLOGIQUE

Lipikar Syndet AP+ duschgel 200 ml

- 76 st i lager
- Skickas från oss idag
- Gratis fraktalternativ

95 kr

Jämförpris: 475 kr/l

PRENUMERERA KÖP

Beskrivning | Innehåll

Lipikar Syndet AP+ duschgel är en lugnande duschkräm för kroppen. Kan användas båda av vuxna och till barn och spädbarn med torr hud. Duschkrämen bidrar till att lindra klåda och irritation orsakad av torrhet.

Lipikar Syndet AP+ duschgel är mycket mild och innehåller karitésmör, niacinamide och Aqua Posae Filiformis, som verkar lugnande för huden. Svider inte i ögonen.

Tvålfri och oparfymerad.

Tub med 200 ml.

Produktfakta

EAN:	3337875537308
Varumärke:	La Roche-Posay
Kategori:	Förälder & Barn > Kroppsvård för barn > Hud Hud & Hår > Rengörande
Förpackningsstorlek:	200 ml

Recept & Rådgivning

Recept Rådgivning

Apotek med tillstånd av Läkemedelsverket

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Varumärken

Alla varumärken

Välj varumärke...

Kategorier

Allergi
Ansikte
Bett & Stick
Djur
Feber & Värk

LA ROCHE-POSAY
LABORATOIRE DERMATOLOGIQUE

Lipikar Balm AP+ 400 ml

- Fler än 100 st i lager
- Skickas från oss idag
- Gratis fraktalternativ

197 kr

Jämförpris: 492,50 kr/l

PRENUMERERA KÖP

Beskrivning | Dosering & användning | Innehåll

Lipikar är en kroppsvårdsserie från franska La Roche-Posay. Produkterna i serien är milda och effektiva för alla typer av känslig hud hos både vuxna och barn. Produkterna innehåller ett minimalt antal ingredienser för optimal tolerans.

Lipikar Balm AP+ är en kräm som har en lugnande effekt på mycket torr hud hos spädbarn, barn och vuxna. Speciellt framtagen för känslig, mycket torr och irriterad hud - även för hud med atopisk tendens. Verkar lugnande på huden och gör huden smidig och mjuk.

Lipikar Balm AP+ innehåller Posae Filiformis - en aktiv ingrediens som förbättrar och stabiliserar hudbarriären. Krämen innehåller även Niacinamide och karitésmör (20%) och är framtagen med ett minimalt antal ingredienser för att vara så snäll mot huden som möjligt.

Produktfakta

EAN:	3337872418570
Varumärke:	La Roche-Posay
Kategori:	Hud & Hår > Återfuktande
Förpackningsstorlek:	400 ml

Breast Cancer: Targets and Therapy

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ORIGINAL RESEARCH

Barrier protective use of skin care to prevent chemotherapy-induced cutaneous symptoms and to maintain quality of life in patients with breast cancer

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Purpose: Chemotherapy with anthracyclines, taxanes, or alkylating agents often causes cutaneous side effects. Nonspecific inhibition of the proliferative activity of keratinocytes has antidifferentiation effects that lead to defects in the barrier function and, thus, to dry, itchy, and irritable skin. These cutaneous symptoms reduce the quality of life of the patients considerably. Conditioning with topical application of niacinamide uses the cytoprotective and barrier stabilizing effect of vitamin B_3.

Patients and methods: A multicenter randomized crossover study investigated the influence of the test preparation on the quality of life compared to standard care for 73 patients with breast cancer undergoing adjuvant or neoadjuvant cytostatic therapy. Primary target parameter was the Dermatology Life Quality Index with its respective subscales after 6 weeks of a twice-daily application of the respective preparations. Additionally, specific symptoms such as pruritus, dryness, and irritability have been assessed using visual analog scales.

Results: Regarding the total score of the Dermatology Life Quality Index, no relevant differences could be observed. However, the results for the "symptoms and feelings" subscale show a significant advantage in favor of the test preparation. Significant superiority of the test preparation could also be observed in the secondary target parameters, the visual analog scales ($P<0.05$).

Conclusion: The results show for the first time a significant superiority of prophylactic application of niacinamide for maintaining quality of life while undergoing cytostatic treatment.

Keywords: supportive therapy, niacinamide, chemotherapy, anthracycline, taxane

Introduction

The prevalence of cancers in industrial nations is steadily increasing.[1] With approximately 75,000 new cases each year, breast cancer is a common tumor in Germany and by far the most frequent malignant tumor in women.[2] Based on guidelines, therapeutic regimens are chosen depending on clinical grading, hormone receptor state, lymph node involving, and the patient's age. For intermediate and high-risk conditions, this almost always involves adjuvant systemic chemotherapy.[3] Usually, combinations of cytostatics are used, sometimes together with targeted therapies. Depending on dosage schedule, treatment period, and the type of combination, therapies show considerable unwanted side effects. Additionally, the severe psychological stress for patients with cancer as well as its social impact has to be taken into account.[4] Therefore, more and more supportive measures are validated in oncology.[5–7]

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Unwanted side effects affecting the skin organ are mostly non-life-threatening, but can seriously reduce patients' quality of life and, thus, endanger therapeutic success by reducing compliance.[8] From a dermatological point of view, various clinical patterns can be determined; these occur quite frequently and, therefore, have a high practical relevance.[9,10] Recommendations for the therapeutical management for some of these patterns exist, the evidence of which is worked on progressively.[11,12] Recommendations for prophylactic measures, on the other hand, have not gone beyond general notes on care so far.[13–15]

However, the success of specific prophylactic strategies depends very much on the pathomechanism of individual reaction patterns, and these are not necessarily specific to substances or their combinations.[16] Also, it is important to distinguish between toxic and nontoxic reactions. Unspecific cytotoxic effects on the epithelium or skin appendages caused by the cytostatics themselves or by their metabolites are the most common events and can be observed in up to 30% of all cancer patients, regardless of the type of the primary tumor, but dependent on the regimen and the combination of chemotherapy. Furthermore, individual pathologic factors such as pharmacogenetics, comorbidities, concomitant medication, sweating, cutaneous vulnerability, and genetic disposition seem to be important. On the whole rather rare, but quite frequent in connection with targeted therapies, specific antiproliferative effects can be observed. The intrinsic tyrosine kinase activity of the epidermal growth factor and its receptors on the cell surface (EGFR) play a major role here.[17] The specific blockade of EGFR by therapeutic antibodies as well as the unspecific inhibition by multikinase inhibitors can cause alterations associated primarily with skin appendages (acne-like rash, paronychia).[9,18–22] Elimination of cytostatics and their metabolites by eccrine sweat can cause both direct toxic effects due to accumulation in the stratum corneum, especially in palmar and plantar skin, and inflammatory phenomena due to depletion of the antioxidative capacity of the skin (chemotherapy-induced acral erythema, also known as palmar-plantar erythrodysesthesia or hand–foot syndrome).[11]

Most frequently, however, barrier disorders caused by complex dysfunction of proliferation and differentiation of interfollicular keratinocytes and epidermal stem cells can be observed. Clinical symptoms are dryness and scaling of the skin, which after latency can lead to inflammatory irritations along with pruritus and, therefore, scratching.[23] Up to now, only individual recommendations for supportive skin care, aiming at barrier substitution, can be found in literature.[16] These recommendations are based on concepts that have been established for chronic inflammatory skin diseases with endogenous barrier deficiency (eg, atopic dermatitis) and have been empirically applied to oncological situations. Here, the different pathomechanism of barrier dysfunction under therapy with cytostatics is ignored, and proactive use is propagated without scientific evidence.[16] The clinical use of a niacinamide-containing preparation implements the concept of using the well-known effects of the natural vitamin proactively to prevent clinically relevant chemotherapy-induced barrier dysfunction.[24–28] The advantages of niacinamide are its anti-inflammatory effects due to inhibition of proinflammatory factors, as well as its ability to increase the expression of serine palmitoyltransferase as the key enzyme for ceramide synthesis.[29–33] Even after repeated epicutaneous application of preparations with 4% niacinamide, no systemic toxic effects or interactions with other systemically applied active substances are to be expected.[34]

A study complying with the principles of Good Clinical Practice investigated the clinical benefits of the proactive use of a semisolid niacinamide-containing preparation in patients with breast cancer undergoing cytostatic therapy.

Patients and methods

Study objective and study design

The objective of this multicenter prospective randomized reference-controlled crossover study was to validate the clinical relevance of the preventive use of a niacinamide-containing barrier-protective preparation under real life conditions in patients undergoing cytostatic therapy. Female patients aged 18 years or older and diagnosed with breast cancer were enrolled in the study on condition that they had an indication for adjuvant or neoadjuvant chemotherapy with anthracyclines or taxanes; combination with trastuzumab was allowed. Not enrolled were patients who: had clinical signs of a barrier dysfunction before study start; had indications for an atopic or psoriatic disposition in their medical history; or were using pharmaceutical or over-the-counter products that have vasoactive, anti-inflammatory, or diuretic effects, or those that affect the lipid metabolism. Study start was the first day patients received chemotherapy. One study group first used the test preparation (TP) for 6 weeks and, subsequently, standard care (SC) for 6 weeks. The other study group first used SC for 6 weeks and, subsequently, TP for 6 weeks. The Dermatology Life Quality Index (DLQI) as primary target parameter was recorded over the time of 12 weeks.[35–38] In addition to the total DLQI score, the six DLQI subscales were included in the analysis (Figure S1).[39,40] As second target parameters, the symptoms pruritus, dryness, and irritability were quantified and recorded via visual analog scales.[41]

Test preparation

TP was a lipophilic cream containing 4% niacinamide, shea butter as lipophilic, and thermal spring water from La Roche-Posay as hydrophilic phase (Lipikar® Baume AP, La Roche-Posay Laboratoire Pharmaceutique, La Roche-Posay, France). TP was applied twice daily on the whole body. Standard care (SC), which was defined as the patients usual body care in their individual quantity and frequency, was chosen as control arm.

Statistics

The confirmative evaluation of the principal target parameter was done by analysis of variance. All other parameters were evaluated descriptively. The number of the values, missing values, mean value, standard deviation, median, quartile, minimum, and maximum were specified for all continuous values. For all other values, frequency tables were generated. The statistical evaluation was carried out using the SAS package version 9.1 (SAS Institute Inc., Cary NC, USA).

Ethics

The study was approved by the Ethics Committee of the Faculty of Medicine Charité, Humboldt University Berlin; the respective ethics committees of the study sites agreed with this approval. All patients gave their written informed consent to their participation in this study. The study was conducted according to the guidelines of Good Clinical Practice.

Results

Patient characteristics

The study was conducted between February 2012 and April 2013 in six breast cancer centers in Germany. A total of 95 patients aged between 25 and 77 years were enrolled (Figure 1). Via block randomization, 46 patients were randomized in group TP/SC and 48 in group SC/TP. Twenty-one patients dropped out before the end of the study and one patient had to be excluded for protocol deviation. A total of 73 patients were included in the analysis.

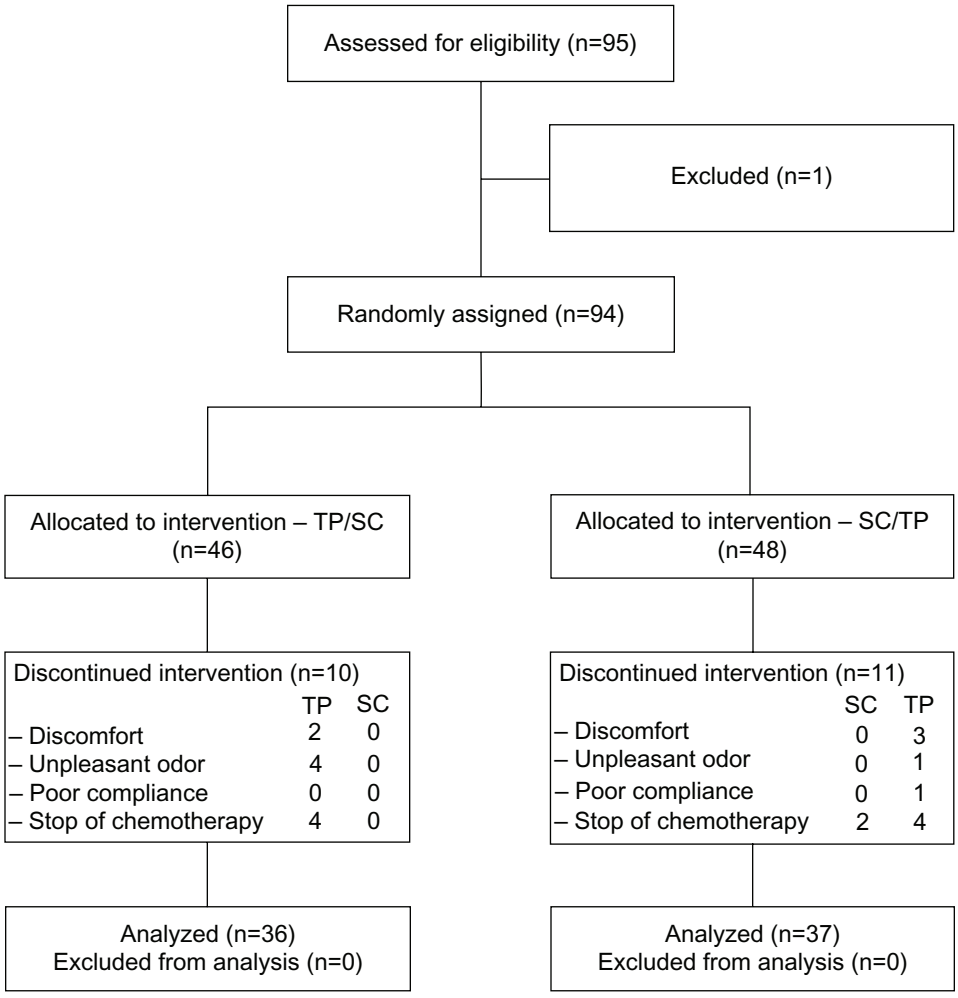

Figure 1 CONSORT diagram.
Abbreviations: SC, standard care; SC/TP, patient group that starts with SC followed by TP; TP, test preparation; TP/SC, patient group that starts with TP followed by SC; CONSORT, Consolidated Standards of Reporting Trials.

Treatment details

The most frequent chemotherapies received by patients were: epirubicin plus cyclophosphamide plus docetaxel or paclitaxel; cyclophosphamide plus epirubicin plus 5-fluorouracil; and doxorubicin plus cyclophosphamide plus docetaxel, sometimes combined with trastuzumab. The respective regimens and their frequencies are shown in Table 1. The study had no influence on the therapeutic decision.

DLQI results

Comparing the total DLQI score between TP and SC after 6 weeks did not show any significant differences (Figure 2A). However, the analysis of the six subscales showed significant superiority of TP for the "symptoms and feelings" aspect after week 4. After crossover, superiority of TP can be observed after week 8 (Figure 2B). For the other subscales, no significant differences could be found. The visual analog scale values for the secondary target parameters of pruritus, dryness, and irritability show significant superiority for TP after 6 weeks (Figure 3A–C).

Table 1 Characteristics of study population

Characteristics	Group TP/SC		Group SC/TP		Total	
	n	%	n	%	n	%
Total	36	49	37	51	73	100
Age, years						
<30	1	1.37	0	0.00	1	1.37
30–40	1	1.37	5	6.85	6	8.22
41–50	11	15.07	13	17.81	24	32.88
51–60	9	12.33	12	16.44	21	28.77
61–70	10	13.70	5	6.85	15	20.55
71–80	4	5.48	2	2.74	6	8.22
Mean	6.0	8.2	6.2	8.4	12.2	16.7
SD	4.2	5.7	4.8	6.6	8.4	11.6
Chemotherapy						
4× EC, 4× Doc	3	4.11	2	2.74	5	6.85
4× EC, 4× Doc, Trastuzumab	1	1.37	0	0.00	1	1.37
3× FEC, 3× Doc	6	8.22	8	10.96	14	19.18
3× FEC, 3× Doc, Trastuzumab	0	0.00	2	2.74	2	2.74
6× TAC	4	5.48	5	6.85	9	12.33
4× EC, 12× Pac	13	17.81	8	10.96	21	28.77
4× EC, 12× Pac, Trastuzumab	5	6.85	5	6.85	10	13.70
4× FEC	0	0.00	1	1.37	1	1.37
6× FEC	1	1.37	3	4.11	4	5.48
6× TCbH	1	1.37	1	1.37	2	2.74
18× Pac + Dox	0	0.00	2	2.74	2	2.74
4× TC	1	1.37	0	0.00	1	1.37
Unknown	0	0.00	1	1.37	1	1.37

Abbreviations: Doc, docetaxel; Dox, doxorubicin; EC, epirubicin plus cyclophosphamide; FEC, 5-fluorouracil plus epirubicin plus cyclophosphamide; Pac, paclitaxel; SC, standard care; SC/TP, patient group that starts with SC followed by TP; SD, standard deviation; TAC, doxorubicin plus cyclophosphamide plus docetaxel; TC, taxane plus carboplatin; TCbH, taxane plus carboplatin plus trastuzumab; TP, test preparation; TP/SC, patient group that starts with TP followed by SC.

Discussion

The need for supportive therapy in oncology is obvious and widely acknowledged.[5] Supportive measures depend on the underlying condition, the stage of the disease, the treatment regimen, as well as on individual pathologic and social factors. If possible, evidence based recommendations should be aspired to. From a dermatological point of view, a prophylactic or proactive approach must be distinguished from therapeutic or reactive strategies. Both strategies interact in the management of unwanted cutaneous reactions and have high practical relevance. Referring to safety data of published studies, the probability of pathogenetic cutaneous symptoms depending on dosage and combination of cytostatics can be estimated. The most common symptom, especially when using anthracyclines, taxanes, or alkylating agents, is dry and itchy skin as expression of complex dysfunctional differentiation. This becomes phenotypically relevant usually after 7–14 days. Substitution, specifically targeted to condition the barrier function, starting at the same time as cytostatic therapy can prevent, slow down, or reduce clinical symptoms. For this conditioning effect, niacinamide provides favorable preconditions. It has cytoprotective effects due to stimulation of DNA repair mechanisms.[42,43] In addition, there are indications that niacinamide supports the release of cytostatics from cells, depending on concentration, and therefore reduces their antiproliferative effects.[44] These effects of the topically applied and, therefore, only cutaneously bioavailable active substance are the basis for the hypothesis of a conditioning proactive use during cytostatic therapy. The above-mentioned additional effects concerning ceramide synthesis and anti-inflammation are cumulative.[29,45,46]

To recruit enough patients that met the inclusion and exclusion criteria in a timely manner, and to avoid seasonal influences, six breast centers were selected for competitive recruitment. The high cumulative dropout rate of 23% in this study is mainly due to discontinuation of chemotherapy for medical reasons. Additionally, some cases of early termination can be attributed to chemotherapy-induced alterations of sweat gland functions (hyperhidrosis) and the olfactory sense (dysosmia). The present study data and published data raise no safety concerns for clinical use.[47–49] Furthermore, niacinamide has been used systemically as a perfusion enhancer for palliative care in patients with breast cancer due to its relaxant effects on vascular smooth muscle cells.[50,51]

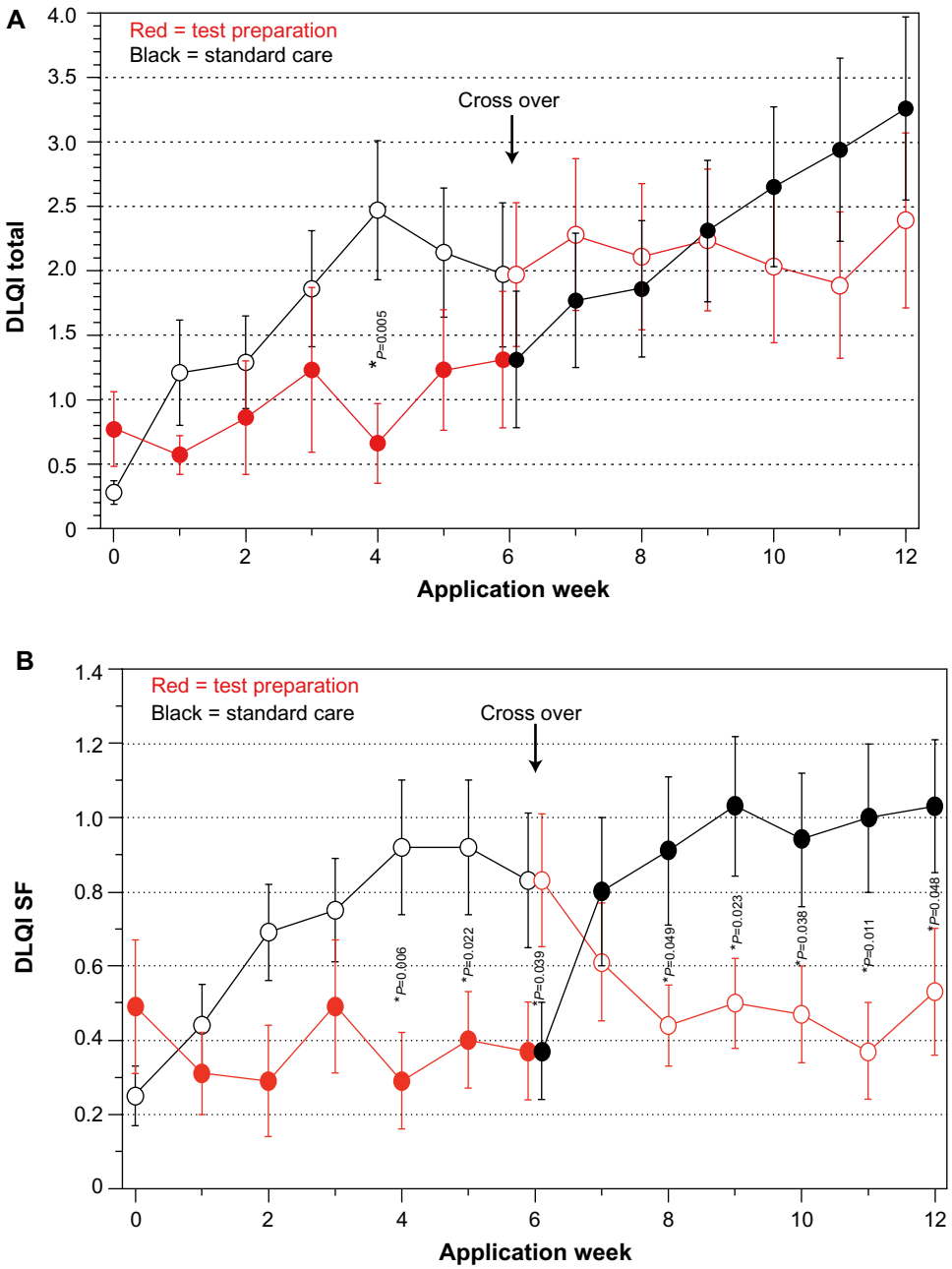

Figure 2 DLQI: comparison of both groups over application time.
Notes: (**A**) DLQI total, (**B**) DLQI SF. SC/TP group SC/TP group n=48; TP/SC group n=46. *Statistical significant difference between the groups, analysis of variance ($P \leq 0.05$).
Abbreviations: DLQI, Dermatology Life Quality Index;[35] SF, subscale Symptoms and Feelings.

The results of this study suggest that cytostatic cutaneous symptoms among other health problems have a negative impact on quality of life for the patients. That supports the usefulness of a proactive prophylactic skin care, which should be applied with the start of cytostatic therapy at the latest. Despite the psychological stress that accompanies the start of a cytostatic therapy, the patients experienced the offer of supportive skin care as motivating rather than as an additional burden. The superiority of TP over SC, regarding the mentioned aspect of quality of life and regarding pruritus, dryness, and irritability, proves the efficacy of TP for prophylactic use within the study setting. Statements regarding the efficacy of the preparation for other pathogenetic patterns of unwanted drug reactions, eg, palmar-plantar erythrodysesthesia, acne-like rash, or toxic exanthema, cannot be made.[9,20,52–54] Also, no therapeutic effects can be propagated regarding established, inflammatory skin conditions.

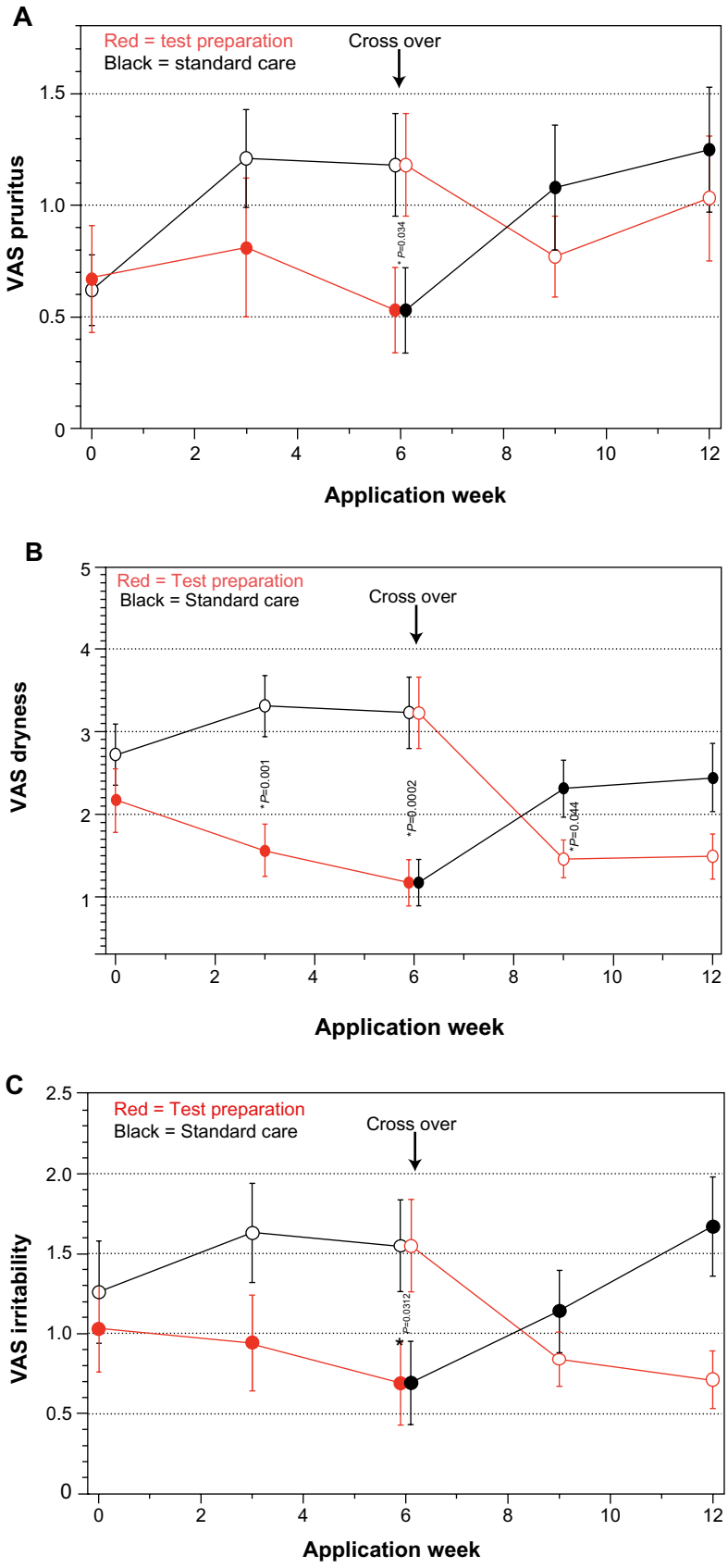

Figure 3 VAS: comparison of both groups over application time.
Notes: (**A**) Pruritus, (**B**) skin dryness, (**C**) irritability. Standard care/test preparation group n=48; test preparation/standard care group n=46. *Statistical significant difference between the groups, analysis of variance ($P \leq 0.05$).
Abbreviation: VAS, visual analog scale.

Conclusion

The results of this study favor the niacinamide-containing TP for proactive treatment accompanying cytostatic therapies with classic antiproliferative substances. Certainly, further investigations are necessary in order to strengthen the evidence for the supportive use of topical niacinamide in oncology.

Acknowledgments

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Disclosure

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PERSPECTIVES

Prevention and treatment of acute and chronic radiodermatitis

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Abstract: More than half the number of patients with cancer, who are treated with radiotherapy, will have radiodermatitis at some point during their treatment. Radiodermatitis either occurs early on in the treatment period or appears months or up to several years later. Acute radiodermatitis is a burn injury that varies in severity according to both treatment and inherent patient factors. Most acute radiodermatitis reactions resolve after several weeks but some reactions persist and can cause complications. Late-onset radiodermatitis is characterized by telangiectasia that forms on atrophic and fragile skin. These radiodermatitis reactions can have a significant negative impact on concomitant and subsequent therapeutic protocols and most particularly on the patient's quality of life. Today, treatment of radiodermatitis reactions is in its infancy. Although there is insufficient evidence available to form recommendations that would prevent or reduce radiodermatitis, some advances have been made using low level light therapy (LLLT) or vascular lasers to control the symptoms. Some recent preclinical and clinical research suggests that LLLT has biostimulating properties which allow the tissues to regenerate and heal faster, reduce inflammation, and prevent fibrosis. Also, in late-onset radiodermatitis pulsed dye laser treatment has been shown to be beneficial in clearing radiation-induced telangiectasia. In the absence of evidence-based recommendations, the objective of this paper is to review how to prevent or manage the symptoms of radiodermatitis reactions.

Keywords: acute radiodermatitis, chronic radiodermatitis, low level light therapy, laser, pulsed dye, prevention, management, skin care

Introduction

International data indicate that 50% of patients diagnosed with cancer will receive some form of radiation therapy. Radiodermatitis is a substantial side effect that arises directly from radiation exposure during cancer treatment, and concerns around 95% of all cancer patients receiving radiation therapy.[1,2] It is particularly problematic in cancers of the breast, perineum, and head and neck region, where the skin is part of the target volume.[3]

Radiodermatitis is referred to as being an acute reaction when it occurs around the time of therapy and either chronic or late onset when it appears 5–10 years after the end of treatment. Symptoms of acute radiodermatitis have been classified into three levels; grade 1 (mild erythema), grade 2 (dry desquamation), and grade 3 (severe moist desquamation).[4] In recent years, skin sparing and modern equipment such as intensity-modulated radiation therapy reduced dose intensity on the skin and new equipment has reduced the severity of acute radiodermatitis for many patients.[5] Nevertheless,

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grade 1 skin toxicity still remains a problem for around 90% of patients and grade 2 for 30% of patients.[6] While radiodermatitis may resolve over time, it can profoundly affect the patient's quality of life and may limit the treatment duration and dose delivered.[2]

Chronic radiodermatitis occurs in a third of all patients and appears up to at least 10 years after radiotherapy treatment.[7] Typical symptoms are telangiectasia, pigmentation, cutaneous atrophy (dry papery skin), dermal sclerosis, and keratoses.[4] Chronic radiodermatitis is an increasing problem, as today >80% of all women treated for breast cancer are now surviving for ≥10 years.[8]

Fortunately, there are several solutions available today to prevent and treat radiodermatitis and skin reactions. Dermocosmetic support is recommended to protect and promote tissue repair; light technology, such as biophotomodulation and vascular laser treatments, is becoming established as safe and effective to protect and treat both acute and chronic radiodermatitis.[9,10]

The objective of this review paper is to provide an overview of the different types of radio and combined chemotherapy-induced radiodermatitis and highlights the evidence for management and treatment.

Radiodermatitis

Radiodermatitis is the result of cutaneous or subcutaneous lesions induced by external beam radiation. The skin is particularly sensitive to radiation damage because it is a continuously renewing organ. In healthy skin tissue, there is a delicate balance between the death and rebirth of each cell type. Acute radiation damage occurs in the dermis with the first radiation dose. A number of basal keratinocytes are destroyed, leaving only the remaining keratinocytes to cornify. Thus, the balance between the normal cell production at the basal layer and cell destruction at the skin surface is disrupted. This process continues with continuing radiation thereby altering the integrity of the epidermis, the skin barrier, and skin healing processes. This leads to structural, histologic, and vasculature changes of the skin and underlying connective tissue.[11]

With cumulative radiation doses, these acute injuries become apparent. The skin barrier dysfunction manifests as erythema, skin dryness, flaking, folliculitis (skin rash), xerosis, pruritus, and hyperpigmentation. Additionally, the physical barrier and cutaneous immune system are compromised and the skin becomes more sensitive to allergens, ultraviolet radiation, and infection.[12]

Some cutaneous cell types grow and renew themselves rapidly and in others the life cycle is slower. Radiation affects these two populations differently and the probability of destroying a skin cell increases with the level of radiation. Thus, it is possible to have different types of skin reactions occurring at the same time postradiation depending on which cell types have been affected.[13]

Supportive dermocosmetic skin care for patients starting radiotherapy

Regular skin care assessment and close collaboration between radiation oncologists and dermatologists to manage skin reactions early and throughout treatment have been repeatedly suggested to improve patient comfort, enhance quality of life, and improve clinical outcome.[14–16] However, there is little evidence concerning skin care products to alleviate the severity of skin reactions.[17]

One recent, multinational, real-life study to evaluate a combination of hygiene products was performed in women starting radiotherapy following breast cancer. The objective was to evaluate the tolerance of a specific dermocosmetic regimen on the irradiated area and the effectiveness in delaying or reducing the intensity of acute radiodermatitis. This was measured by erythema, edema, skin dryness, desquamation, physical appreciation, and patient appreciation using the patient benefit index at the start and end of treatment (6±2 weeks).[18] Patients were provided with a dermocosmetic kit before the first radiotherapy session. The kit included five products specifically formulated with gentle ingredients that respect skin physiology and tested for use on sensitive skin. In total, 253 women were included in the study, following a tumor excision, partial or full mastectomy. The results revealed two categories of users who were defined by the number (0–5) and frequency of products used (never, sometimes, often, and every day). Low users made up 36% of the study group and 57% were heavy users. This study shows that this skin care regimen was well tolerated on irradiated skin and heavy product users observed less frequent radiodermatitis reactions than low product users (Figure 1). These results were further supported by a recent conference communication that found that the frequency of severe (grade 3 or 4) radiodermatitis was significantly lower in the intervention group (chi-square =4.61; p=0.03), although the time to onset of skin toxicity was similar among the intervention group compared with a previous cohort (median time to onset, 17 vs 17.5 days),[19] thus indicating that patient education can improve adherence to skin care plans and reduce radiation dermatitis. These reports continue to provide support for international recommendations for supportive skin care in radiotherapy.

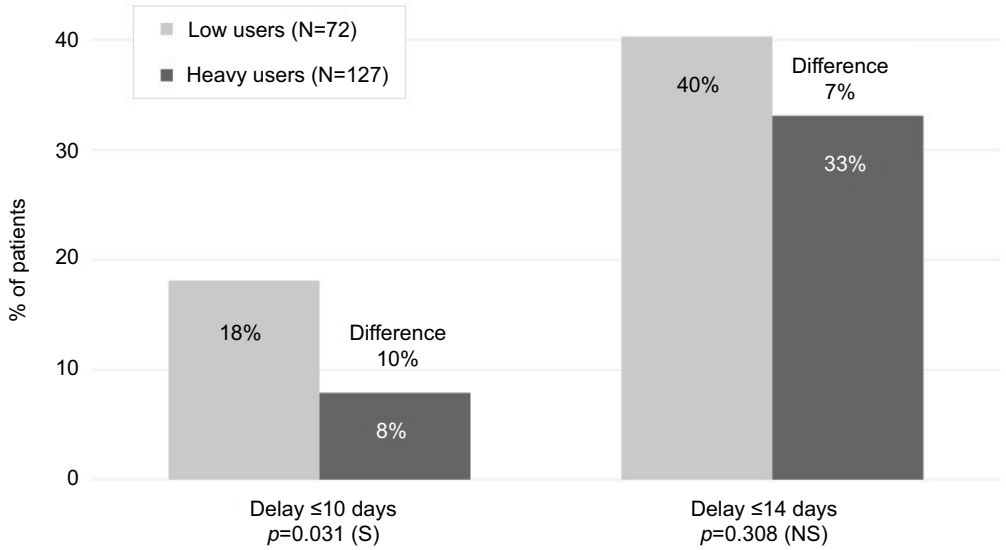


Figure 1 Time to onset of radiodermatitis from radiotherapy start.
Abbreviations: S, significant; NS, non significant.

Acute radiodermatitis

Acute radiodermatitis is a burn injury that varies in severity according to both treatment and inherent patient factors.[1] Treatment-related factors that influence the degree to which skin tissues are damaged include the total dose, fractionation, type and quality of the beam, and surface area and volume of tissue exposed.[11] Also, certain anatomical regions where the target is close to the skin are more susceptible to developing radiodermatitis. These areas include skin folds around the breast and inguinal areas, thin cutaneous regions (clavicle, periauricular area, or axilla), mucosal regions (vulva, anus, and mouth), or altered skin following a previous treatment.

Concomitant radiotherapy with chemotherapy such as epidermal growth factor receptor (EGFR) inhibitors seems to increase the intensity of the EGFR inhibitors-induced rash and delays the appearance by 2–5 weeks after the beginning of treatment.[20–22]

Typical radiotherapeutic treatment such as a dose intensity of 20 Gy with conventional fractionation (2 Gy/fraction; five fractions/week) results in sustained erythema that usually appears between 10 and 14 days after radiotherapy.[23] Although most acute radiodermatitis reactions resolve after 2–3 weeks, some reactions persist and can cause complications such as treatment delays, diminished esthetic appeal, and reduced quality of life.[2,24,25]

Treatment of acute radiodermatitis

Today, there is insufficient evidence available to form recommendations that would prevent or reduce radiodermatitis. However, several multidisciplinary groups have proposed guidelines that suggest management strategies with the objective to avoid or reduce the severity of radiodermatitis reactions: Association Francophone des Soins Oncologiques de Support,[26] Multinational Association of Supportive Care in Cancer,[4] European Skin Management in Oncology,[16] and consensus guidelines for the management of radiodermatitis and coexisting acne-like rash.[21,27] Nevertheless, many centers develop their own protocols.

The general recommendations are presented in Table 1. Low level light therapy (LLLT), otherwise known as photobiomodulation (PBM) or "soft laser" (red light or infrared, power <150 mW), is better known in dermatology to treat ulcers.[28] However, the biological mechanisms behind the therapeutic effect are currently not well understood. Recent molecular and cellular research suggests that LLLT has biostimulating properties which allow the tissues to regenerate and heal faster.[9,10] Animal and clinical studies suggest that LLLT has analgesic properties, reduces inflammation, and prevents fibrosis.[29–31]

Treating radiodermatitis with LLLT is based on previously demonstrated decreased severity and duration of oral mucositis.[32–34] However, its preventative and curative use in acute radiodermatitis is currently under evaluation. It was reported that the incidence of radiodermatitis reduced with light emitting diode treatments immediately after radiation therapy for breast cancer. However, a further controlled clinical study was unable to reproduce the results.[35] Nevertheless, based on the strong level of evidence available, Bensadoun and Nair proposed a protocol to prevent or treat radiation dermatitis using LLLT. The authors suggest that laser therapy can be

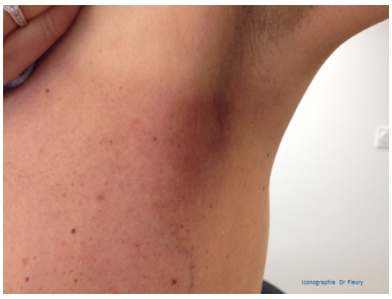
Table 1 General recommendations

General advice

- Skin cleansing
  - Liquid soap or dermatological soap bar with a pH close to 5, without perfume, plant or fruit extracts
  - Dry skin delicately but meticulously
- Skin hydration
  - Apply a non-comedogenic emollient cream without perfume, lanoline, 1 or 2 times per day, preferably after the radiotherapy session
  - Avoid applying topical creams to the radiation zone at least 1 hour before the radiotherapy session. This will avoid a bolus effect (increased radiation dose delivered to the epidermis)
- Photoprotection
  - Protect the irradiated skin zone from sun exposure
  - Apply a sunscreen SPF 50+ with UVA /UVB protection.
- Clothing
  - Wear ample, soft cotton clothing
  - Avoid wearing synthetic clothes
- Additional advice
  - Use an electric razor and do not shave too close to the skin.
  - Avoid applying products that contain alcohol (perfume, eau de toilette, ether, talcum powder)
  - Avoid applying sticky plaster
  - Avoid rubbing or scratching

Acute radiodermatitis

Grade 1
Mild to moderate erythema
Desquamation dry and moderately sensitive

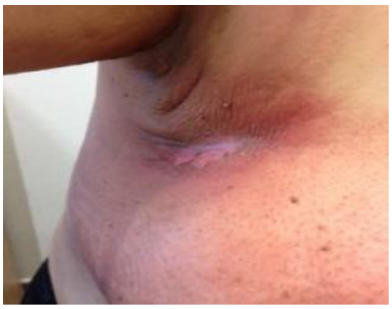


- Follow local hygiene routine

If needed:

- Emollient cream
- Topical corticotherapy
- Protective hydrogel, hydrobalance hydrocellular dressing
- Avoid "Tulle gras" dressing
- Low-energy laser (currently under evaluation)

Grade 2
Intense sensitive and mildly painful erythema
Moist lesions confined to skin folds
Edema

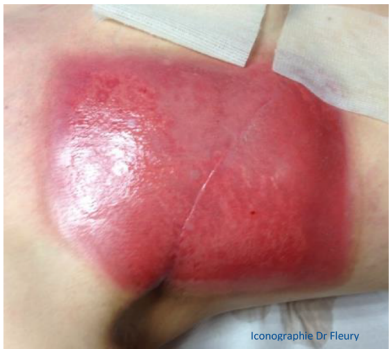


- Continue local hygiene routine

If needed:

- Emollient cream
- Healing cream, acid hyaluronic cream
- Topical corticosteroid
- Drying lotion
- Absorbent, nonadhesive, protective dressing (hydrogel, hydrocellular, hydrobalance)
- Expose to fresh air as much as possible
- Avoid antibacterial application
- Low-energy laser (currently under evaluation)

Grade 3
Intense, painful erythema
Extensive weeping moist zones larger than skin fold areas
Bleeding wounds



If needed:
Clean the wound with physiological serum

- Tulle gras dressing 1 or 2 times a day
- Nonadhesive, absorbent dressings, hydroabsorbant, hydrocellular
- Alginate dressing if bleeding
- Hydrofiber dressing if abundant exudate

After radiotherapy

- Continue using nonirritant local skin care, emollient, and sunscreen
- Avoid wearing constricting clothing, synthetic fabric for several weeks
- Watch daily for life

Notes: Data from these studies.[16,42,43]

started after only a few radiation sessions and before erythema appears or even after erythema has appeared. The treatment was shown to be painless and can be practiced thrice per week, either before or after the radiotherapy session.[36] More recently, Censabella et al performed an open, prospective, comparative study and found that skin toxicity improved significantly following multiwave locked system® laser therapy.[37]

Chronic radiodermatitis

Chronic radiodermatitis, otherwise referred to as late reaction, is characterized by its highly variable, delayed apparition. This late-onset reaction can appear from 6 months up to 20 or 30 years after treatment and can reappear when provoked by the administration of a different treatment such as chemotherapy or antibiotics. The frequency and severity have been shown to be linked with the total dose (+50 Gy to the skin) and favored by short treatment intervals, limited fraction size, large treatment areas, and tumor infiltrate. Other external factors that aggravate chronic radiodermatitis include repetitive trauma, sun exposure, and further irradiation. Chronic radiodermatitis is dominated by telangiectasia that forms on atrophic and fragile skin, associated with areas of hyper or hypopigmentations.[38] Less commonly, a more severe form of delayed radionecrosis occurs where the skin sits close to bone or cartilage such as the nose, ears, or scalp.[23]

Pulsed dye laser treatment has been shown to be beneficial in clearing radiation-induced telangiectasia. The first prospective study reported by Lanigan et al was performed on eight individuals. This study demonstrated that lesions could be whitened using very short pulse durations (0.45 ms) using a 585 nm pulsed dye laser.[38] The study was later supported by a larger comparative study with 13 participants that compared three sessions of either pulsed dye laser or pulsed intense light laser. Patients treated with the pulsed dye laser had a reduction in lesion size of 90%, compared to 50% with the intense pulsed light (IPL). IPL systems are high-intensity light sources, which emit polychromatic light. Unlike laser systems, IPL works with noncoherent light in a broad wavelength spectrum of 515–1200 nm. Both procedures were well tolerated, except for one case of achromia with the IPL.[39] Furthermore, over a number of years, Dr JM Mazer performed several open clinical studies on large patient numbers to further refine the number treatment modality (Figure 2).[40] The first study included 110 women, treated with a pulsed dye vascular laser (ScleroPlus laser [Candela] followed by Vbeam laser [Candela]) at 1.5 ms pulse duration, wavelength 595 nm, with a spot size diameter of 7 mm, and fluence of 9–11.5 J/cm². Between one and five sessions were required to reduce the number of telangiectasias

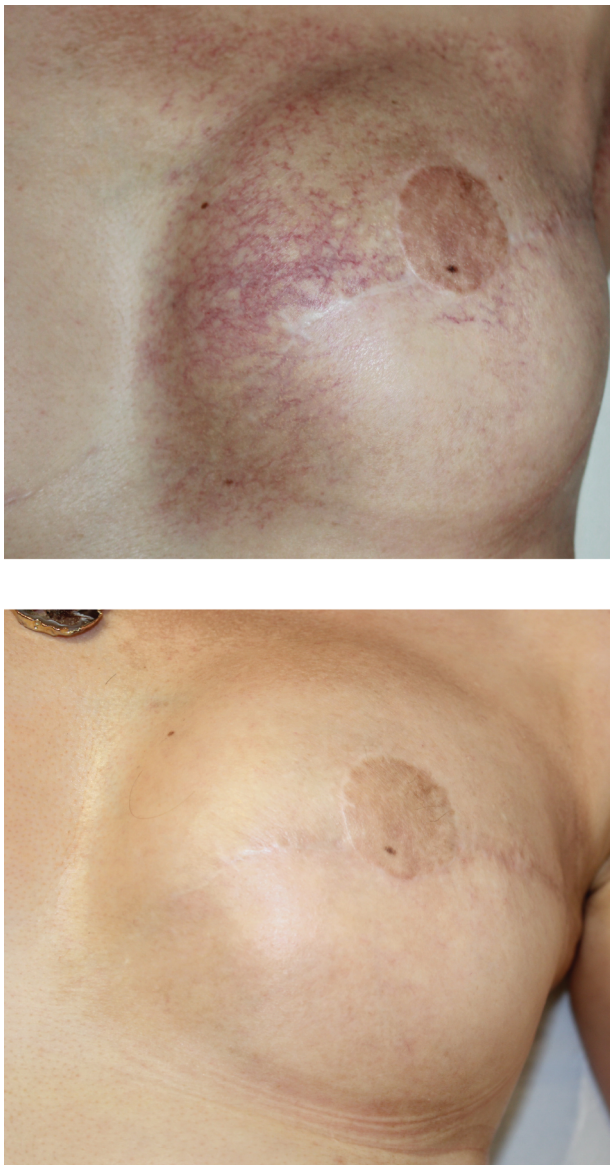


Figure 2 Example of results obtained after two sessions of vascular laser and two sessions of fractional non-ablative laser.
Note: (A) Before treatment; **(B)** after treatment.

by 80%. A second study was performed with a more recent pulsed dye laser (Vbeam Perfecta laser [Candela]) comparing 1.5 to 6 ms pulse durations, with purpuragenic fluences, for the same spot size diameter and the same wavelength of 595 nm. The number of patients included for post-breast cancer radiotherapy was 176, presenting a total of 234 different lesions, 144 on the presternal area and 90 on the lateral side of the breast. The main criterion of efficacy was the number of needed sessions to obtain 80% reduction in telangiectasias, according to both the patient and the physician. The objective was to investigate if longer pulse durations would be more effective on more dilated vessels, typical of radiodermatitis, according

to the rules of selective photothermolysis. However, although the efficacy was satisfactory for both pulse times, the shorter pulse durations were more effective: all patients obtained at least 80% regression in telangiectasia, after two or three sessions for 84% of cases with the 1.5 ms, and in less than five sessions in 95% of cases.[41] Pulsed dye laser has been shown to be safe and well tolerated in this population with particularly atrophied skin. Purpura resolved within 10–15 days. No further supportive care is required apart from sunscreen for at least 6 weeks following the procedure. No severe side effects were observed, neither scars nor skin necrosis nor ulceration. Patients reported a significant improvement in quality of life. The physicians noticed an improved skin thickness, probably related to the remodeling effect, known with this laser. The authors suggested that other lasers, particularly fractional ablative lasers or, on this fragile skin, non-ablative lasers, could be effective in reducing atrophy and improving the skin texture.

Conclusion

Today, there is increasing evidence to support various strategies to limit and treat cutaneous reactions to radiotherapy. To prevent acute radiodermatitis, daily dermocosmetic use is useful from the beginning of radiotherapy. There is evidence for the efficacy of PBM to both prevent and cure acute radiodermatitis. In chronic radiodermatitis, treatment with vascular lasers, especially pulsed dye laser, using short pulse durations, has been shown to be effective with an excellent tolerance, inducing a better quality of life for the patients.

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Disclosure

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