MINISTRY OF EDUCATION
University of Medicine and Pharmacy of Craiova
DOCTORAL SCHOOL

MANAGEMENT OF SKIN TOXICITY IN CANCER PATIENTS TREATED WITH EPIDERMAL GROWTH FACTOR RECEPTOR INHIBITORS

SUMMARY OF THE PhD THESIS

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INTRODUCTION

The introduction of molecularly targeted therapy, in particular EGFR inhibitors, was an important step in the field of oncology, targeting tumour cells in the human body with minimal effect on healthy cells.

In recent years, oncology studies have focused on molecularly targeted therapy, developing numerous agents with a role in inhibiting the epidermal growth factor receptor (EGFR), a receptor that when overexpressed plays an extremely important role in the growth of certain tumour cells.

Compared to classical chemotherapy, the systemic side effects of molecularly targeted therapy are much less. However, 80-100% of patients treated with epidermal growth factor receptor inhibitors develop a separate class of adverse effects, namely dermatological adverse reactions ranging from mild-to-severe forms.

Epidermal growth factor inhibitors (EGFRI) are used in the treatment of several types of advanced solid cancers such as colorectal cancer, non-small cell lung cancer, oral cancer, breast cancer, gastric cancer, ovarian cancer and prostate cancer.

Due to the cumulative skin toxicity, the dermatological effects have a major impact on the psychosocial state of these patients. Correct and rapid management is essential in allowing the continuation of molecularly targeted therapy, with increased survival rates.

This thesis is a prospective, interdisciplinary study that highlights the importance of early identification of all dermatological adverse effects following EGFRI treatment and the importance of correct and rapid management with minimal impact on the gut microbiome.

The main objective of this PhD thesis was to obtain new information, useful both in scientific research and in the adjustment of protocols aimed at

the management of skin toxicity in cancer patients undergoing treatment with EGFRI.

This PhD thesis aims to investigate cancer patients being treated with various EGFRI agents, some recently approved in the treatment regimen, in order to identify, count, stage early the totality of dermatological adverse effects triggered by EGFRI therapy, to follow them dynamically throughout the 4-year study or until the patient's death, given the short life span of these patients.

In order to provide comprehensive clinical data on each dermatological adverse effect, the clinical examination was completed for the first time with dermoscopic examination at the patient's bedside. This made it possible to compare the degree of toxicity observed clinically and the degree of toxicity established by supplementing the clinical examination with imaging, obtaining information at the microscopic level.

CURRENT STATE OF KNOWLEDGE

The first section of the PhD thesis, entitled Current state of knowledge, offers an updated overview on skin toxicity in cancer patients following molecularly targeted therapy with EGFRI with particular identification of all dermatological effects according to each therapeutic agent, assessment of the severity of these reactions by dermoscopic evaluation and international scales, as well as assessment of the impact on quality of life and microbiota of these reactions characteristic of the whole class of EGFRIs. Additionally, there are also reviewed epidemiological data and the etiopathogenesis of these dermatological adverse effects.

Specifically, the first chapter presents new data regarding the main classes of epidermal growth factor inhibitors currently used in the treatment

of advanced solid tumours such as colorectal cancer, non-small cell lung cancer, head and neck cancer, breast cancer, gastric cancer, ovarian cancer and prostate cancer [1-3].

EGFR inhibitors fall into 2 categories:

- monoclonal antibodies (Cetuximab/Erbitux, Panitumumab/Vectibix and Pertuzumab/Perjeta) with special action in the extracellular domain;
- tyrosine kinase inhibitors (Erlotinib/ Tarceva, Lapatinib/Tyverb) (1) acting on the intracellular domain.

In the second chapter new data about skin toxicity is reviewed, highlighting the full range of skin manifestations, adverse effects on skin appendages and hair follicles. The entire EGFRI class is characterised by dermatological adverse effects, of varying severity, with impact on quality of life, psychological, emotional and psychosocial state [4,5].

The localization of these adverse effects highlights the role of EGFR in the skin, hair follicle and nails [6].

The third chapter has the purpose of introducing the reader in the sector of dermatoscopic evaluation and assessment of severity of adverse effects using international scales such as NCI CTACE, developed by the National Cancer Institute and MESTT (MASCC EGFRI Skin Toxicity Tool) developed by MASCC- Multinational Association for Suportive Care in Cancer highlighting the importance of categorizing these adverse skin reactions into different degrees of severity in order to manage skin toxicity early and accurately and prevent oncological dose changes or even discontinuation of EGFRI therapy. Even in mild severity cases, skin toxicity has an important emotional and psychological impact with impaired quality of life [7].

The usefulness of dermoscopy has increased impressively in the last decade, being used both in monitoring treatment and assessing prognosis in various inflammatory diseases, infections, hair and nail diseases [8-12].

The fourth chapter presents data regarding the presence of IgE antibodies against alpha-1,3-galactose (alpha-Gal) in patients receiving Cetuximab and the implications of their serum levels. The determination of alpha-Gal specific IgE can be performed by 2 methods: from serum using ELISA or by ImmunoCAP determination.

The presence of IgE antibodies against alpha-1,3-galactose specific antibodies prior to the start of Cetuximab treatment is an important consideration, as most severe adverse effects occurred in patients with elevated pre-treatment specific antibody levels [13-14].

The fifth chapter contains information on therapeutic ways to combat dermatological side effects by topical treatments or antibiotic treatment. The management of skin toxicity is a controversial topic as there is currently no specific guideline on the institution of pre-reactive or reactive antibiotic treatment, most often guided by the personal experience of the treating physician.

The sixth chapter presents recent data on the human microbiome and its variations according to antibiotic treatment. The frequent occurrence of EGFRI-induced dermatological adverse effects in colorectal cancer patients often requires antibiotic treatment with tetracyclines to manage dermatological and mucosal toxicity [15], with the production of varying degrees of gut dysbiosis.

PERSONAL CONTRIBUTIONS

Study 1: Identification and analysis of dermatological adverse effects following EGFRI treatment

Compared to classical chemotherapy, systemic effects are much less in patients treated with EGFRI. However, due to the location of EGFR and its role, EGFR inhibitors are characterised by the extremely frequent occurrence of dermatological adverse effects, loss of integument integrity.

Skin toxicity presents a broad picture consisting of papulopustular eruptions, xerosis, pruritus, fissures, blepharitis, paronychia, hair changes, hypo, hyperpigmentation.

Both subclasses of EGFRI are characterised by skin toxicity. However, studies show a higher incidence of papulopustular rash and a higher degree of severity in patients treated with monoclonal antibodies compared to patients treated with tyrosine kinase inhibitors [3,16].

Due to these hypotheses, the study included 41 patients with different types of cancer, treated with different EGFRI agents in order to identify and characterize as comprehensively as possible the skin toxicity in the Romanian population, achieving a complete skin toxicity profile according to the EGFRI agent administered.

Although the frequency of dermatological effects is very high, with only 10-20% of patients experiencing serious, life-threatening effects, EGFRI-induced skin toxicity frequently also generates emotional, physical and psychosocial changes with impact on quality of life (QoL). An important role is played by extensive, facially localised and debilitating forms [17,18].

The main objectives of this study are:

-to obtain epidemiological data regarding skin toxicity occurring in Romanian oncological patients with different types of cancer under treatment with different epidermal growth factor receptor inhibitors (EGFRI),
-identification and complex characterisation of dermatological adverse effects and skin appendages in EGFRI patients in Romania by clinical examination supplemented with imaging assessment using portable dermatoscope at the bedside,
-introducing dermatoscopic assessment for classification into various degrees of severity with greater accuracy,
-correlations between EGFR expression and clinico-pathological parameters (age, gender, location)
-assessment of rash severity using international scales, correlations between rash severity and various EGFRI agents,
-obtain information on the impact of skin toxicity on quality of life and adherence to treatment, in relation to epidemiological data obtained on: age, gender, type of cancer and class of EGFRI used.

Study 2: Analysis of EGFRI-induced skin toxicity. Clinical and IgE antibodies against alpha-1,3-galactose correlations

The use of EGFRI has increased considerably due to much reduced systemic effects compared to classical chemotherapy, however EGFRI-induced adverse effects are divided into severe hypersensitivity reactions (may occur with the first infusion, rarely with subsequent infusions), reactions mediated by pre-existing IgE antibodies and dermatological adverse effects occurring during EGFRI treatment. [19,20].

Alpha-gal is the only oligosaccharide known to date that reacts with preformed IgE antibodies.

The increased presence of these specific antibodies in the serum of patients pre-treatment with cetuximab was correlated with the severity of hypersensitivity reactions (HSR) (laryngeal oedema, urticaria, anaphylactic shock, hypotension, myocardial infarction), divided into various degrees of severity according to HSR CTCAE (Common Terminology Criteria for Adverse Events) [21].

Not only HSR reactions are important to manage but also dermatological adverse effects occurring during treatment with EGFRI. Like HSR reactions, skin toxicity occurring during treatment with EGFRI can lead to discontinuation of cancer treatment or even death of the patient.

The extent of dermatological adverse effects following EGFRI treatment and the impact on quality of life prompted us to assess serum levels of IgE antibodies against alpha-1,3-galactose (alpha-Gal) in patients with varying degrees of severity. This study is the first to assess the feasibility and applicability of alpha-Gal values related to the severity of dermatological adverse effects occurring during EGFRI treatment, evaluating the utility of IgE antibodies against alpha-1,3-galactose not only in triggering HSR.

19 patients (16 males/ 3 females) receiving Cetuximab were included in the study. Patients were examined clinically and dermatoscopically on a regular basis. Blood samples were collected for determination of IgE antibodies against alpha-1,3-galactose (alpha-Gal) and to study a possible association between anti-alpha-galactose IgE level and the severity of skin reactions present. Two international NCI CTCAE and MESTT questionnaires were used to assess the severity of skin toxicity in order to obtain comprehensive information on the full range of dermatological adverse effects.

The purpose of this study was dictated by the importance of dermatological adverse effects and the massive impact they have on the lives

of cancer patients, assessing IgE antibodies against alpha-1,3-galactose levels in patients on EGFRI (cetuximab) treatment, resulting in data on the assessment of the accuracy and applicability of alpha-Gal in evaluating skin toxicity developed during EGFRI treatment. Another aim of this study was to correlate IgE antibodies against alpha-1,3-galactose levels with the severity of dermatological adverse effects during EGFRI treatment.

According to the serum IgE antibodies against alpha-1,3-galactose values in this study we have seen significant serum changes that are easily seen in patients with intense and persistent pruritus, which often require antihistamine treatment. Also hair changes show an increase in direct relation to serum alpha-Gal determinations.

According to ELISA test results, serum IgE antibodies against alpha-1,3-galactose levels are directly proportional to the severity of rashes in patients with purpura and hair changes.

Following data correlation, in the studied group patients with mild intermittent pruritus and not requiring anti-pruritic treatment (grade 1) showed values between 0.712-1.323 ng/ml with a mean of 1.039, patients with moderate pruritus requiring treatment (grade 2 A and 2 B) showed values 0.873-10.39 ng/ml with a mean of 2.36 ng/ml of IgE antibodies against alpha-1,3-galactose, thus showing an increase in IgE antibodies against alpha-1,3-galactose levels with pruritus severity.

Also in patients with hair changes we recorded directly proportional increase in severity of adverse effects in correlation with IgE antibodies against alpha-1,3-galactose level with values ranging from 0.712-10.39 ng/ml compared to patients with no hair changes (grade 0) who had 1.028-1.062 ng/ml.

Early identification of IgE antibodies against alpha-1,3-galactose levels and initiation of prophylactic treatment may be a first starting point in the

development of a standardized guideline for the use of prophylactic or reactive treatment, so necessary in daily medical practice.
The use and determination of IgE antibodies against alpha-1,3-galactose levels for another purpose as well, namely for the assessment of skin toxicity, is achieved for the first time with this study.

Study 3: Integration of dermoscopy in the evaluation of patients with EGFRI and its role in the prophylactic management of antibiotic treatment

Dermatoscopy or epiluminescence microscopy is an in vivo diagnostic method that allows for magnified imaging of skin structures: the epidermis, the dermal-epidermal junction as well as the dermal papillae [22, 23, 24]. Dermoscopy has many uses and can be used in both the assessment and diagoscopy of neoplastic skin disorders [22], nail disorders (onychoscopy) [25], scalp and hair disorders (trichoscopy) [26], inflammatory dermatoses (inflammoscopy) or infectious skin diseases (entomodermoscopy) [9].

The introduction of dermoscopy in the assessment of dermatological adverse effects arising from various medical treatments has been highlighted by numerous studies.

Eleven colorectal cancer patients treated with molecular targeted therapy (EGFRI) who were free of skin adverse reactions at the time of enrolment were included in the study.

The 11 patients were monitored dermatologically on an ongoing basis for the development of papulopustular rash. Using the Heine 30 dermatoscope, we were able to perform accurate and thorough assessment of adverse skin features in patients treated with EGFRI, also identifying features invisible to the eye at the time of examination. The portable availability of this

dermatoscope allowed the evaluation of patients directly in the oncology centre where they were undergoing EGFRI treatment.

Dermoscopic evidence of papulopustular eruption allowed the 11 patients to be classified into 2 groups. The first group of patients received antibiotic treatment with prophylactic doxycycline. The pustules were visible only microscopically and could not be identified by the naked eye. Group 2 patients received reactive doxycycline treatment after clinical evidence of papulopustular rash.

Although the study was single-centre, conducted on a relatively small group of patients, the analysis highlighted the importance of full dermatological assessment and the introduction of dermoscopic assessment in patients with EGFRI as a possible starting point for the timing of antibiotic treatment.

By integrating dermoscopic analysis, the time required for antibiotic treatment until resolution of the papulopustular rash was 2.5 weeks in group 1 where treatment was administered at the microscopic pustule stage, compared to a treatment duration of approximately 5 weeks in patients who received antibiotic treatment after clinical evidence of the initially dermoscopically visualized rash.

The aim of this study was to perform a comprehensive clinical dermatological examination of EGFRI-induced skin toxicity and to obtain information on the microscopic aspects of these effects, as well as to provide information on the administration of pre-reactive or reactive antibiotic treatment directed by microscopic pustules identification.

Early identification and rapid management at the stage of microscopic pustules shortened the duration of antibiotic treatment compared to patients who received antibiotic treatment after clinical formation of these pustules.

Study 4: Management of EGFRI-induced skin toxicity and implications on microbiome

There is no specific guidance on the management of skin toxicity with doxycycline. Most commonly, the management of dermatological treatment is related to the experience of the treating physician, with treatment being prophylactic or reactive in these patients.

Controversies regarding antibiotic treatment in colorectal cancer patients are based on literature reports that these patients have altered gut flora and that antibiotic treatment would add to the already existing dysbiosis.

The use of antibiotic treatment causes numerous changes in the intestinal flora. Most commonly these changes consist of a decrease in beneficial, protective bacteria and an overexpression of pathogenic or putrefactive bacteria [27].

In the present study we have highlighted the variations in the intestinal bacterial and fungal flora found in cancer patients treated with EGFRI and doxycycline for short and long periods of time, respectively, showing overexpression of Escherichia coli (E.coli) values in all patients treated with doxycycline for 8 weeks.

Overexpressions of Escherichia coli were also identified in the colorectal cancer patients in this study treated with antibiotic treatment (doxycycline). All patients on long-term (8 weeks) doxycycline treatment showed dysbiosis of the putrefactive flora characterised by overexpression of E coli, compared to the group of patients on short-term (2 weeks) antibiotic treatment where only one patient showed a slight increase in E coli levels.

Also in terms of fungal populations in patients with a longer duration of antibiotic treatment (group 2) an overexpression of Candida albicans, other Candida species and Geotrichum species present in 4/5 of the patients was

identified compared to patients who received antibiotic treatment for a shorter period (group 1) in which only one patient showed overexpression of Geotrichum species.

As for the patients included in the study, both groups of patients showed acute dysbiosis of species defining the protective flora.

In the group of patients treated with antibiotics for a longer duration (8 weeks), a greater deficiency of Enterococcus species was observed compared to patients receiving antibiotic treatment for 2 weeks.

Through this study we reported dysbiosis occurring in colorectal cancer patients undergoing treatment with EGFRI and doxycycline making a personal contribution to the literature, from our data it is the first study of its kind conducted in Romania. Representing a starting point for a larger study on a larger number of patients to allow the development of a guideline on prophylactic or reactive treatment. The main limitation of this study is the relatively small number of patients. Another limitation is related to the lack of microbiome analysis even before the start of antibiotic treatment, thus being able to dynamically highlight the totality of changes in the gastrointestinal microbiome.

This study represents a personal contribution to the study of the gut microbiome in colorectal cancer patients on EGFRI and skin toxicity. By identifying the bacterial and mycotic species that cause gut dysbiosis, and highlighting dysbiosis occurring following treatment with doxycycline, widely used in these patients. Understanding these data could facilitate the choice of prophylactic or reactive doxycycline treatment and hence the duration of antibiotic treatment in patients with skin toxicity on EGFRI, and represent a starting point for larger studies with larger numbers of patients.

GENERAL CONCLUSIONS AND NOVELTY

This Phd thesis offers new perspectives regarding the emerging role of early and accurate identification of skin toxicity and management of skin adverse effects with minimal impact on the gut microbiome, increasing the quality of life of EGFRI patients. The present studies have several elements of innovation.

Study 1 showed that the identification and detailed analysis of dermatological adverse effects according to each EGFRI agent allowed the development of a complete skin toxicity profile characteristic of each EGFRI agent in the Romanian population. Obtaining epidemiological data on the incidence, type and severity of dermatological adverse effects generated by the classes of anti-EGFR agents represents an opportunity to guide future dermatological prevention and treatment strategies and to allocate the necessary resources to reduce morbidity and mortality rates and the socio-economic impact of these cancers.

Study 2 was the first study in the literature comparing IgE antibodies against alpha-1,3-galactose level with severity of skin toxicity during EGFRI treatment.

The frequency and impact on quality of life of dermatological adverse effects following EGFRI treatment requires intensive studies to detect markers of severity and to guide prophylactic or reactive dermatological treatment. Following evaluation of the applicability and feasibility of IgE antibodies against alpha-1,3-galactose, correlations were found between increased alpha-

Gal levels and severity of pruritus and hair changes using these markers may further dictate both oncological and dermatological management. Prospective studies enrolling a larger number of patients are needed to validate the hypotheses of this study.

Study 3 showed the usefulness of dermoscopic examination in the evaluation of adverse skin effects during EGFRI treatment.

The current study demonstrated that dermoscopic analysis complements the clinical examination and can intervene in the institution of prophylactic antibiotic treatment at the time of dermoscopic visualization of the pustules, before they become clinically manifest, facilitating the attending physician's decision to administer antibiotic treatment over a shorter period of time with minimal effects on the gut microbiome.

To our knowledge, no study has been published highlighting the importance of integrating dermoscopic analysis into the consultation and management of EGFRI patients with skin toxicity. Therefore, this study represents a personal contribution to the monitoring of dermatological treatment with doxycycline in EGFRI patients by dermoscopic examination.

Study 4 report for the first time intestinal dysbiosis triggered by antibiotic treatment in colorectal cancer patients receiving EGFRI.

The use of antibiotic treatment has profound and sometimes persistent effects on the gut microbiota by depleting beneficial species and overexpressing pathogenic species, especially in colorectal cancer patients with an already altered gut flora. Overexpression of Escherichia coli species and overexpression of candida species in patients who received doxycycline for a longer period of time compared to the 2-week group could form the basis for further studies to provide a starting point for the development of a standardised guideline for the use of pre-reactive or reactive antibiotic treatment. At the same time, we stress the importance of analysing the

intestinal microbiome of these patients, which, by highlighting overexpressed species or identifying the deficiency of certain protective species, can guide the administration of probiotics to cover and repair the affected intestinal flora. Originality of the thesis is also given by the multidisciplinary nature of the research.

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