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CUTANEOUS SIDE EFFECTS OF TARGETED THERAPY FOR COLORECTAL CARCINOMA

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Summary

Research in cancer development has led to the new treatment strategies based on gene and protein changes in cells that cause cancer. Such targeted drugs work differently than standard chemotherapy agents, and have different and usually less severe side effects.

Targeted chemotherapies have, however, enormous cutaneous adverse events which may lead to poor adherence, dose interruption and discontinuation of these therapeutic regimens. Skin changes have a significant influence on the quality of life of affected patients.

In colorectal cancer, several targeted drugs are currently employed. Agents administered in colorectal cancer that have resulted in significant cutaneous side effects include primarily the epidermal growth factor receptor inhibitors (EGFRIs) and capecitabine.

Common EGFRIs dermatologic adverse events are acneiform rash and xerosis. Less common findings are paronychia, regulatory abnormalities of hair growth, maculopapular rash, mucositis and postinflammatory hyperpigmentation. Management of skin rash should be individualized for each patient, depending on the type, severity and location of the skin toxicity caused by EGFRIs.

Hand-foot syndrome (HFS), or palmar-plantar erythrodysestesia, is the most common dose-limiting toxicity and the only clinically significant adverse event that frequently occurs with capecitabine compared to 5-FU/leucovorin intravenous administration.

Cutaneous side effects affect compliance, patients' quality of life, as well as the therapy regimen.

It is important to recognize and treat, as well as to administer efficacious prophylactic and therapeutic measures in a timely manner. This enables regular administration of adequate chemotherapy regimens and prolongs lives of oncology patients.

Studies have demonstrated a positive correlation between treatment efficacy and cutaneous side effects for both EGFRI and capecitabine. Therefore, cutaneous side effects can serve as a predictor of improved survival in these patients.

Since frequency and severity of skin lesions are dose-dependent, a gradual increase in dose until a cutaneous side-effect develops might be a good strategy to maximize the efficacy of EGFRIs and capecitabine.

Keywords: targeted therapy; cutaneous side effects; colorectal cancer.

INTRODUCTION

Research in cancer development has led to the new treatment strategies based on gene and protein changes in cells that cause cancer. Such targeted drugs work differently than standard chemotherapy agents, and have different and usually less severe side effects. In colorectal cancer several targeted drugs are currently employed. Vascular endothelial growth factor (VEGF) inhibitors include bevacizumab (Avastin®) and ziv-aflibercept (Zaltrap®). Epidermal growth factor receptor (EGFR) targeted drugs include cetuximab (Erbitux®) and panitumumab (Vectibix®). Rigorafenib (Stivarga®) is another targeted drug for advanced colorectal cancer and is known as kinase inhibitor [1].

Capecitabine is an oral fluoropyrimidine widely administered in patients with colorectal cancer [2].

Targeted chemotherapies have, however, enormous cutaneous adverse events which may lead to poor adherence, dose interruption and discontinuation of these therapeutic regimens. Skin changes have a significant influence on the quality of life of affected patients [3].

Agents administered in colorectal cancer that result in significant cutaneous side effects include primarily EGFRIs and capecitabine. Therefore, this article will in particular focus on side effects occurring in these two therapy regimens.

EGFRI

The epidermal growth factor receptor (EGFR) is overexpressed or dysregulated in several solid tumors including lung, head and neck and colorectal carcinoma. Dysregulated EGFR may result in uncontrolled cell growth, proliferation and angiogenesis and is associated with poorer prognoses, manifested by increased metastatic potential and poorer overall survival (OS). Thus, EGFR is an ideal target for antitumor therapy. EGFR inhibitors (EGFRIs) include tyrosin

kinase inhibitors (erlotinib and gefitinib) and the monoclonal antibodies (panitumumab, cetuximab) that competitively bind to the extracellular domain of EGFR and block cytoplasmic-domain phosphorilation. EGFR blockade results in growth arrest and apoptosis in cells dependent on EGFR for survival through the inhibition of downstream pathways [4,5].

As a class, EGFRIs are characterized by cutaneous adverse effects, mainly papulopustular reactions involving skin. In addition to leaving skin vulnerable to bacterial overgrowth and serious infection, skin rash can lead to dose modification or treatment discontinuation, potentially affecting the overall clinical benefits of the therapy [5].

EGFRI – cutaneous side effects

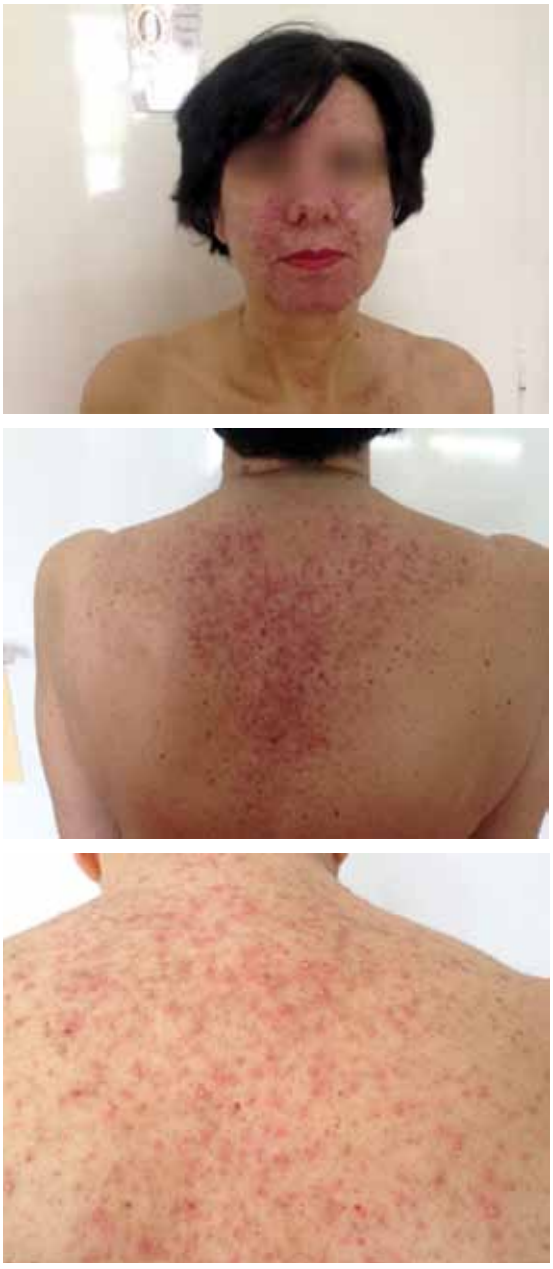
Pathobiology of EGFRI – associated cutaneous toxicity

EGFRIs affect basal keratinocytes which results in some of the cutaneous side effects. Inhibition of the EGFR mediated signaling pathways induces in keratinocytes growth arrest and apoptosis, decreasing cell migration, increasing cell attachment and differentiation and stimulating inflammation. All of these result in distinctive cutaneous manifestations [4].

Due to the interference of epidermal growth factor signaling in the skin, cutaneous adverse events are common. Common dermatologic adverse events are acneiform rash and xerosis [3].

Acneiform (papulopusutlar) rash

Acneiform rash is the most common EGFRI cutaneous adverse event reported in 50-100% of clinical trials. It can appear between day 2 to week 6 following initiation of therapy. Eruption is present in seborrhoic areas and resembles lesions of acne, but comedones, primary acne lesions, are absent. Such lesions can be painful, burning, irritating or pruritic. The periorbital region as well as palms and soles are usually spared [3]. *Figures 1-3* present some of our patients receiving EGFRI with characteristic acneiform lesions. Acneiform rash is consistent with NCI CTCAE, version 4.0, graded into 5 grades, as shown in *table 1* [6]. Lynch et al. described the clinical severity of acneiform rash as presented in *table 2* [7].



Figures 1.-3. Acneiform rash in patients on EGFRI therapy

Table 1. Acneiform rash grading*

Grade	Clinical status
1	Papules and/or pustules covering <10%BSA (body surface area), which may or may not be associated with symptoms of pruritus or tenderness
2	Papules and/or pustules covering 10-30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; associated with psychosocial impact; limiting instrumental ADL (activities of daily life)
3	Papules and/or pustules covering >30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; limiting self-care ADL; associated with local superinfection with oral antibiotics indicated
4	Papules and/or pustules covering any % BSA, which may or may not be associated with symptoms of pruritus or tenderness and are associated with extensive superinfection with IV antibiotics indicated; life-threatening consequences
5	Death

*according to NCI CTCAE, version 4.0. [6]

Table 2. Acneiform rash severity*

Toxicity	Description
Mild	Generally localized Minimally symptomatic No impact on ADL No sign of superinfection
Moderate	Generalized Mild symptoms (pruritus, tenderness) Minimal impact on ADL No sign of superinfection
Severe	Generalized Severe symptoms (pruritus, tenderness) Significant impact on ADL Potential for superinfection

*according to Lynch et al. [7]

Acneiform rash treatment

Prophylactic treatment of acneiform rash: based on randomized clinical trials, tetracycline and tetracycline class antibiotics (doxycycline 100 mg bid) for the first 6 weeks are recommended [7-11]. Hydrocortisone 1% combined with moisturizer, avoidance of prolonged sun exposure and application of sunscreen, although lacking evidence, should still be considered as general patient recommendations [3,8].

Reactive treatment

If patients develop EGFRI-associated toxicity, treatment based on clinical severity of the rash is suggested. In mild toxicities only topical therapy such as hydrocortison (1% or 2,5%) cream or clindamycin (1%) gel is recommended. There is no need to alter the EGFRI dosage [7].

In patients who develop moderate toxicity, local therapy as mentioned above is recommended, with an addition of tetracycline class of antibiotics. Doxycycline 2x100 mg bid is mainly advisable due to its more favorable safety profile compared to minocycline [7].

In cases of severe toxicity, reduction in the EGFRI dose is recommended. Therapy recommended for moderate toxicity should be administered, with an addition of a methyprednisolone dose pack. If toxicity does not diminish within 2-4 weeks of therapy interruption of EGFRI treatment is recommended according to the prescribing information [7].

In order to avoid dermal toxicity as well as increased risk for bacterial or viral superinfection, pulsed application of topical corticotsterods is advisable [7].

EGFRI induced acneiform rash differs from acne vulgaris, therefore topical therapy advised for this disease, such as topical retinoids or benzoyl peroxide, is not recommended [12].

Xerosis cutis

Xerosis cutis is the second most common cutaneous adverse event from EGFRI, which occurs in over 35% in most reports. It is presented as a dry, itchy scaly area of the skin and can progress to painful fissuring and eczema (eczema cracquelée). It may take place at sites where papulopustules have developed; however, more widespread involvement usually occurs. Symptomatic treatment including use of emolients is advisable [3,12].

In case of occurrence of fissures, which mainly develop on the hands and feet, creams or ointments with dexpanthenol are used to soften the skin and enhance healing [12].

Less common findings are paronychia, regulatory abnormalities of hair growth, maculopapular rash, mucositis and postinflammatory hyperpigmentation [3].

Paronychia

Paronychia is described in 5-20% of patients and usually develops after 1-2 months. In severe cases ingrown nail, periungual abscess and pyogenic granuloma-like lesions can occur [3].

Management strategies include wearing comfortable shoes, trimming nails but avoiding aggressive manicuring, and wearing gloves while cleaning. Topical corticosteroids and anti-inflammatory dose tetracyclines to decrease periungual inflammation and antibiotic soaks are advisable. Electrocautery, sliver-nitrate and nail avulsion are recommended to eliminate excessive granulation tissue [8].

Hair growth disturbances

Abnormalities of hair growth occur infrequently and usually develop 2-5 months after initiating EGFRI. Trichomegaly and facial hypertrichosis (hirsutism) can be seen after the first 1-2 months of therapy, and they tend to persist for the duration of EGFRI therapy. Temporary or permanent hair removal may be advised. Aberrant eyelashes may lead to corneal irritation and ulceration. Trichomegaly can be treated with lash clipping every 2-4 weeks and referral to an ophthalmologist is indicated for patients with irritation or persistent discomfort [3,8].

Non-scarring alopecia may occur after 2-3 months of therapy. It may progress to diffuse alopecia and generally resolves after treatment discontinuation, although hair regrowth may be of varying quality. Minoxidil 2% and 5% may be used. Scarring alopecia has also been reported, and treatment options include topical corticosteroids (shampoos, creams and lotions), [8].

Mucositis

Oral mucositis is rare in EGFRI treated patients and may present as erythema, aphthous-like stomatitis or superimposed upon those of radiation and conventional chemotherapy. Prevention and treatment of oral complications include thorough oral care, aggressive pain management with topical analgesics and systemic analgesics as needed, adequate nutritional support, radiation treatment planning that optimizes therapeutic index, benzydamine oral rinse [8].

Postinflammatory hyperpigmentation

Postinflammatory hyperpigmentation occurs in approximately 10% of patients with acneiform rash. It is therefore recommended that patients take appropriate sun protective measures while receiving EGFRIs [13].

Management of skin rash should be individualized for each patient, depending on the type, severity and location of the skin toxicity caused by EGFRIs [5].

Patient should be referred to a dermatologist in following situations:

1) If the skin toxicity does not improve within 1-2 weeks of treatment;
2) If the patient is severely symptomatic;
3) If the skin toxicity has an uncharacteristic appearance of distribution [5].

The effect of EGFRI and concomitant radiotherapy

EGFRIs are very often administered concomitantly with radiotherapy. Effects can be divided into the early and late phases. In the early phase, when EGFRIs are introduced simultaneously with radiation compared to radiation alone, radiation dermatitis as well as EGFRI side effects increase. Skin eruption occurs predominantly in irradiated areas. This is due to synergistic cytotoxicity and the therapeutic response of to two agents [3].

In the late phase, however, prolonged radiation leads to the absence of skin toxicity to EGFRIs in the preirradiated area. The reason for this is depletion of basal layer stem cells due to apoptosis induced by radiation [3].

EGFRI efficacy and severity of skin rash

It has been shown that the presence and severity of cutaneous side effects have a positive correlation with patient survival and tumor response. Since frequency and severity of skin lesions are dose dependent, a gradual increase in dose until skin eruption develops may be a good strategy to maximize the efficacy of EGFRIs [3,7].

Capecitabine

Capecitabine is registered for the treatment of several tumor entities including colorectal-, gastric- and breast cancer. It is an orally administered 5-fluorouracil (5-FU) prodrug designed to mimic the pharmacokinetics of infusional 5-FU [14].

It is generally well-tolerated , with hand foot syndrome beeing the only clinical adverse event that commonly occurs with capecitabine treatment [2].

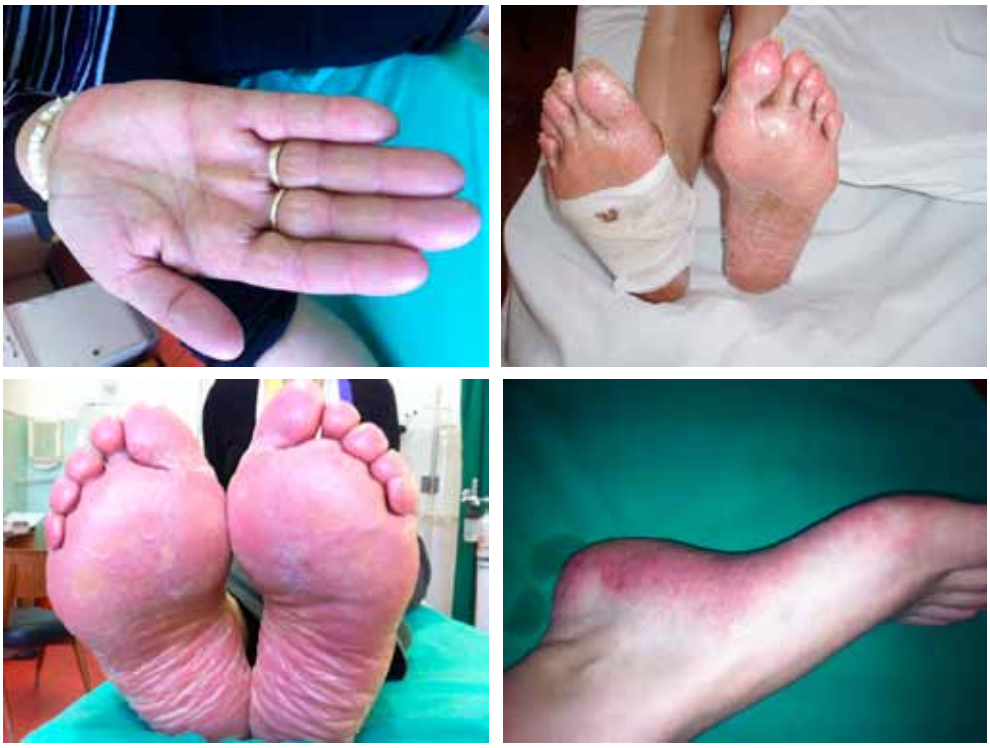
Hand-foot syndrome (HFS), or palmar-plantar erythrodysestesia is the most common dose-limiting toxicity and the only clinically significant adverse event that frequently occurs with capecitabine compared to 5-FU/leucovorin intravenous administration [2]. HFS incidence in patients receiving capecitabine is 50-60%, while grade III toxicity appears in 10-17% of patients [15].

This side effect is common with administration of some other cytotoxic drugs such as continuous 5-FU infusion, doxorubicin, cytarabine or docetaxel [16].

The mechanism responsible for HFS is unknown, although it is frequently considered as a type of inflammation [15]. Recent data indicate that HFSR (Hand-foot-skin-reaction) may be caused by a reduction in the oxidative potential of the skin due to intensive radical formation [14].

The risk factors of HFS have been reported to be older age, female sex, improved performance, continuous infusion of chemotherapy agents as well as inclusion of docetaxel in chemotherapy regimen [15].

Patients usually present with a prodrome of dysesthesia affecting palms and soles. The condition progresses in a few days to burning pain sensations together with well-defined swelling and erythema. If the drug dose is not adjusted there may be skin breakdown, desquamation, bullous formation or secondary infections. This is the reason why HFS can lead to reduced compliance and quality of life [2]. Clinical aspects of hand foot syndrome in our patients are shown in *Figures 4-7*. The hand-foot syndrome grading scale is shown in *Table 3* [6]. Treatment-options for HFS are described in *Table 4* [2].



Figures 4.-7. Hand foot syndrome in patients receiving capecitabine.

Table 3. Hand-foot syndrome grading*

Grade	Clinical status
1	Minimal skin changes or dermatitis (erythema, edema, hyperkeratosis) without pain
2	Skin changes (peeling, blisters, bleeding, edema or hyperkeratosis) with pain, limiting instrumental ADL
3	Severe skin changes (peeling, blisters, bleeding, edema, hyperkeratosis) with pain; limiting self-care ADL

*according to NCI CTCAE, version 4.0.[6]

Table 4. Management of the hand- foot syndrome*

Grade I	Maintain dose Apply skin barrier cream and apply MEBO (moist exposed burn ointment)
Grade II	Maintain or reduce dose by 25% Apply MEBO Supportive care
Grade III	Interrupt one cycle Adjust dose Apply MEBO Supportive care
Supportive care	Avoid extremes in temperature, pressure and friction of hand and foot Cooling the hand and foot Cushioning sore skin Keeping the skin exposed to air Preventing excess sweating

*according to Son et al [2]

Zhang et al. demonstrated in a single-center, prospective, randomized phase II trial that celecoxib (COX-2 inhibitor) can prevent capecitabine-related hand foot syndrome in stage II and III colorectal cancer patients [15].

Several studies confirmed that HFSR is a predictor of improved survival in patients with colorectal cancer [14,17,18]. A study by Hofheniz et al. indicates that the development of HFSR may be regarded as an independent clinical predictor of improved survival in patients with colorectal cancer regardless of the time point of HFSR development. Testing individual dose optimization or titration of capecitabine according to development HFSR may be an appealing strategy for future studies [14].

Azuma et al. confirmed significant association between the hand-foot syndrome and the efficacy of capecitabine in patients with metastatic breast cancer [19].

CONCLUSION

Cutaneous side effects affect compliance, patients' quality of life, as well as the therapy regimen.

It is important to recognize and treat as well as to administer efficacious prophylactic and therapeutic measures in a timely manner. This enables regular administration of adequate chemotherapy regimens and prolongs the lives of oncology patients.

Studies have demonstrated a positive correlation between treatment efficacy and cutaneous side effects for both EGFRI and capecitabine. Therefore, cutaneous side effects can serve as a predictor of improved survival in these patients.

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Sažetak

Kožne nuspojave u bolesnika na ciljanoj terapiji raka kolorektuma

Istraživanja nastanka zloćudnih tumora dovela su do novih vrsta liječenja koje se zasnivaju na promjenama gena i proteina u stanicama zloćudnih tumora. Takvi ciljani lijekovi imaju drugačiji mehanizam djelovanja od standardnih citostatika, te obično blaže nuspojave.

Ciljani lijekovi međutim imaju značajne nuspojave na koži koje mogu dovesti do slabije suradljivosti bolesnika, izostavljanja pojedinačne doze ali i prekida liječenja. Promjene na koži znatno utječu na kvalitetu života bolesnika.

U liječenju kolorektalnog karcinoma primjenjuje se nekoliko ciljanih lijekova. Od njih značajne nuspojave na koži imaju inhibitori epidermalnog čimbenika rasta (EGFRI), te kapecitabin.

Česte dermatološke nuspojave EGFRI su akneiformni osip i suhoća kože, dok su manje česti paronihija, poremećaji u rastu dlaka, makulopapulozni osip, mukozitis i postinflamatorne hiperpigmentacije. Liječenje nuspojava na koži treba biti prilagođeno svakom bolesniku, ovisno o vrsti, težini i mjestu nastanka promjena.

Hand-foot syndrom (HFS, sindrom šaka i stopala) ili palmo-plantarna eritrodizestezija je najčešća toksičnost koja ograničava doziranje lijeka i jedina klinički značajna nuspojava koja se često javlja tijekom liječenja kapecitabinom u usporedbi s intravenskom primjenom 5-FU/leukovorina.

Nuspojave na koži utječu na suradljivost, kvalitetu života bolesnika te provođenje terapije.

Važno je na vrijeme prepoznati, liječiti te primijeniti učinkovite profilaktičke i terapijske mjere. Na taj način se osigurava redovita primjena odgovarajuće terapije i produžava život onkoloških bolesnika.

Kliničkim studijama je dokazana pozitivna povezanost učinkovitosti liječenja onkoloških bolesnika i nuspojava na koži kod uporabe EGFRI i kapecitabina. Stoga nuspojave na koži mogu poslužiti kao prediktor boljeg ishoda bolesnika.

Budući su učestalost i težina nuspojava na koži ovisne o dozi lijeka, postupno povišenje doze do pojave nuspojava na koži može biti dobar način povećanja učinkovitosti kako EGFRi tako i kapecitabina.

Ključne riječi: ciljana terapija; nuspojave na koži; kolorektalni karcinom.

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