An Investigation into the Acneiform Eruption Induced by Epidermal Growth Factor Receptor Inhibitors

Rachel Bierbrier

Division of Experimental Medicine
Faculty of Medicine and Health Sciences
McGill University
Term: Summer 2022

A thesis submitted to McGill University as part of the requirements of the degree Master of Science in Experimental Medicine.

Table of Contents

TABLE OF CONTENTS 2

ABSTRACT 4

RESUMÉ 5

ACKNOWLEDGEMENTS 6

CONTRIBUTION OF AUTHORS 7

TABLES AND FIGURES 8

ABBREVIATIONS 9

INTRODUCTION AND LITERATURE REVIEW 10

Tyrosine Kinase Signaling and Targeted Cancer Therapy 10
Spectrum of Cutaneous Adverse Events Caused by EGFR inhibitors 12
Acneiform Eruptions Secondary to EGFR inhibitors 12
Pathogenesis of Acneiform Eruptions Secondary to EGFR inhibitors 12
Clinical Assessment and Assessment of Severity 13
Management of Acneiform Eruptions 14
Objectives of Research 17
Description of Study Population, Inclusion and Exclusion Criteria 17
Design and Description of Methodology 18
Definition of End Points 18
Details on Confidentiality and Ethical Considerations 19

CHAPTER ONE: RETROSPECTIVE REVIEW TO IDENTIFY RISK FACTORS FOR THE DEVELOPMENT OF ACNEIFORM ERUPTIONS IN PATIENTS ON EPIDERMAL GROWTH FACTOR RECEPTOR INHIBITORS 20

Prognostic factors for the development of acneiform eruptions in patients on epidermal growth factor receptor inhibitors 21
Key Points *21*
Abstract *21*
Background and Rationale *22*
Methods *23*
Study Design *24*
Statistical Analysis *25*
Results *26*
Discussion *27*
Conclusions *31*
References *31*

CHAPTER TWO: AN ANALYSIS OF THE TREATMENT PATTERNS ACNEIFORM ERUPTIONS SECONDARY TO EPIDERMAL GROWTH FACTOR RECEPTOR INHIBITORS IN DERMATOLOGISTS AND ONCOLOGISTS IN CANADA 41

An Analysis of the Treatment Patterns Acneiform Eruptions in Dermatologists and Oncologists in Canada 42
Abstract *42*
Background and Introduction *42*
Methods *44*
Results *44*
Discussion *45*
Conclusions *48*
References *49*

CHAPTER THREE: A SYSTEMATIC REVIEW OF ORAL RETINOIDS FOR TREATMENT OF ACNEIFORM ERUPTIONS INDUCED BY EPIDERMAL GROWTH FACTOR RECEPTOR INHIBITORS **55**

A SYSTEMATIC REVIEW OF ORAL RETINOIDS FOR TREATMENT OF ACNEIFORM ERUPTIONS INDUCED BY EPIDERMAL GROWTH FACTOR RECEPTOR INHIBITORS 56

Abstract *56*

Background and Introduction *57*

Methods *58*

Results *59*

Discussion *61*

References *63*

DISCUSSION **79**

CONCLUSIONS **81**

REFERENCES **82**

Abstract

The use of targeted therapy against epidermal growth factor receptors, a tyrosine kinase receptor, has come to the forefront for many cancers including lung cancer, head and neck cancers and gastrointestinal malignancy. Although these agents are associated with a lower incidence of systemic side effects, there is a higher frequency of mucocutaneous side effects, specifically an acneiform eruption. Little is known about patient risk factors for the development of severe acneiform eruptions. Given that the onset of the eruption is soon after initiating EGFR therapy, identifying high risk groups and starting prophylactic therapy early on may prevent severe cutaneous adverse reactions. Chapter one is an investigation into risk factors for the development of acneiform eruptions in a cohort of non-small cell lung cancer patients in Montreal, Canada. Effective management of cutaneous adverse events can improve patient outcomes and prevent cancer therapy discontinuation. There is data demonstrating different strategies used by oncologists and dermatologists for management of the acneiform eruptions. However, little is known regarding the Canadian landscape on management of the eruption between specialties. Chapter two is a cross sectional investigation into the management strategies of acneiform eruptions by dermatologists and oncologists across Canada. Currently, the preferred systemic therapy for management of acneiform eruptions in guidelines are tetracycline antibiotics, with little data on alternative therapeutic options. Therefore, the objective of Chapter three is to explore the current literature on the management of the acneiform eruption using systemic retinoids.

Resumé

L'utilisation d'une thérapie ciblée contre les récepteurs du facteur de croissance épidermique, un récepteur de la tyrosine kinase, est passée au premier plan pour de nombreux cancers, notamment le cancer du poumon, les cancers de la tête et du cou et les tumeurs malignes gastro-intestinales. Bien que ces agents soient associés à une incidence plus faible d'effets secondaires systémiques, il existe une fréquence plus élevée d'effets secondaires cutanéo-muqueux, en particulier une éruption acnéiforme. On sait peu de choses sur les facteurs de risque des patients pour le développement d'éruptions acnéiformes sévères. Étant donné que l'apparition de l'éruption survient peu de temps après le début du traitement par EGFR, l'identification des groupes à haut risque et le démarrage précoce du traitement prophylactique peuvent prévenir les effets indésirables cutanés graves. Le chapitre un est une enquête sur les facteurs de risque de développement d'éruptions acnéiformes dans une cohorte de patients atteints d'un cancer du poumon non à petites cellules à Montréal, au Canada. Une gestion efficace des événements indésirables cutanés peut améliorer les résultats pour les patients et prévenir l'arrêt du traitement anticancéreux. Il existe des données démontrant différentes stratégies utilisées par les oncologues et les dermatologues pour la prise en charge des éruptions acnéiformes. Cependant, on sait peu de choses sur le paysage canadien de la gestion de l'éruption. Par conséquent, le chapitre deux est une enquête transversale sur les stratégies de prise en charge des éruptions acnéiformes par les dermatologues et les oncologues à travers le Canada. Actuellement, la thérapie systémique préférée pour la prise en charge des éruptions acnéiformes dans les lignes directrices sont les antibiotiques tétracyclines, avec peu de données sur les options thérapeutiques alternatives. Par conséquent, l'objectif du chapitre trois est d'explorer la littérature actuelle sur la prise en charge de l'éruption acnéiforme à l'aide de rétinoïdes systémiques.

Acknowledgements

I would like to thank my loving family (Mom, Dad, Josh, Jordan, Jared and Stitch) and my boyfriend MacKay Russell for their unwavering support in pursuit of this degree and my other academic endeavours. I thank my grandparents: Grandma Margaret, Grandpa Cyril, Grandma Dorothy and Grandpa Harry for their unconditional love.

I express my sincere gratitude to my supervisors, Dr. Kevin Pehr and Dr. Nathalie Johnson, for their support and mentorship throughout this degree. Both went above and beyond to support my projects.

I would like to thank the members of my thesis committee, Dr. Denis Sasseville and Dr. Khashayar Esfahani, as well as my academic advisor Dr. Raquel Aloyz for their support. I thank my residency program director Dr. Khue Nguyen for his support and accommodation in pursuit of this degree concurrently with my residency training.

I thank Goulnar Kasymjanova for her advisory role in the first chapter of my thesis. I thank Sophie Dell'Aniello for her statistical support. I thank Kathleen D'Aguanno and Megan Lam for their assistance with data collection.

I would like to thank my mentor, Dr. Del Harnish. Del taught me how to think creatively, learn effectively, manage uncertainty and search independently for answers. I would not be the person I am today without his mentorship early in my academic career.

Finally, I would like to thank oncology patients who inspire me through their courage and resiliency. This project was inspired by *Gramps*, a family member of mine who developed an acneiform eruption while on targeted cancer therapy. He inspired my research work in this field.

Contribution of Authors

Rachel Bierbrier developed the study proposal and obtained research ethics board approval to conduct her clinical research, under the supervision of Dr. Kevin Pehr.

For Chapter one, cohort access was obtained from the Department of Pulmonary Oncology under the leadership of Dr. Jason Agulnik. Goulnar Kasymjanova assisted with transfer of research data and acted in an advisory role on the project. Rachel developed templates for data extraction and manually extracted data from both paper and electronic medical records. Data extraction was assisted by Kathleen D'Aguanno, a medical student at McGill University. Statistical analysis was completed by Sophie Dell'Aniello. The manuscript was prepared by Rachel with input from Dr. Kevin Pehr, Goulnar Kasymjanova, Sophie Dell'Aniello, Kathleen D'Aguanno and Dr. Jason Agulnik.

For Chapter two, Rachel developed the study protocol and survey to be sent to participants, under the supervision of Dr. Pehr. Rachel performed data analysis and wrote the manuscript, under the supervision of Dr. Pehr. Dr. Khashayar Esfahani contributed to manuscript preparation and review.

For Chapter three, Rachel developed the study protocol and search strategy for the systematic review, with input by McGill librarian Andrea Quaiattini. Rachel screened papers and performed data extraction for the systematic review. Screening and data extraction were duplicated by Megan Lam, a medical student at McMaster University. Rachel prepared the manuscript which was reviewed by Dr. Kevin Pehr and Megan Lam.

All chapters of this thesis were written by Rachel Bierbrier, under the supervision of Dr. Pehr and Dr. Nathalie Johnson.

Tables and Figures

Chapter 1: Retrospective Review to Identify Risk Factors for the Development of Acneiform Eruptions in Patients on Epidermal Growth Factor Receptor Inhibitors

Table 1: Baseline Demographic and Clinical Features of the Cohort

Table 2: Association Between Baseline Demographic and Clinical Features and the Development of Acneiform Eruption

Table 3: Descriptive Management of Acneiform Eruptions

Table 4: Overall Survival

Figure 1: Kaplan Meier Curve – Time to Rash Overall and Based on Type of TKI

Chapter 2: An Analysis of the Treatment Patterns Acneiform Eruptions Secondary to Epidermal Growth Factor Receptor Inhibitors in Dermatologists and Oncologists in Canada

Table 1: Participant Characteristics

Table 2: Likert Scale Questions

Table 3: Management of Acneiform Eruptions

Chapter 3: A Systematic Review of Oral Retinoids for Treatment of Acneiform Eruptions Induced by Epidermal Growth Factor Receptor Inhibitors

Table 1: Study Characteristics

Table 2: Participant Characteristics

Table 3: Study Results

Figure 1: Search Strategies

Figure 2: Study Selection

Abbreviations

Abbreviation	Definition
EGFR	Epidermal growth factor receptor
EGFRi	Epidermal growth factor receptor inhibitor
RTK	Receptor tyrosine kinase
TKI	Tyrosine Kinase Inhibitor
BSA	Body surface area
CTCAE	Common Terminology Criteria for Adverse Events
MASCC	Multinational Association for Supportive Care in Cancer
ESMO	European Society for Medical Oncology

Introduction and Literature Review

Tyrosine Kinase Signaling and Targeted Cancer Therapy

With advancing knowledge of the mechanisms underlying the development of malignancy, new targeted therapies have been developed to specifically target dysregulated cellular pathways. One such pathway found to be dysregulated in many cancers is a tyrosine kinase pathway entitled the epidermal growth factor receptor (EGFR) signaling pathway. EGFR belongs to the family of receptor tyrosine kinases receptors. (1) Proteins in this family are transmembrane proteins composed of an N terminus, which is the receptor tyrosine kinase proper, which upon dimerization, leads to the activation of intracellular downstream signaling pathways; and a C terminus, the ligand binding domain, which binds a ligand. Intracellular pathway activation is triggered by autophosphorylation. The EGFR pathway is important in the growth, differentiation and survival of mammalian cells. In cancer cells, this pathway becomes over activated, leading to uncontrolled cellular proliferation. The mechanism by which the pathway is over activated can either be ligand dependent or independent. (2) (3) Examples of EGFR ligand that may be upregulated in cancer include transforming growth factor-alpha, epiregulin, epidermal growth factor, heparin binding EGF-like growth factor. (4) Ligand independent activation occurs when a mutations in EGFR lead to dimerization and constitutive receptor activation. (5)

New cancer therapies are directed towards targeting this dysregulated EGFR pathway and can be accomplished through multiple mechanisms. The first is through the creation of a monoclonal antibody which competes with the ligand binding domain of EGFR. Medications in this class include cetuximab, panitumumab and necitumumab. A second strategy is the development of medications that bind to the intracellular domain of the receptor, called the receptor tyrosine kinase. The inhibition of the RTK site blocks EGFR's catalytic site thereby preventing the initiation of downstream signaling. Medications in this class include erlotinib, gefitinib, afatinib and osimertinib. Ultimately, both medication subtypes – the monoclonal antibodies and RTK inhibitors - lead to decreased intracellular signal transduction pathways that are abnormally activated by EGFR mutated cancers. However, there are some notable differences between the two subtypes of EGFR inhibitors. Monoclonal antibodies must be administered via intravenous

where as RTK inhibitors can be taken orally. RTK inhibitors inhibit EGFR downstream signaling whether or not the ligand binding site of EGFR is mutated. However, in contrast to monoclonal antibodies, RTK inhibitors do not down regulate EGFR expression. Monoclonal antibodies, on the other hand, cannot bind a mutated EGFR ligand receptor. If the ligand receptor of EGFR is not mutated, upon binding, monoclonal antibodies can both inhibit EGFR function and lead to downregulation of EGFR expression. (2)

Upon the diagnosis of cancer, molecular studies are performed on biopsied sites. This step is important with the advent of targeted cancer therapy, as it identifies which specific gene mutations a cancer contains, and therefore which treatments it will likely respond to. In this step, the laboratory can identify if the cancer is positive or negative for an EGFR mutation, as well as the specific area of the receptor that is mutated. For example, most common EGFR mutations in lung cancer are exon 19 deletions or exon 21point mutations. Exon 19 deletions are associated with a favorable response to EGFR targeted therapy, whereas exon 21 point mutations are associated with a higher mortality rate. (6) RTK inhibitors are first line therapy for non-small cell lung cancer (NSCLC) patients with EGFR mutations. (7)

RTK inhibitors are divided into three generations. The first RTK inhibitor FDA approved for the treatment of NSCLC was erlotinib in 2004. (8) A landmark trial demonstrated that compared to placebo, in patients with previously treated lung cancer, there was a statistically significant improvement in overall survival and progression free survival with erlotinib. (9) Subsequently, getifinib, another first generation RTK inhibitor, and afatinib, a second generation RTK inhibitors were developed. Unfortunately, despite promising results from clinical trials for these targeted medications, the emergence of acquired resistance has limited their long term and has driven the development of newer, irreversible RTK inhibitors. Osimertinib is a third line RTK inhibitor developed in response to emerging resistance of earlier generation RTK inhibitors. Omsimertinib yields a longer progression free survival rate and more than doubled the duration of response compared to earlier generation RTK inhibitors. (10) Based on this data, omsimertinib received full approval by the FDA in 2017.

Spectrum of Cutaneous Adverse Events Caused by EGFR inhibitors

As EGFR and downstream signaling pathways are also present in the skin, it is unsurprising that many of the adverse events associated with this class of medication are cutaneous. The spectrum of cutaneous adverse reactions includes alopecia, changes to hair texture and colour, increased growth of eyelashes, paronychia, pyogenic granuloma like lesions, facial redness, photosensitivity, mucositis/stomatitis, xerosis, eczema, pruritus, purpuric pustular eruptions and an acneiform eruption. In dermatology, the cutaneous adverse events caused by this class of medications are summarized as the PRIDE complex: papulopustular eruption, regulatory abnormalities of hair growth, itching, dryness due to EGFR inhibitors. (11)

Extracutaneous adverse events associated with EGFR inhibitors include diarrhea, elevations in liver enzymes, fatigue, suppressed appetite, vomiting, shortness of breath, among others. (12) Oncologists monitor for adverse events of EGFR inhibitors with routine patient follow up and bloodwork.

Acneiform Eruptions Secondary to EGFR inhibitors

The most common cutaneous reaction caused by EGFR inhibitors is the development of an acneiform eruption. This reaction occurs in 80 -100% patients treated with EGFR inhibitors. (13) (14) (15) Importantly, the development of the acneiform eruption is associated with improved response to therapy, and is therefore considered a positive prognostic sign. (16) (17) (18)

The eruption begins early in treatment, usually within the first two weeks, and can last up to four months after initiation of therapy. It is composed of inflammatory papules and pustules distributed on the head and neck, chest and back. The development of the eruption can adversely affect quality of life of oncology patients. In severe cases, the eruption may lead to either patient or physician directed discontinuation of targeted therapy. (19)

Pathogenesis of Acneiform Eruptions Secondary to EGFR inhibitors

Although this eruption is termed acneiform eruption, its underlying pathogenesis differs from acne vulgaris (teenage onset acne). Acne vulgaris is a hormonally driven process related to increased sebum production, follicular plugging and inflammation, in part triggered by the commensal organism *Propionibacterium acnes*. In acne vulgaris, androgens influence sebum production and composition, a key pathophysiologic feature of the development of inflammatory and non-inflammatory acne lesions. (20)

In the context of EGFR inhibitors, the pathogenesis is driven by off target inhibition of EGFR in the skin and adnexal tissues. In the proposed model, EGFR inhibitors affect keratinocyte proliferation in the epidermis by up regulation of p27. (21) p27 inhibits cell cycle progression, and when up regulated, leads to cell cycle dysregulation. This dysregulation causes, epidermal cell apoptosis, hyperkeratinisation and abnormal desquamation in the epidermis and follicular infundibula. Ultimately leading to a final common pathway of follicular plugging, and the development of inflammation. (22) Not only does follicular plugging lead to inflammation, but EGFR signaling also increases the release of cytokines and chemokines involved in inflammatory cell recruitment. (23) (24) There is no role for hormones in the pathogenesis of EGFR inhibitor-induced acneiform eruptions.

Clinical Assessment and Assessment of Severity

Adverse events from cancer therapy are reported using the Common Terminology Criteria for Adverse Events (CTCAE) which is currently on its sixth version. Acneiform eruptions can be graded using this system, where Grade 1 includes papules and pustules covering <10% body surface area (BSA) and may or may not be associated with symptoms of tenderness and pruritus. A Grade 2 eruption covers a greater BSA (10-30%) and impacts quality of life and activities of daily living. A Grade 3 eruption covers >30% BSA and has moderate to severe symptoms, requiring intravenous therapy, a Grade 4 eruption has life threatening consequences and a Grade 5 eruption is death.

Although the CTCAE guidelines provide standardized reporting of adverse events in oncology patients, dermatologists note limitations in its use. Specifically, the CTCAE grading is based on

total body surface area involvement. However, the eruption occurs within only certain body areas, therefore limiting the percent of *total* BSA, and can give a falsely low grade for a severe reaction. For example, the head and neck of an adult is equivalent to approximately 10% of total BSA, which would characterize the CTCAE as grade 1 if there is only partial involvement, and grade 2 if there is confluent involvement. (25) With this example, it is illustrated that a patient may categorized in a lower CTCAE grade despite having a severe eruption in a limited BSA. Further, the CTCAE criterion rely on subjective symptoms as part of the staging system, which does not provide a completely objective measure of the acneiform eruption severity. In summary, from a dermatologic perspective, a more accurate system is required to characterize the severity of the eruption and track the patient's progress over time.

In dermatology, alternate scales for the classification of acneiform eruptions exist. The Wollenberg-Mossmann (WoMo) score was developed in 2008 to provide a more specific grading scoring system for acneiform eruptions secondary EGFR inhibitors. In this scoring system, the percent of facial involvement is scored separately. Further, in contrast to the CTCAE, no subjective symptoms are included in the scoring system to allow for a purely objective measure. (26) This tool is used in clinical trials assessing response of acneiform eruptions to prophylactic therapy. (27) Another proposed acneiform eruption grading system was created by the Multicenter Association of Supportive Care in Cancer (MASCC) group, where individual papule and pustule counts or centimetric measurement of involvement are used instead of percent BSA. The MASCC criterion also include subjective measures of patient symptoms and impairment in function as modifiers to sub-classify as A or B within the three tiered grading system. (28) Additional scoring systems are available for acne vulgaris, which can be applied to the acneiform eruptions. Examples include the Leeds Revised Acne Grading Scale, Global Acne Grading Scale and lesion counting, among others. (29)

Management of Acneiform Eruptions

Several guidelines exist for the management of acneiform eruptions. All guidelines recommend gentle skincare regiments, routine moisturizer use and minimizing sun exposure for preventative

management. There is evidence for the use of low potency steroids as well as tetracycline antibiotics for prevention of acneiform eruptions.

Tetracyclines are a family of antibiotics used in dermatology for antimicrobial and anti-inflammatory effects. The family includes three medications: tetracycline, doxycycline and minocycline. Although usually viewed as antibiotics, tetracyclines also exert anti-inflammatory effects through inhibiting pathways involved in neutrophil recruitment, granuloma formation and the innate immune system. They are favoured for management of acne and acneiform eruptions due to their high concentrations and activity in pilosebaceous units. Doxycycline is generally used due to its favourable safety profile. It is Health Canada approved for use in acne vulgaris and rosacea. It is also used off label for treatment of immunobullous, granulomatous and inflammatory dermatologic disorders as well as drug induced acneiform eruptions. Adverse effects from therapy include photosensitivity, nausea, abdominal discomfort and esophagitis. It is pregnancy category D. (30)

Randomized trials for use of prophylactic systemic antibiotics, namely tetracycline antibiotics, for the prevention of acneiform eruptions demonstrate conflicting data. *Scope et al.* demonstrated that compared to placebo, minocycline offered a statistically significant improvement in skin lesion count at 4 weeks, but this difference tapered by week 8. (31) *Jatoi et al.* demonstrated in 2008 that there was no difference in incidence of acneiform eruption between tetracycline and placebo at four weeks however did note a statistically significant difference in eruption severity between the two groups. (32) In a follow on study in 2011, *Jatoi et al.* confirmed that the rate of acneiform eruption is the same between the tetracycline and placebo group, and that severity did not differ between the two groups. (33) In contrast, work by *Lacouture et al.* demonstrate a 50% reduction in CTCAE grade 2 and higher acneiform eruptions in patients treated with a pre-emptive regimen which included doxycycline. (34) Despite conflicting evidence, tetracycline family antibiotics are recommended in combination with topical steroids for prophylaxis of acneiform eruptions in patients on EGFR inhibitors for the first six weeks of therapy. (35) It is important to note that although the guidelines recommend systemic antimicrobial therapy for management of acneiform eruptions secondary EGFR inhibitors, there are no randomized control trials to support this recommendation.

Canadian recommendations for management of acneiform eruptions were published in 2009. The guidelines suggest management based on the CTCAE grading of the acneiform eruptions. For grade 1, topical antibiotic and topical steroid creams are recommended, for grade two, a systemic antibiotic is added for management and for grade three and above, discontinuation of the EGFR inhibitors is recommended, in addition to the aforementioned topical and systemic therapy. (36) Guidelines from the MASCC were published in 2011 and built on the Canadian recommendations with similar recommendations divided into topical and systemic therapeutic options. One addition was the low-grade recommendation for low dose isotretinoin as a second line agent after tetracyclines for systemic management of acneiform eruptions. (37)

The most recent guidelines are the European Society for Medical Oncology (ESMO) clinical practice guidelines which were published in November 2020. In the ESMO guidelines, management of acneiform eruptions is divided into categories, CTCAE grades 1-2 and CTCAE grade 3 or above. For grades 1-2, it is recommended to continue EGFR inhibitors start tetracycline antibiotics for 6 weeks and a low to moderate potency topical steroid. For grade three and above, recommendations include holding EGFR inhibitors, tetracycline antibiotic, low to moderate potency topical steroid and systemic prednisone. An alternate systemic therapy includes isotretinoin, a systemic retinoid, at low doses.

Isotretinoin is a first-generation synthetic retinoid that elicits clinical effects by activating nuclear receptors and altering gene expression, ultimately altering cellular pathways involved in inflammation, apoptosis, sebaceous gland activity and cellular differentiation. It is an oral medication generally taken once daily at a dose of 0.5 to 1 milligram per kilogram per day. Treatment duration varies but is usually three to six months. Isotretinoin is a known teratogen; other common adverse effects include transaminitis, and elevated cholesterol and triglycerides. (38) Isotretinoin is Health Canada approved for use in severe acne vulgaris. In recent years, indications have expanded to include acne with severe impact on quality of life. (30) Isotretinoin's expanding indications have led to investigation in its use in acneiform eruptions in cancer patients. Although isotretinoin has some overlapping side effects with EGFR inhibitors,

most notably xerosis, dermatitis, and cheilitis, these are dose-dependent, and the dosages used in treating acneiform eruptions are lower than standard acne therapy.

Objectives of Research

Given that acneiform eruptions occur early in initiation of treatment with EGFR inhibitors, early identification of individuals with acneiform eruptions and effective management can prevent discontinuation of lifesaving cancer therapy and prevent adverse impacts on quality of life. Therefore, the objective of Chapter one is to determine potential risk factors for the development of acneiform eruptions, so that high risk individuals are identified and initiated on treatment early. Even with identification of at-risk populations, effective management of acneiform eruptions is the next step to maintain the quality of life of oncology patients who develop this cutaneous adverse event. In Chapter two, the objective of the investigation is to compare practice patterns between dermatologists and oncologists in Canada for the treatment of acneiform eruptions secondary to EGFRi. Given the paucity of data on the most effective systemic agent for management of acneiform eruptions, in Chapter three, the objective of the study is to summarize available data on the use of systemic retinoids for the management of acneiform eruptions.

Description of Study Population, Inclusion and Exclusion Criteria

Over one hundred fifty thousand Canadians are diagnosed with cancer each year. Quebec has the highest rates of lung cancer of any Canadian province, with almost 10 000 new cases diagnosed annually. With the introduction of new targeted therapy, median lung cancer survival has increased in Quebec by fifty percent between 2002-2004 and 2014-2016. (39) In Chapter one of this thesis, patients on first line RTK inhibitors for advanced NSCLC treated at the Peter Brojge Lung Cancer Centre in Montreal, Quebec, Canada between February 2015 and Dec 2021 were included. Every patient diagnosed with lung cancer is entered into a registry and information is updated as the patient progresses through treatment. Patients referred to the Peter Brojde Lung Cancer Centre for a second opinion were excluded due to lack of follow up information.

In Chapter 2 of this thesis, all independently licenced dermatologists and oncologists who are members of Canadian dermatology and medical oncology associations were included in the

study. Exclusion criteria were non-English or French speaking participants, participants who are unable to access the online survey due to technical or physical limitations and non-Canadian licensed physicians.

Design and Description of Methodology

This thesis is composed of chapters with differing but complimentary areas of this field explored.

In the first chapter, risk factors for the development of acneiform eruptions were assessed in a retrospective chart review composed of NSCLC patients treated with first line EGFR inhibitors for advanced disease from 2015 until 2021. Baseline demographic and laboratory values were assessed for their predictive value in the development to of acneiform eruptions.

In the second chapter, a cross sectional survey study was conducted to assess differences in management of acneiform eruptions between oncologists and dermatologists in Canada. An online survey based on LimeSurvey was sent out via Canadian organizational maligning lists. Results were compared between specialities.

In the third chapter, evidence for the use of systemic retinoids for management of acneiform eruptions was summarized in a systematic review. This review was conducted in compliance with the PRISMA guidelines. No meta-analysis was conducted given that no controlled trials exist in this field.

Definition of End Points

In Chapter one, the endpoint is defined as the development of an acneiform eruption while on therapy with an RTK inhibitors. Secondary endpoints include a descriptive analysis of the management of acneiform eruptions by medical oncology and dermatology. Further, the association between the development of acneiform eruptions and overall survival was explored.

In Chapter two, the primary endpoint was selection of management strategies for presented clinical scenarios representing mild, moderate and severe acneiform eruptions. Results were compared between oncologists and dermatologists.

In Chapter three, the primary endpoint was response of acneiform eruption to systemic retinoid therapy. The measurement of endpoint varied based on the method used in the published report. Measurement strategies included physician global assessments, photography and acneiform eruption grading scales. A secondary endpoint was to describe the rate of adverse events to systemic retinoid therapy and, if available, the response of the patient's cancer to EGFR inhibitor therapy after the initiation of systemic retinoid.

Details on Confidentiality and Ethical Considerations

Medical/Biomedical (MBM) Research Ethics Committee of the CIUSSS West-Central Montreal (CIUSSS WCM) approval was obtained prior to the initiation of the chart review conducted in Chapter one of this thesis. Ethics approval using the same regulatory body was obtained prior to initiation of Chapter two of this thesis. All patient data was kept strictly confidential as per CIUSSS West-Central Montreal Guidelines and was stored on hospital based secure software in encrypted files. All data used for analysis and publication is anonymized.

Chapter One: Retrospective Review to Identify Risk Factors for the Development of Acneiform Eruptions in Patients on Epidermal Growth Factor Receptor Inhibitors

In this chapter, we explored the relationship between demographic and clinical characteristics and the development of acneiform eruptions. Given that acneiform eruptions occur in EGFRi treatment initiation, identifying high risk groups would allow for prompt referral to dermatology and the use of preventive therapy. Currently in the literature, there is minimal evidence regarding potential risk factors for development of acneiform eruptions. Whereas some studies report an increased risk of acneiform eruption with older age, this was refuted in other work. Other potential risk factors that are reported include lighter skin phototype, negative smoking status and male sex. (40) (41) However, none of these potential risk factors have been confirmed in subsequently published data. (42) (41) (43) Therefore, the aim of this project is to contribute to the data on potential risk factors for development of acneiform eruptions.

Prognostic factors for the development of acneiform eruptions in patients on epidermal growth factor receptor inhibitors

Bierbrier R[1], D'Aguanno K[2], Kasymjanova G[3], Dell'Aniello S[4], Agulnik J[3], Pehr K[1,5]

[1]Division of Dermatology, McGill University, Montreal Canada
[2] Faculty of Medicine, McGill University, Montreal, QC, Canada
[3]Division of Pulmonary Diseases, Sir Mortimer B. Davis Jewish General Hospital, McGill University, Montreal Canada
[4]Center for Clinical Epidemiology, Lady Davis Institute, Sir Mortimer B. Davis Jewish General Hospital, Montreal, QC
[5]Lady Davis Institute, Sir Mortimer B. Davis Jewish General Hospital, McGill University, Montreal Canada

Key Points

1. Question: Are there baseline demographic or clinical risk factors for the development of acneiform eruptions in patients on tyrosine kinase inhibitors (TKI)?
2. Findings: Compared to first generation TKI, third generation TKI are associated with a decreased risk of acneiform eruptions. No baseline clinical or laboratory characteristics were associated with an increased risk of acneiform eruption.
3. Meaning: There are no clearly defined risk factors for acneiform eruptions secondary to TKI. Newer generation TKI are associated with a decreased risk of acneiform eruptions.

Abstract

Importance: Acneiform eruptions occur frequently and early in patients on epidermal growth factor receptor- tyrosine kinase inhibitors (TKI). Identification of baseline patient risk factors would prompt earlier referral to dermatology to optimize prevention and management.

Objectives: The primary objective of this retrospective study is to determine the association between clinical and demographic characteristics and the development of acneiform eruptions.

The secondary objective is to provide real world data on the incidence and management of acneiform eruptions in patients on TKI. The third objective was to determine the association between development of acneiform eruption and overall survival.

Design, Setting and Participants: A retrospective chart review was conducted on patients diagnosed with non-small cell lung cancer (NSCLC) between February 2015 and December 2021.

Main Outcomes and Measures: Baseline demographic and clinical parameters, including bloodwork and mutation status were documented, and were reviewed from time of diagnosis to most recent visit for the development and management of an acneiform eruption. Regression analyses were performed to determine the association between baseline characteristics and the development of acneiform eruptions.

Results: One hundred and two patients were included. Forty-six (45%) patients developed an acneiform eruption on average within four months of initiation of TKI. Only one patient developed a severe eruption. Third generation TKI were associated with lower risk of acneiform eruptions compared to first line (HR (Hazard Ratio) = 0.41 (0.19 - 0.89) p-value = 0.0237). No other baseline demographic or clinical features were clearly associated with acneiform eruptions. The majority of patients were treated with topical steroids and/or oral tetracycline antibiotics; none discontinued TKI treatment.

Limitations: Single center study, and moderately small sample size.

Conclusions and Relevance: Newer generation TKI are associated with lower risk of acneiform eruptions.

Background and Rationale

The use of targeted therapy against epidermal growth factor receptors (EGFR), a type of tyrosine kinase receptor (TKI), has become standard of care for the management of EGFR mutated non-

small cell lung cancer (NSCLC). Although these agents are associated with a lower incidence of systemic side effects than traditional cancer treatments, there is a higher frequency of mucocutaneous side effects, in 45-100% of patients, that severely impact quality of life and may lead to discontinuation of life-saving treatment. (1) (2)

EGFR is expressed in the skin and adnexal structures and is shown to be important in keratinocyte proliferation and differentiation. (1) Although the precise mechanism of action underlying TKI triggered acneiform eruption is yet to be completely elucidated, current consensus is that TKI affect keratinocyte proliferation in the epidermis by up regulation of p27, which leads to hyperkeratinisation and abnormal desquamation, ultimately resulting in follicular plugging. (3) Cutaneous adverse events include papulopustular/acneiform eruptions, xerosis and hair and nail changes.

Evidence suggests that an acneiform eruption is associated with a favorable response to cancer therapy. (4) (5) (6) (7) However, it can significantly impact the quality of life of oncology patients. In a minority of cases, the eruption is severe enough to interrupt lifesaving cancer therapy. Limited data is available outlining patient risk factors for the development of severe acneiform eruptions.

Given that the onset of the eruption is soon after initiating EGFR therapy, identifying high risk groups and starting prophylactic therapy early on may prevent severe cutaneous adverse reactions. Further, it is possible that risk factors are conserved amongst those who react to other targeted oncologic therapies, and therefore this data may be more broadly used by oncologists to trigger early referral to dermatology.

Methods

Objectives

The primary objective of the study was to determine baseline demographic and clinical risk factors for the development of acneiform eruptions in this cohort. The secondary objective was

to describe the treatment pattern for acneiform eruptions and responses to such treatment. Finally, we aimed to describe the association between development of acneiform eruptions and overall survival.

Study Design

This is an observational, retrospective cohort study of an EGFR mutant metastatic NSCLC patient population which aims to assess risk factors for the development of acneiform eruptions as well as real world incidence of acneiform eruptions. All patients were seen and treated at the Peter Brojde Lung Cancer Centre in Montreal, Quebec, Canada. Data were extracted from the local lung cancer registry, which contains data on all lung cancer cases treated at the Peter Brojde Lung Cancer Centre since 2001. Every patient diagnosed with lung cancer is entered into the registry and information is updated as the patient progresses through treatment. This study was approved by the institutional Research Ethics Board (Protocol #2021-2635).

All cases of EGFR mutant positive metastatic lung cancer diagnosed between February 2015 and December 2021 that were treated with first line TKI monotherapy were included in this study. First generation TKI erlotinib and gefitinib, second generation afatinib and poziotinib, and third generation osimertinib were included. From the database, the following information was extracted:

1. Patient characteristics: NSCLC diagnosis date, stage at time of initial diagnosis, sex, age at time of diagnosis, ethnicity, Eastern Cooperative Oncology Group performance status (ECOG-PS), smoking history and current smoking status.
2. Past medical history and medication history. In particular, medications known to cause acneiform eruptions were identified. (8)
3. Tumor characteristics and other laboratory values: EGFR mutation, baseline blood tests including WBC, CRP, ALT, Cr, LDH, albumin
4. Cancer treatment characteristics: name of EGFR inhibitor, start and stop dates of therapy, number of cycles, reason for treatment discontinuation
    a. Duration of TKI treatment was calculated as the time (in months) elapsed between the start and end dates of the treatment.

b. Response to treatment was defined by the treating physician as per RECIST 1.1 criteria and was based on radiographic imaging (CT/PET) and categorized for analysis purposes as an objective response [complete response (CR) + partial response (PR), stable disease (SD) and progressive disease (PD)].

Acneiform eruption outcome data was obtained by reviewing both electronic and older, archived paper charts. The following information regarding acneiform eruptions was obtained from clinical charts: date of first documented acneiform eruption, timing of eruption relative to start of TKI, CTCAE V5 grading of acneiform eruption, management of acneiform eruption by oncology, patient's response to oncology's therapy, referral to dermatology, management of acneiform eruption by dermatology, response to dermatologic therapy. Management of acneiform eruptions was characterized as: conservative measures (topical emollient or observation), topical steroids, benzoyl peroxide (BPO), topical antibiotics and oral antibiotics. If CTCAE grade was not reported, one was assigned for mild, two for moderate and three for severe.

Baseline laboratory values were defined as blood tests available on the hospital network within a timeframe of two months prior to beginning the TKI. Baseline past medical history was defined as any documented past medical history at an oncologist's or emergency physician's notes, prior to the diagnosis of NSCLC.

Index date was defined as the date of starting TKI therapy. Database was locked on January 1, 2022 and patients were followed-up until death or January 1, 2022, whichever came first. Patients referred to the Peter Brojde Lung Cancer Centre for a second opinion were excluded due to lack of follow up information.

Statistical Analysis

Demographics, clinical characteristics, and treatment patterns are described using frequencies and proportions for categorical data and using means with standard deviation or medians for continuous data.

We defined an acneiform eruption if documented as “acne-like, papules and/or pustules” distributed on the head, neck and upper trunk. Acneiform eruptions were included in the analysis if they occurred while the patient was on TKI, or within one month of TKI discontinuation.

Univariate Cox proportional hazards regression models was performed to identify predictive factors for the development of acneiform eruptions and is presented as hazard ratios with 95% confidence intervals (95% CI). Survival analysis is presented in table format and Kaplan-Meier curves. Overall survival according to development of an acneiform eruption was estimated using a time-dependent Cox regression model adjusted for sex and age. In this analysis, patients are considered to have no rash from index date until their first acneiform eruption and classified as having a rash only after the eruption until the end of follow-up. This approach was used to avoid immortal time bias. (9) Statistical analyses were conducting using SAS (version 9.4; SAS, Cary, NC, USA). A p value of <0.05 was considered statistically significant.

Results

Four hundred and ninety-four patients were diagnosed with advanced/metastatic NSCLC, of those 107 patients were EGFR mutant and were started on first line TKI treatment. Of those, five patients were excluded as they were only seen for second opinion and were not followed at our institution. Therefore, a total of 102 patients were included in the analysis.

Table 1 summarizes the baseline demographic characteristics of the study cohort. The study population was mostly female, Caucasian and never smokers. The mean age of the cohort was 71. Majority of patients received first generation TKI (gefitinib) and had a significant past medical history at time of diagnosis, including 11 with a history of prior cancers, 10 with cardiovascular disease and 19 with diabetes. At the time of TKI initiation all patients were in advanced/metastatic stage.

Baseline clinical features are summarized in Table 1. The most common EGFR mutations were Exon19 (49%) and Exon21 (45.1%). The majority of patients had normal kidney and liver function with mean (standard deviation) of 71.3 (22.8) umol/L and 21.7 (19.3) IU/L respectively. The average baseline C-reactive protein (mean, SD: 20.9, 37.0) and lactate dehydrogenase (mean, SD: 259.2,128.5) were elevated.

Forty-six (45%) patients developed acneiform eruptions while on treatment with TKI over a total of 674 months of follow-up, yielding an incidence rate of 6.8 per 100 person-months. Severity of the rash was documented for 19 pts: 15 were mild, three were moderate and one was severe. Patients treated with first or second generation more frequently developed rash

comparing to those who were treated with osimertinib (57% and 57% vs 24%). The cumulative incidence of the rash increased from 24% at 5 weeks to 42% at two months (Figure 1).

Treatment with third generation TKI osimertinib was associated with a lower hazard ratio for the development of acneiform eruption, compared to first generation gefitinib and erlotinib (HR = 0.41 (0.19 - 0.89) p-value = 0.0237). No other baseline demographic or clinical characteristic was associated with an increased or decreased risk of acneiform eruption (Table 2). The sex, race, age, baseline WBC and CRP were not prognostic factors (Table 2).

Table 3 provides a description of the management of patients who developed an acneiform eruption. Management of the eruption by oncology included conservative management, topical steroids and topical retinoids. No patients stopped TKI therapy. Of the 46 patients that developed acneiform eruptions, 24 (51%) were referred to dermatology. Of the 24 referred to dermatology, 5 were treated with conservative measures, 4 were treated with topical steroids, 4 were treated with topical antibiotics and seven were treated with systemic antibiotics.

After adjusting for age and sex, development of acneiform eruption was not associated with a statistically significant survival benefit 0.93 (0.57 - 1.53) (Table 4).

Discussion

This retrospective study was performed to determine real world frequencies of acneiform eruptions in patients on first line TKI monotherapy, as well as to determine patient risk factors for the development of acneiform eruptions. Almost half of the patients in our cohort developed acneiform eruptions within an average of four months after initiating TKI. Only one patient developed a severe reaction, defined as a CTCAE grade 3 or above. In our analysis, the third generation TKI was associated with a decreased risk of acneiform eruption. None of the

investigated baseline demographics or clinical variables conferred an increased risk for the development of acneiform eruptions on TKI.

Lower incidence of acneiform eruptions in patients on newer generation TKI is consistent with the literature. Osimertinib is a third generation TKI, which compared to earlier generations of TKI, has both broader coverage for EGFR mutations but less effect on wild type EGFR, thus decreasing the frequency of severe adverse events. (10) In clinical trials for osimertinib, the rate of acneiform eruption is as low as 34%. (11) Higher incidences of acneiform eruptions are reported in first and second generation TKI including erlotinib, gefitinib and afatinib. (12) (13) (14) (2)

We were unable to identify any other statistically significant risk factors for the development of acneiform eruptions. Risk factors identified in prior studies have either not been reproduced in later studies, or in some cases studies contradict each other. For example, *Wheatley-Price et al.* identified that patients greater than or equal to 70 years old had a statistically higher rate of severe acneiform eruptions with the first generation TKI erlotinib. (15) Conflicting evidence was found by *Jatoi et al*, who found a higher incidence of cetuximab induced acneiform eruption in patients younger than 70. (16)

Other individual studies report that lighter phototype, elevated BMI, male sex and non-smoking status confer a greater risk of acneiform eruptions, however none of these results were reproduced in subsequent analyses. (17) (16) (18)

The consensus regarding the pathogenesis of acneiform eruptions secondary to TKI is that it is caused by off target inhibition of EGFR in the skin and adnexal tissues, leading to keratinocyte dysregulation. (19) This results in follicular plugging, and the development of inflammation. (3) Based on this proposed pathogenesis, two main theories exist for the association between baseline characteristics and the development of acneiform eruptions. The first is that factors that decrease drug metabolism, and thus increase circulating drug levels, lead to increased off target EGFR inhibition in the skin. The second is that certain baseline characteristics are associated with intrinsic susceptibility of EGFR dysregulation, and this effect is enhanced with the addition of EGFR inhibitors.

TKI are metabolized in the liver through the CYP P450 pathway. (20) Factors that decrease drug metabolism include increasing age and baseline liver dysfunction. (21) In our cohort, there was no statistically significant increased risk of acneiform eruptions with increasing age. However, given the low hazard ratio, there is a trend that age > 70 years old may be associated with a lower risk of acneiform eruptions. The vast majority of the included patients had normal baseline liver function, and therefore the possibility of underlying liver dysfunction as a risk factor could not be explored.

Smoking is known to interfere with CYP P450 function by induction of hepatic enzymes. (18) This is shown to lower incidence of adverse events in patients on TKI who smoke. However, no association was found in our analysis.

The second hypothesis is that factors associated with intrinsic EGFR dysregulation in keratinocytes may increase the rate of acneiform eruptions. Such factors include ultraviolet radiation (UVR) mediated dysregulation, hormonal effects on EGFR expression and concurrent use of medications known to act on EGFR. (22) (23) EGFR signaling is activated with exposure to UVR, which leads to the development of epidermal hyperplasia. (23) Given that lighter phototypes are more UVR sensitive, there is evidence to support that lighter phototypes are associated with increased severity of acneiform eruptions. (17) Our results demonstrate a trend towards patients with darker skin types having decreased risk of acneiform eruptions, however this did not reach statistical significance (p-value: 0.21). Given the known adverse effects of UVR on the skin, photoprotection is recommended for all patients on TKI.

Basic science research suggests that estrogen effects baseline EGFR function and may decrease susceptibility to dysregulation. (22) This theory was not supported with our data. It is known that TKI used in combination with cytotoxic chemotherapy is associated with higher rates of high grade acneiform eruptions, due to synergistic effects on EGFR. (24) (25) This relationship was not explored in our analysis as all patients were on TKI monotherapy.

In addition to the two explored theories for risk factors underlying TKI-induced acneiform eruptions, our group explored a third possibility. It is known that EGFR signaling increases the release of cytokines and chemokines involved in inflammatory cell recruitment, independently of

follicular plugging. (26) (23) Therefore, in our analysis, we explored the relationship between baseline elevations in WBC and C-reactive protein and the development of acneiform eruptions. Interestingly, results of our data suggest the inverse relationship, where low hazard ratios associated with elevated baseline inflammatory status. Further research, with larger sample sizes, is necessary to confirm the possible relationship between elevated baseline inflammatory markers and the development of acneiform eruptions. Furthermore, given the effect of diabetes on immune dysregulation, we explored this possible association. (27) However, there was no association between diabetes and the development of acneiform eruptions.

As a secondary objective of the study, we aimed to provide a descriptive analysis of the treatment patterns of acneiform eruptions in our cohort. The management of acneiform eruptions by oncologists included conservative measures, topical steroids and rarely oral tetracyclines. Dermatologists were more likely than oncologists to prescribe a topical antibiotic, BPO, or even an oral tetracycline. If a systemic tetracycline were used, dermatologists were more likely to prescribe doxycycline rather than minocycline, compared with oncologists, who preferred the latter. Further, although minocycline has better penetration into the pilosebaceous unit, the use of doxycycline is preferred by dermatologists due to decreased risk of minocycline induced autoimmune connective tissue disease. (28) (29) (30)

Finally, our group analyzed the association between the development of acneiform eruptions and overall patient survival. In previous reports, development of acneiform eruptions was associated with a survival benefit. (12) In our analysis, which was free of immortal time bias, we were unable to identify an association between the development of acneiform eruptions and overall survival.

There are limitations to our study. The first is the small sample size of our cohort limited the power to detect statistically significant associations. However, our data does provide some signal to possible associations that require confirmation in studies with larger sample sizes. Secondly, this study is a single center, which may not be generalizable to other patient populations. Given that the study was a retrospective review, time to onset of acneiform eruptions was documented based on routine clinical follow up notes, not prospective patient reporting, which may prolong our calculated time to acneiform eruption onset. Further, we relied upon physician reporting of

skin toxicity, not a standardized or objectively quantified method of assessment. In the context of the COVID19 pandemic, the authors also wonder if the shift towards virtual medicine biased results regarding the lower incidence of acneiform eruptions reported in newer TKI, given that in our cohort, osimertinib was almost exclusively prescribed from January 2020 onwards. With a shift to virtual care, there may be under-reporting of cutaneous adverse events that are not confirmed with a physician's routine physical exam.

Conclusions

In our cohort, approximately half of patients developed acneiform eruptions secondary to TKI. Third generation TKI are associated with a lower risk of acneiform eruptions. There was a trend towards age, sex, ethnicity and baseline WBC as potential risk factors for acneiform eruptions, which may achieve statistical significance with a larger study population.

Further investigations with larger sample sizes might clarify if these trends achieve statistical significance for other baseline risk factors for the development of acneiform eruptions. Given that up to half of patients develop acneiform eruptions and to date there are no clearly-defined risk factors, it is prudent for all physicians prescribing this class of medications to inquire about any new skin changes, so that patients are initiated on therapy in a timely manner.

References

1. Lacouture ME. Mechanisms of cutaneous toxicities to EGFR inhibitors. Nat Rev Cancer. 2006 Oct;6(10):803–12.

2. Melosky B, Leighl NB, Rothenstein J, Sangha R, Stewart D, Papp K. Management of egfr tki–induced dermatologic adverse events. Curr Oncol. 2015 Jan 8;22(2):123.

3. DeWitt CA, Siroy AE, Stone SP. Acneiform eruptions associated with epidermal growth factor receptor–targeted chemotherapy. J Am Acad Dermatol. 2007 Mar;56(3):500–5.

4. Giovannini M, Gregorc V, Belli C, Roca E, Lazzari C, Viganò MG, et al. Clinical Significance of Skin Toxicity due to EGFR-Targeted Therapies. J Oncol. 2009;2009:1–8.

5. Petrelli F, Borgonovo K, Barni S. The predictive role of skin rash with cetuximab and panitumumab in colorectal cancer patients: a systematic review and meta-analysis of published trials. Target Oncol. 2013 Sep;8(3):173–81.

6. Liu H, Wu Y, Lv T, Yao Y, Xiao Y, Yuan D, et al. Skin Rash could Predict the Response to EGFR Tyrosine Kinase Inhibitor and the Prognosis for Patients with Non-Small Cell Lung Cancer: A Systematic Review and Meta-Analysis. Kuwano M, editor. PLoS ONE. 2013 Jan 30;8(1):e55128.

7. Petrelli F, Borgonovo K, Cabiddu M, Lonati V, Barni S. Relationship between skin rash and outcome in non-small-cell lung cancer patients treated with anti-EGFR tyrosine kinase inhibitors: A literature-based meta-analysis of 24 trials. Lung Cancer. 2012 Oct;78(1):8–15.

8. Bolognia, Jean., Jorizzo, Joseph L.Schaffer, Julie V., eds. Dermatology. [Philadelphia] :: Elsevier Saunders, 2018. Print.

9. Suissa S. Immortal Time Bias in Pharmacoepidemiology. Am J Epidemiol. 2008 Jan 7;167(4):492–9.

10. Soria J-C, Ohe Y, Vansteenkiste J, Reungwetwattana T, Chewaskulyong B, Lee KH, et al. Osimertinib in Untreated EGFR -Mutated Advanced Non–Small-Cell Lung Cancer. N Engl J Med. 2018 Jan 11;378(2):113–25.

11. Chu C-Y, Choi J, Eaby-Sandy B, Langer CJ, Lacouture ME. Osimertinib: A Novel Dermatologic Adverse Event Profile in Patients with Lung Cancer. The Oncologist. 2018 Aug 1;23(8):891–9.

12. Lee SM, Khan I, Upadhyay S, Lewanski C, Falk S, Skailes G, et al. First-line erlotinib in patients with advanced non-small-cell lung cancer unsuitable for chemotherapy (TOPICAL): a double-blind, placebo-controlled, phase 3 trial. Lancet Oncol. 2012 Nov;13(11):1161–70.

13. Yang JJ, Zhou Q, Yan HH, Zhang XC, Chen HJ, Tu HY, et al. A phase III randomised controlled trial of erlotinib vs gefitinib in advanced non-small cell lung cancer with EGFR mutations. Br J Cancer. 2017 Feb;116(5):568–74.

14. Tada H, Mitsudomi T, Misumi T, Sugio K, Tsuboi M, Okamoto I, et al. Randomized Phase III Study of Gefitinib Versus Cisplatin Plus Vinorelbine for Patients With Resected Stage II-IIIA Non–Small-Cell Lung Cancer With *EGFR* Mutation (IMPACT). J Clin Oncol. 2022 Jan 20;40(3):231–41.

15. Wheatley-Price P, Ding K, Seymour L, Clark GM, Shepherd FA. Erlotinib for Advanced Non–Small-Cell Lung Cancer in the Elderly: An Analysis of the National Cancer Institute of Canada Clinical Trials Group Study BR.21. J Clin Oncol. 2008 May 10;26(14):2350–7.

16. Jatoi A, Green EM, Rowland, Jr. KM, Sargent DJ, Alberts SR. Clinical Predictors of Severe Cetuximab-Induced Rash: Observations from 933 Patients Enrolled in North Central Cancer Treatment Group Study N0147. Oncology. 2009;77(2):120–3.

17. Luu M, Boone SL, Patel J, Sullivan P, Rademaker AW, Balagula Y, et al. Higher severity grade of erlotinib-induced rash is associated with lower skin phototype: Higher-grade erlotinib rash in patients with lighter skin phototype. Clin Exp Dermatol. 2011 Oct;36(7):733–8.

18. Hughes AN, O'Brien MER, Petty WJ, Chick JB, Rankin E, Woll PJ, et al. Overcoming CYP1A1/1A2 Mediated Induction of Metabolism by Escalating Erlotinib Dose in Current Smokers. J Clin Oncol. 2009 Mar 10;27(8):1220–6.

19. Malik SN, Siu LL, Rowinsky EK, deGraffenried L, Hammond LA, Rizzo J, et al. Pharmacodynamic evaluation of the epidermal growth factor receptor inhibitor OSI-774 in human epidermis of cancer patients. Clin Cancer Res Off J Am Assoc Cancer Res. 2003 Jul;9(7):2478–86.

20. Li J, Zhao M, He P, Hidalgo M, Baker SD. Differential Metabolism of Gefitinib and Erlotinib by Human Cytochrome P450 Enzymes. Clin Cancer Res. 2007 Jun 15;13(12):3731–7.

21. McLachlan AJ, Pont LG. Drug Metabolism in Older People--A Key Consideration in Achieving Optimal Outcomes With Medicines. J Gerontol A Biol Sci Med Sci. 2012 Feb 1;67A(2):175–80.

22. Wang L, Xiao J, Gu W, Chen H. Sex Difference of *Egfr* Expression and Molecular Pathway in the Liver: Impact on Drug Design and Cancer Treatments? J Cancer. 2016;7(6):671–80.

23. Pastore S, Mascia F, Mariani V, Girolomoni G. The Epidermal Growth Factor Receptor System in Skin Repair and Inflammation. J Invest Dermatol. 2008 Jun;128(6):1365–74.

24. Balagula Y, Wu S, Su X, Lacouture ME. The effect of cytotoxic chemotherapy on the risk of high-grade acneiform rash to cetuximab in cancer patients: a meta-analysis. Ann Oncol. 2011 Nov;22(11):2366–74.

25. Feng FY, Varambally S, Tomlins SA, Chun PY, Lopez CA, Li X, et al. Role of epidermal growth factor receptor degradation in gemcitabine-mediated cytotoxicity. Oncogene. 2007 May;26(23):3431–9.

26. Mascia F, Mariani V, Girolomoni G, Pastore S. Blockade of the EGF Receptor Induces a Deranged Chemokine Expression in Keratinocytes Leading to Enhanced Skin Inflammation. Am J Pathol. 2003 Jul;163(1):303–12.

27. Zhong J, Gong Q, Mima A. Inflammatory Regulation in Diabetes and Metabolic Dysfunction. J Diabetes Res. 2017;2017:1–2.

28. Schlienger RG, Bircher AJ, Meier CR. Minocycline-Induced Lupus. Dermatology. 2000;200(3):223–31.

29. Shapiro LE, Knowles SR, Shear NH. Comparative safety of tetracycline, minocycline, and doxycycline. Arch Dermatol. 1997 Oct;133(10):1224–30.

30. Lenert P, Icardi M, Dahmoush L. ANA (+) ANCA (+) systemic vasculitis associated with the use of minocycline: case-based review. Clin Rheumatol. 2013 Jul;32(7):1099–106.

Table 1: Baseline Demographic and Clinical Features of the Cohort

Characteristic	N (%)
Age at diagnosis	70.6 (11.1)
70+	52 (51.0)
<70	50 (49.0)
Sex	
Female	65 (63.7)
Male	37 (36.3)
Race	
Asian	36 (35.3)
Black	8 (7.8)
Caucasian	58 (56.9)
Smoking Status	
Current or past	34 (33.3)
never	68 (66.7)
TKI	
First Generation: Gefitinib, erlotinib	63 (61.8)
Second generation: Afatinib, poziotinib	6 (5.9)
Third Generation: Osimertinib	33 (32.4)
Past Medical History	72 (70.6)
Healthy	30 (29)
History of other Cancer	11 (10.8)
History of Cardiovascular Disease	10 (9.8)
History of Diabetes	19 (18.6)
EGFR Mutation	
Exon 18	5 (4.9)
Exon 19	50 (49)
Exon 20	1 (1)
Exon 21	46 (45.1)
Albumin	
mean (SD)	38.4 (5.0)
median	39
<35g/l	25 (24.5)
>=35g/l	77 (75.5)
Alanine transferase	
mean (SD)	21.7 (19.3)
median	17
<=40	99 (97.1)
>40	3 (2.9)
Creatinine	
mean (SD)	71.3 (22.8)
median	69
<=95	93 (91.2)
>95	8 (7.8)
Missing	1 (1.0)
C reactive protein	
mean (SD)	20.9 (37.0)

median	8
<=10	57 (55.9)
>10	43 (42.2)
Missing	2 (2.0)
Hemoglobin	
mean (SD)	126.7 (19.1)
median	128
<120	33 (32.4)
>=120	69 (67.6)
Lactate dehydrogenase	
mean (SD)	259.2 (128.5)
median	225
<=220	45 (44.1)
>220	53 (52.0)
Missing	4 (3.9)
White blood cells	
mean (SD)	9.2 (4.0)
median	8.3
<=11	76 (74.5)
>11	25 (24.5)
Missing	1 (1.0)

Table 2: Association Between Baseline Demographic and Clinical Features and the Development of Acneiform Eruption

Demographic feature	Number of patients	Number with rash	person time	rate	Crude HR	p-value
Age at lung ca dx						
70+	52	20	410	4.9	0.58 (0.32 - 1.04)	0.0673
<70	50	26	265	9.8	1.00 (Reference)	
Sex						
Men	37	14	259	5.4	0.67 (0.36 - 1.26)	0.2116
Women	65	32	415	7.7	1.00 (Reference)	
Race						
Asian	36	14	247	5.7	1.00 (Reference)	
Black	8	3	111	2.7	0.76 (0.22 - 2.67)	0.6723
Caucasian	58	29	316	9.2	1.50 (0.79 - 2.85)	0.2139
Smoking status						

Current or past	34	14	227.5	6.2	0.90 (0.48-1.68)	0.7315
never	68	32	447	7.2	1.00 (Reference)	
Chemo Type						
First Generation: Gefitinib, erlotinib	63	34	432	7.9	1.00 (Reference)	
Second generation: Afatinib, poziotinib	6	4	24	16.4	1.79 (0.63 - 5.06)	0.2714
Third Generation: Osimertinib	33	8	218	3.7	0.41 (0.19 - 0.89)	0.0237
EGFR						
Exon18 or Exon 20	6	3	8	37	2.06 (0.60 - 7.10)	0.2512
Exon19	50	21	465	4.5	1.00 (Reference)	
Exon21	46	22	201	10.9	1.37 (0.74 - 2.51)	0.3153
Albumin						
<35g/l	25	9	135	6.6	0.83 (0.40 - 1.72)	0.6145
>=35g/l	77	37	539	6.9	1.00 (Reference)	
Creatinine						
<=95	93	42	610	6.9	1.00 (Reference)	
>95	8	3	64	4.7	0.80 (0.25 - 2.57)	0.7042
Missing	1	1	0	253.6		
C reactive protein						
<=10	57	29	432	6.7	1.00 (Reference)	
>10	43	15	239	6.3	0.74 (0.39 - 1.38)	0.3434
Missing	2	2	3	57.4		
Hemoglobin						
<120	33	14	166	8.5	1.03 (0.55 - 1.93)	0.9346
>=120	69	32	509	6.3	1.00 (Reference)	
Lactate dehydrogenase						
<=220	45	24	317	7.6	1.00 (Reference)	
>220	53	19	350	5.4	0.62 (0.34 - 1.13)	0.1183
Missing	4	3	7	41.3		
White blood cells						
<=11	76	38	557	6.8	1.00 (Reference)	

>11	25	7	117	6	0.61 (0.27 - 1.37)	0.2299
Missing	1	1	1	108.7		
Past medical history						
Y	72	31	544	5.7	0.69 (0.37 - 1.29)	0.2440
N	30	15	131	11.4	1.00 (Reference)	
History of						
Other cancer						
Y	11	3	90	3.3	0.48 (0.15 - 1.54)	0.2149
N	91	43	585	7.3	1.00 (Reference)	
CVD						
Y	10	3	115	2.6	0.52 (0.16 - 1.68)	0.2723
N	92	43	560	7.7	1.00 (Reference)	
Diabetes						
Y	19	7	166	4.2	0.74 (0.33 - 1.66)	0.4643
N	83	39	509	7.7	1.00 (Reference)	

Table 3: Descriptive Management of Acneiform Eruptions

Characteristic	N (%)
Number with Acneiform Eruption	46
CTCAE Grading	
1 – Mild	15 (32.6)
2 – Moderate	3 (6.5)
3 - Severe	1 (2.1)
Not Reported	27 (58.7)
Oncology Initial Management	
Conservative management	21 (45.6)
Topical steroid	6 (13.0)
Oral Tetracycline	19 (41.3)
Stop or Hold TKI	0
Oncology Management Result	
Improvement	18 (39.1)
Unchanged	6 (13.0)
Worsening	2 (4.3)
Not Reported	20 (43.5)
Dermatology Referral	
Yes	24 (52.2)
No	22 (47.8)
Dermatology Management	
Conservative management	5 (20.8)
Topical steroid	4 (16.6)
Topical Antibiotic	4 (16.6)

Oral Tetracycline	7 (29.2)
Stop or Hold TKI	0
Missing or Not Reported	4 (16.6)
Dermatology Management Result	
Improvement	9 (37.5)
Unchanged	1 (4.2)
Worsening	0
Missing or Not Reported	14 (58.3)

Table 4: Overall Survival

	Number of patients	Number of death	person-month	rate (per 100 person per month)	Crude HR	Adjusted HR
Age at lung ca dx						
70+	52	37	1088	3.4	1.16 (0.72 - 1.87)	1.15 (0.70 - 1.88)
<70	50	32	1066	3.0	1.00 (Reference)	1.00 (Reference)
Sex						
Men	37	27	633	4.3	1.53 (0.94 - 2.48)	1.53 (0.94 - 2.49)
Women	65	42	1520	2.8	1.00 (Reference)	1.00 (Reference)
RASH Time dependent definition						
Yes		33	1064	3.1	0.89 (0.55 - 1.43)	0.93 (0.57 - 1.53)
No		36	1090	3.3	1.00 (Reference)	1.00 (Reference)

**Adjusted for each other*

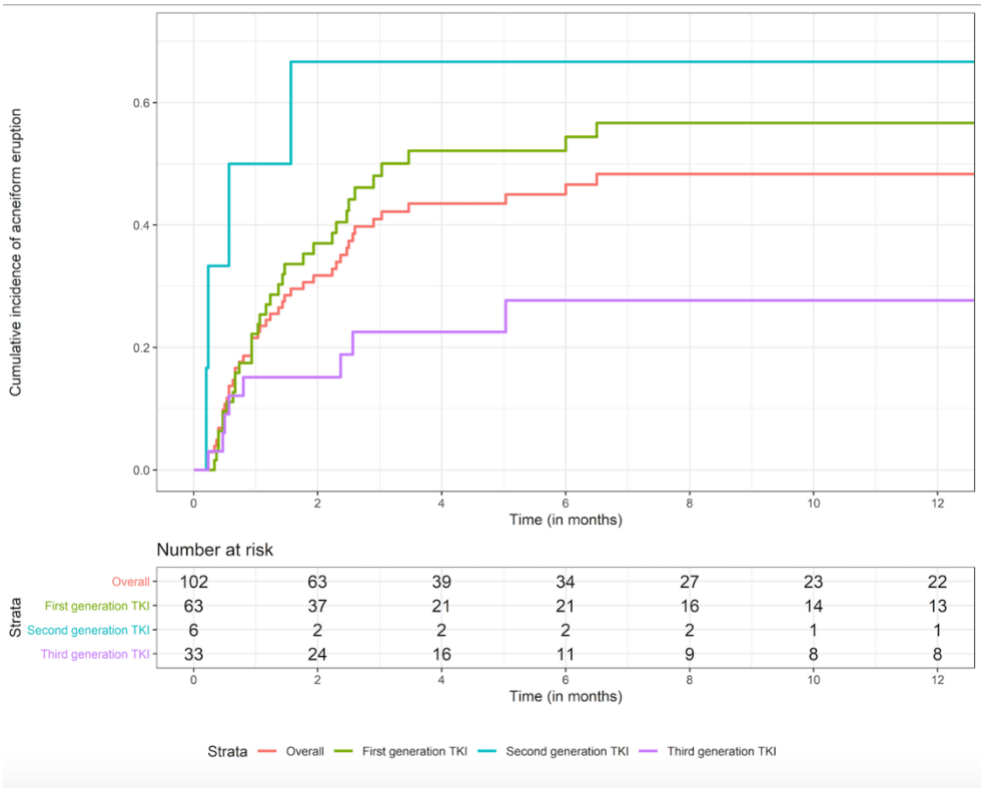


Figure 1: Kaplan Meier Curve – Time to Rash Overall and Based on Type of TKI

Chapter Two: An Analysis of the Treatment Patterns Acneiform Eruptions Secondary to Epidermal Growth Factor Receptor Inhibitors in Dermatologists and Oncologists in Canada

Given in the first chapter of this thesis, we were unable to identify any statistically significant risk factors associated with an increased risk of acneiform eruption, our focus shifted to optimizing care for patients who develop this cutaneous adverse event. Multiple guidelines exist for the management of acneiform eruptions. Although these guidelines are relatively uniform across organizations, there is little evidence to support the recommendations. This has therefore led to heterogeneity of management strategies between dermatologists and oncologists. For example, in a European study, dermatologists are more likely to recommend isotretinoin for management of acneiform eruptions and are less likely to recommend holding EGFRi therapy. (44) No evidence exists for practice patterns of dermatologists and oncologists in Canada. Therefore, the aim of the project in Chapter two is to describe the landscape for management of acneiform eruptions by dermatologists and oncologists in Canada, as well as to compare management strategies between the two specialties.

An Analysis of the Treatment Patterns Acneiform Eruptions in Dermatologists and Oncologists in Canada

Bierbrier R[1], Esfahani K[2], Pehr K[1,3]

[1]Division of Dermatology, McGill University, Montreal Canada
[2] Departments of Medicine and Oncology, Segal Cancer Centre, Sir Mortimer B. Davis Jewish General Hospital, Rossy Cancer Network, McGill University, Montreal, QC, Canada
[3]Lady Davis Institute, Sir Mortimer B. Davis Jewish General Hospital, McGill University, Montreal Canada

Abstract

Acneiform eruptions are a common cutaneous adverse event experienced by patients on epidermal growth factor receptor inhibitors (EGFRi). Current treatment guidelines exist for the management of acneiform eruptions, however, data from Europe demonstrates heterogeneity in management strategies between dermatologists and oncologists. The objective of this study is to compare practice patterns between dermatologists and oncologists in Canada for the treatment of acneiform eruptions secondary to EGFRi. A twenty-two-question online-based survey was sent to oncologists and dermatologists across Canada to assess management strategies for acneiform eruptions. A total of 53 physicians responded to the survey. Dermatologists were more likely to prescribe a topical retinoid or benzoyl peroxide for mild eruptions, versus oncologists who were more likely to prescribe topical steroids ($p<0.001$). Critically, for management of severe eruptions, no dermatologists recommended stopping EGFRi, compared to 66% of oncologists who would discontinue therapy ($p <0.001$). Early involvement and co-management by Dermatology is recommended to prevent EGFRi treatment discontinuation.

Background and Introduction

Acneiform eruptions are one of the most commonly encountered adverse events in patients on epidermal growth factor receptor inhibitors (EGFRi). (1) The eruption is similar to acne vulgaris,

with papules and pustules distributed on the face, trunk and back, but lacks comedones, occurs suddenly, and is associated with pain, pruritus, and burning. The eruption is disruptive to the quality of life of patients and, if severe, can lead to early life-saving cancer therapy discontinuation. (2)

In addition to the relatively minor clinical differences with acne vulgaris, the pathogenesis differs. The development of the acneiform eruption due to EGFRi is related to disrupted keratinocyte differentiation in the epidermis, which leads to follicular plugging and inflammation. This is because keratinocyte differentiation relies on the epidermal growth factor receptor (EGFR) tyrosine kinase pathway signaling. The acneiform eruption is associated with cancer therapy response and prolonged progression-free survival. (3)

Currently, multiple guidelines exist for the management of acneiform eruptions secondary to EGFRi including Canadian recommendations, European guidelines, Brazilian guidelines, and American guidelines. (4) (5) (6) (7) However, they are all based on expert opinion/consensus; none are evidence-based.

There are no data on the current practice patterns for the management of acneiform eruptions in Canada. In a study from the USA, although the majority of oncologists monitor for skin toxicity during treatment with EGFRi, less than 30% of initiate treatment grade 2 to 3 acneiform eruptions. (8) The majority of oncologists in Germany refer to dermatology only occasionally for the management of acneiform eruptions due to EGFRi. (9)When compared to oncology colleagues, dermatologists are more likely to initiate both topical and systemic therapy for acneiform eruptions, and are less likely to recommend EGFRi dose reduction or treatment discontinuation. (9)

Given that the acneiform eruption correlates with tumor response to EGFRi, effective treatment of the skin is paramount to improving quality of life and decreasing the frequency of EGFRi discontinuation. The objective of this study is to compare practice patterns between dermatologists and oncologists in Canada for the treatment of acneiform eruptions secondary to EGFRi.

Methods

The study population consisted of licensed practicing dermatologists and oncologists in Canada. Exclusion criteria were non-English or French-speaking participants, participants who are unable to access the online survey due to technical or physical limitations, and non-Canadian licensed physicians. Surveys were distributed via Canadian oncology and dermatology association mailing lists with one initial email and one follow-up email. In total, participant recruitment lasted three months. This study was approved by the local institutional Research Ethics Board (Protocol # 2022-3193).

The survey was hosted on an online platform (LimeSurvey) and included 22 questions. Questions were a mixture of multiple-choice questions, Likert scale questions, and short answer questions. Questions on the management of acneiform eruptions included a clinical photograph obtained from Dermnet.nz or our own clinical collections with patient consent. Clinical photos used in the survey included diverse skin phototypes.

Incomplete surveys were not included in the analysis. Categorical data obtained from survey results was compared between groups using a two-proportion z test. Differences were considered statistically significant with a p-value of <0.05. Statistical analyses were performed using the R software.

Results

In total 53 participants completed the survey. Thirty-two (60.3%) participants were oncologists and 21 (40.0%) were dermatologists. The greatest number of survey respondents were from Quebec (49.0%), followed by Ontario (15%) and British Columbia (15%). The majority of study participants practiced in an academic hospital (79.2%), followed by private practice (22.6%). Forty-nine percent of participants had more than fifteen years of clinical experience, 28% had less than five years of clinical experience as an independently licensed physician. (Table 1)

The majority of dermatologists (85.7%) and oncologists (100%) strongly agree or agree that the management of acneiform eruptions is important for patients. The majority of dermatologists (80.1%) and oncologists (84.3%) report that patients were symptomatic from acneiform eruptions secondary to EGFRi. Oncologists were more likely to monitor for the development of acneiform eruptions, compared to dermatologists (46.9% vs 9.52%, p= 0.004). Both oncologists and dermatologists feel comfortable counseling on cutaneous adverse events of EGFRi. Both specialties were comfortable managing mild and moderate acneiform eruptions. Oncologists feel less comfortable than dermatologists in managing severe acneiform eruptions (40.7% vs. 76.8%, p=0.001). Dermatologists and oncologists feel comfortable managing acneiform eruptions across the spectrum of skin phototypes. (Table 2)

Compared to dermatologists, more oncologists believe the Common Terminology Criteria for Adverse Events (CTCAE) scale is best for assessing the severity of acneiform eruptions in cancer patients (p=0.028). For prevention of acneiform eruptions secondary to EGFRi, dermatologists and oncologists recommend multiple modalities including gentle cleansing of the face, avoidance of irritants, moisturizing cream, and daily sunscreen use. Management of mild acneiform eruptions differed between the two specialties, where dermatologists were more likely to prescribe a topical retinoid or benzoyl peroxide to patients, versus oncologists who were more likely to prescribe topical steroids (p<0.001). (Table 2)

For management of moderate acneiform eruptions, oncologists were more likely to prescribe topical steroids. Dermatologists were more likely to prescribe topical retinoids, benzoyl peroxide and doxycycline. For management of severe eruptions, no dermatologists recommended stopping EGFRi, compared to 66% of oncologists who would discontinue therapy (p <0.001). Dermatologists were more likely to prescribe isotretinoin for the management of severe eruptions, compared to oncologists (p <0.001). (Table 3)

Discussion

Both dermatologists and oncologists agree that the acneiform eruption is an important cutaneous adverse event that is common to patients on EGFRi. Both specialties agree that this cutaneous

adverse event is bothersome to patients. Thus, effective management of this eruption is important to maintain adequate quality of life for patients on EGFRi therapy. In this study, we identified statistically significant differences in the approach to the management of acneiform eruptions between dermatologists and oncologists. In some cases, Dermatological consultation could prevent premature discontinuation of life-saving cancer treatment.

Guidelines for the management of acneiform eruptions secondary to EGFRi exist in the literature, however, they are all based on expert consensus, and none are evidence-based. In Canada, there are recommendations developed by Melosky *et al.* in 2009. (4) They are based on CTCAE grading, and only include topical medications and systemic antibiotics; systemic retinoids are introduced later as a possible third-line treatment. (4) International guidelines from Europe and the United States also exist. The European Society for Medical Oncology's (ESMO) recommendations are also based on CTCAE grading system. The management of grade 1-2 acneiform eruptions includes oral doxycycline and topical steroids, with the continuation of the EGFRi. For grade 3-4 eruptions, EGFRi treatment is held and a combination of tetracycline antibiotics, topical steroids, and systemic corticosteroids is recommended. In the ESMO guidelines, isotretinoin is also listed as a third-line therapeutic option for more severe eruptions but is not standard of care. (5). Multinational Association of Supportive Care in Cancer (MASCC) guidelines from the United States, Brazil, and Italy have similar recommendations to ESMO, favoring topical therapy with steroids or antibiotics for mild eruptions, and systemic therapy with oral tetracyclines. Low dose isotretinoin is recommended as a second or third line for severe eruptions. (7) (6) (10)

More oncologists than dermatologists believe that the CTCAE grading system is best to assess the severity of acneiform eruptions. The CTCAE grading system represents a means for rapid classification of adverse events to cancer therapy and includes a scale for acneiform eruptions. The CTCAE scale is a useful tool to standardize clinical assessment in oncology but may not accurately describe the severity of the eruption from a dermatologic perspective. For example, the use of body surface area as a measure of severity is less representative when the eruption is localized on the face, chest, and back (which comprises less than 30% of the BSA). (11) As such, alternate scales were developed to more precisely describe clinical severity. In addition to a

physician's global assessment (PGA), scores such as the Leeds Revised Acne Grading Scale, the EGFRI-induced rash severity score (ERSS), the MASCC EGFR inhibitor skin toxicity tool (MESTT) may be used. (12) (13) (14)

In our study population, oncologists responded to surveys which reflected the aforementioned guidelines; selecting topical steroids and tetracycline antibiotics for management of acneiform eruptions. Dermatologists, however, recommend alternative therapeutic options. For example, dermatologists were more likely to select topical retinoids and benzoyl peroxide for the management of mild to moderate acneiform eruptions. Further, dermatologists are more likely than oncologists to prescribe isotretinoin for severe eruptions. The findings in our study are similar to the literature reported from other countries. In a study based in Germany, dermatologists were more likely than oncologists to prescribe topical antibiotics and were less likely to prescribe topical steroids. In the same study, more dermatologists were likely to use isotretinoin as systemic therapy. (9)

Although the majority of the published guidelines for the management of acneiform eruptions are consistent across organizations, there is minimal evidence to support these recommendations. *Bachet et al* report a paucity of prospective data on the use of tetracycline antibiotics for the management of acneiform eruptions. (15) In their systematic review, all available data on the use of tetracyclines was in the form of case reports and case series. There is increasing evidence for the use of isotretinoin for the management of acneiform eruptions secondary to EGFRi, however, no controlled trials exist for this medication either. (16) The lack of robust data to support the treatment recommendations may explain the different treatment strategies seen between the two specialties. The management strategies selected by dermatologists more closely reflect the treatment ladder used in acne vulgaris. (17)

There is, however, published evidence for the use of tetracycline antibiotics for the prevention of acneiform eruptions. Both oncologists and dermatologists recommended oral tetracyclines at similar rates for the management of acneiform eruptions. This is supported by a meta-analysis that demonstrated that systemic antibiotics were the most effective at reducing the rate of acneiform eruptions compared to other modalities. (18)

In our study population, no dermatologists recommended treatment discontinuation for severe acneiform eruptions. This finding is supported by previous work. (9) The authors note this as a significant difference in management between the two specialties. There is a growing body of evidence to support the role of dermatologists as co-consultants to optimize cancer patient outcomes. Dermatologists can provide early and effective therapy to patients experiencing cutaneous adverse events, which can decrease interruptions of anticancer therapy. (19) In a study by *Yu et al* (2020), a comprehensive skin toxicity program for patients on EGFRi, which included dermatologic consultation, led to decreased rates of acneiform eruptions and EGFRi treatment discontinuation. (20) Given that there is evidence to support the positive prognostic implications of the acneiform eruption in patients on EGFRi, maintaining targeted therapy while effectively managing acneiform eruptions would lead to improved patient outcomes. (21) Unfortunately, outside of structured programs, dermatologists are uncommonly consulted to co-manage patients started on EGFRi therapy. (8) (22)

The authors note limitations to this investigation. Firstly, survey respondents were not uniformly distributed across Canada, and therefore results may be skewed towards regional practices. Aside from photographs, little clinical information was provided for questions on the management of mild, moderate and severe acneiform eruptions. Information on patient symptomatology and quality of life disturbance is used in real clinical settings to guide appropriate management. Finally, given the design of the study, results may be subject to reporting bias.

Conclusions

Canadian dermatologists and oncologists agree that acneiform eruptions secondary to EGFRi therapy are common and important cutaneous adverse events. Management of acneiform eruptions, especially moderate and severe eruptions, differs between dermatologists and oncologists. This may be due to a lack of robust evidence in this area. Dermatologic expertise is an important aspect of the comprehensive care of oncology patients. Early involvement by dermatology for patients who develop acneiform eruptions is recommended to prevent EGFRi treatment discontinuation.

References

1. Annunziata MC, Ferrillo M, Cinelli E, Panariello L, Rocco D, Fabbrocini G. Retrospective Analysis of Skin Toxicity in Patients under Anti-EGFR Tyrosine Kinase Inhibitors: Our Experience in Lung Cancer. Open Access Maced J Med Sci. 2019 Mar 27;7(6):973–7.

2. Melosky B, Leighl NB, Rothenstein J, Sangha R, Stewart D, Papp K. Management of egfr tki–induced dermatologic adverse events. Curr Oncol. 2015 Jan 8;22(2):123.

3. Giovannini M, Gregorc V, Belli C, Roca E, Lazzari C, Viganò MG, et al. Clinical Significance of Skin Toxicity due to EGFR-Targeted Therapies. J Oncol. 2009;2009:1–8.

4. Melosky B, Burkes R, Rayson D, Alcindor T, Shear N, Lacouture M. Management of Skin Rash during egfr-Targeted Monoclonal Antibody Treatment for Gastrointestinal Malignancies: Canadian Recommendations. Curr Oncol. 2009 Jan 1;16(1):16–26.

5. Lacouture ME, Sibaud V, Gerber PA, van den Hurk C, Fernández-Peñas P, Santini D, et al. Prevention and management of dermatological toxicities related to anticancer agents: ESMO Clinical Practice Guidelines☆. Ann Oncol. 2021 Feb;32(2):157–70.

6. Cury-Martins J, Eris APM, Abdalla CMZ, Silva G de B, Moura VPT de, Sanches JA. Management of dermatologic adverse events from cancer therapies: recommendations of an expert panel. An Bras Dermatol. 2020 Mar;95(2):221–37.

7. MASCC Skin Toxicity Study Group, Lacouture ME, Anadkat MJ, Bensadoun RJ, Bryce J, Chan A, et al. Clinical practice guidelines for the prevention and treatment of EGFR inhibitor-associated dermatologic toxicities. Support Care Cancer. 2011 Aug;19(8):1079–95.

8. Lowe KA, Sangaré L, Bergstresser R, McNamara M, Kafatos G, Garawin T. A National Survey of Medical Oncologist's Opinions and Perceptions for Managing Rash Among mCRC Patients Treated with Panitumumab. Dermatol Ther. 2019 Jun;9(2):337–53.

9. Hassel JC, Kripp M, Al-Batran S, Hofheinz RD. Treatment of Epidermal Growth Factor Receptor Antagonist-Induced Skin Rash: Results of a Survey among German Oncologists. Onkologie. 2010;33(3):94–8.

10. Pinto C, Barone CA, Girolomoni G, Russi EG, Merlano MC, Ferrari D, et al. Management of Skin Toxicity Associated with Cetuximab Treatment in Combination with Chemotherapy or Radiotherapy. The Oncologist. 2011 Feb;16(2):228–38.

11. Wollenberg A, Moosmann N, Klein E, Katzer K. A tool for scoring of acneiform skin eruptions induced by EGF receptor inhibition. Exp Dermatol. 2008 Sep;17(9):790–2.

12. O'brien S, Lewis J, Cunliffe W. The Leeds revised acne grading system. J Dermatol Treat. 1998 Jan;9(4):215–20.

13. Gerber PA, Meller S, Eames T, Buhren BA, Schrumpf H, Hetzer S, et al. Management of EGFR-inhibitor associated rash: a retrospective study in 49 patients. Eur J Med Res. 2012 Dec;17(1):4.

14. Chan A, Tan EH. How well does the MESTT correlate with CTCAE scale for the grading of dermatological toxicities associated with oral tyrosine kinase inhibitors? Support Care Cancer. 2011 Oct;19(10):1667–74.

15. Bachet J, Peuvrel L, Bachmeyer C, Reguiai Z, Gourraud PA, Bouché O, et al. Folliculitis Induced by EGFR Inhibitors, Preventive and Curative Efficacy of Tetracyclines in the Management and Incidence Rates According to the Type of EGFR Inhibitor Administered: A Systematic Literature Review. The Oncologist. 2012 Apr;17(4):555–68.

16. Bierbrier R, Lam M, Pehr K. A systematic review of oral retinoids for treatment of acneiform eruptions induced by epidermal growth factor receptor inhibitors. Dermatol Ther [Internet]. 2022 Mar 3 [cited 2022 Apr 29]; Available from: https://onlinelibrary.wiley.com/doi/10.1111/dth.15412

17. Bolognia, Jean., Jorizzo, Joseph L.Schaffer, Julie V., eds. Dermatology. [Philadelphia] :: Elsevier Saunders, 2018. Print.

18. Gorji M, Joseph J, Pavlakis N, Smith SD. Prevention and management of acneiform rash associated with EGFR inhibitor therapy: A systematic review and meta-analysis. Asia Pac J Clin Oncol. 2022 Mar 29;ajco.13740.

19. Barrios DM, Phillips GS, Freites-Martinez A, Hsu M, Ciccolini K, Skripnik Lucas A, et al. Outpatient dermatology consultations for oncology patients with acute dermatologic adverse events impact anticancer therapy interruption: a retrospective study. J Eur Acad Dermatol Venereol JEADV. 2020 Jun;34(6):1340–7.

20. Yu Z, Dee EC, Bach DQ, Mostaghimi A, LeBoeuf NR. Evaluation of a Comprehensive Skin Toxicity Program for Patients Treated With Epidermal Growth Factor Receptor Inhibitors at a Cancer Treatment Center. JAMA Dermatol. 2020 Oct 1;156(10):1079.

21. Lee SM, Khan I, Upadhyay S, Lewanski C, Falk S, Skailes G, et al. First-line erlotinib in patients with advanced non-small-cell lung cancer unsuitable for chemotherapy (TOPICAL): a double-blind, placebo-controlled, phase 3 trial. Lancet Oncol. 2012 Nov;13(11):1161–70.

22. Peuvrel L, Bachmeyer C, Reguiai Z, Bachet JB, André T, Bensadoun RJ, et al. Survey on the management of skin toxicity associated with EGFR inhibitors amongst French Physicians: Skin toxicity and EGFR inhibitors. J Eur Acad Dermatol Venereol. 2013 Apr;27(4):419–29.

Table 1: Participant Characteristics

Characteristic	N (%)
Dermatologists	21 (39.6)
Practice Setting: [a]	
1. Academic Hospital	15 (71.4)
2. Community Hospital	2 (9.5)
3. Private Practice	11 (52.4)
Number of Years in Practice	
1. 0-5	7 (33.3)
2. 5-10	4 (19.0)
3. 10-15	1 (4.8)
4. 15+	9 (42.9)
Province of Practice	
1. Quebec	14 (66.7)
2. British Columbia	3 (14.2)
3. Ontario	1 (4.8)
4. Nova Scotia	1 (4.8)
5. New Brunswick	1 (4.8)
1. Alberta	1 (4.8)
2. Prince Edward Island	0
6. Manitoba	0
Oncologists	32 (60.4)
Practice Setting:	
1. Academic Hospital	27 (84.3)
2. Community Hospital	6 (18.9)
3. Private Practice	1 (3.1)
Number of Years in Practice	
1. 0-5	8 (25.0)
2. 5-10	6 (18.8)
3. 10-15	5 (15.6)
4. 15+	13 (40.6)
Province of Practice	
3. Quebec	12 (37.5)
4. British Columbia	5 (15.6)
5. Ontario	7 (21.9)
6. Nova Scotia	1 (3.1)
7. New Brunswick	0
8. Alberta	1 (3.1)
9. Prince Edward Island	1 (3.1)
10. Manitoba	5 (15.6)

[a] Participants were able to select more than one option, if applicable.

Table 2: Likert Scale Questions

Question	Response Options	Dermatologists (n)	Oncologists (n)	p-value
It is important to manage acneiform eruptions secondary to epidermal growth factor receptor inhibitors (EGFRi).	Strongly Agree	12	24	0.173
	Agree	6	8	0.773
	Neutral	3	0	0.028
	Disagree	0	0	-

	Strongly Disagree	0	0	-
Acneiform eruptions secondary to EGFRi are common amongst my patients	Strongly Agree	5	12	0.296
	Agree	8	13	0.853
	Neutral	3	3	-
	Disagree	4	4	0.515
	Strongly Disagree	1	0	-
I monitor my patients for the development of acneiform eruptions while on EGFRi	Strongly Agree	2	15	0.004
	Agree	7	13	0.592
	Neutral	11	3	0.0005
	Disagree	1	1	-
	Strongly Disagree	0	0	-
Patients are not bothered by acneiform eruptions secondary to EGFRi.	Strongly Agree	1	0	-
	Agree	1	1	-
	Neutral	2	4	-
	Disagree	14	20	0.757
	Strongly Disagree	3	7	0.490
Acneiform eruptions are a sign that the patient's cancer is responding to EGFRi.	Strongly Agree	4	1	-
	Agree	12	11	0.102
	Neutral	5	15	0.090
	Disagree	0	4	-
	Strongly Disagree	0	1	-
I am comfortable counselling patients on the possible cutaneous adverse events of EGFRi.	Strongly Agree	7	12	0.757
	Agree	10	19	0.400
	Neutral	4	1	-
	Disagree	0	0	-
	Strongly Disagree	0	0	-
I am not comfortable managing mild acneiform eruptions secondary to EGFRi.	Strongly Agree	2	0	-
	Agree	2	3	-
	Neutral	1	0	-
	Disagree	7	14	0.448
	Strongly Disagree	9	15	0.774
I am not comfortable managing moderate acneiform eruptions secondary to EGFRi.	Strongly Agree	1	0	-
	Agree	1	4	-
	Neutral	4	3	-
	Disagree	6	15	0.182
	Strongly Disagree	9	10	0.389
I am not comfortable managing severe acneiform eruptions secondary to EGFRi.	Strongly Agree	0	3	-
	Agree	3	19	0.001
	Neutral	3	4	-
	Disagree	7	3	-
	Strongly Disagree	8	3	-
I feel comfortable diagnosing acneiform eruptions in dark skin phototypes.	Strongly Agree	6	3	-
	Agree	9	14	0.949
	Neutral	5	11	0.413
	Disagree	1	4	-
	Strongly Disagree	0	0	-
I feel comfortable diagnosing acneiform eruptions in light skin phototypes.	Strongly Agree	11	7	0.022
	Agree	9	22	0.061
	Neutral	1	2	-
	Disagree	0	0	-
	Strongly Disagree	0	1	-
To grade severity of acneiform eruptions secondary to EGFRi, I use	CTCAE	7	17	0.019
	Physician Global Assessment	15	25	0.579

The CTCAE grading system is the best system to assess severity of acneiform eruptions in cancer patients.	Agree Disagree	8 13	22 12	0.028 0.082

Table 3: Management of Acneiform Eruptions

Clinical Scenario	Management Options	Dermatologists	Oncologists	P value
Prevention	1. Wash face with lukewarm water	6	10	0.835
	2. Avoidance of skin irritants	10	16	0.865
	3. Moisturizing cream	11	16	0.865
	4. Avoidance of UVR	8	18	0.196
	5. Daily sunscreen use	9	17	0.465
	6. Mild topical steroid	5	13	0.206
	7. Moderate topical steroid	2	4	-
	8. Topical retinoid	5	0	-
	9. Topical antibiotic	8	10	0.607
	10. Oral tetracycline	9	15	0.528
Mild Eruption	1. Watch and wait	5	9	0.727
	2. Dose reduction EGFRi	0	0	-
	3. Hold EGFRi	2	2	-
	4. Topical steroids	3	21	<0.001
	5. Topical antibiotics	10	12	0.465
	6. Topical retinoid	12	2	<0.001
	7. Benzoyl peroxide	13	0	<0.001
	8. Doxycycline	3	5	-
	9. Minocycline	1	3	-
	10. Isotretinoin	1	0	-
	11. Acitretin	0	0	-
Moderate Eruption	1. Watch and wait	3	2	-
	2. Dose reduction EGFRi	1	2	-
	3. Hold EGFRi	0	3	-
	4. Topical steroids	5	22	<0.001
	5. Topical antibiotics	14	14	0.102
	6. Topical retinoid	10	0	<0.001
	7. Benzoyl peroxide	14	2	<0.001
	8. Doxycycline	15	12	0.016
	9. Minocycline	7	14	0.448
	10. Isotretinoin	2	0	-
	11. Acitretin	0	0	-
Severe Eruption	1. Watch and wait	1	0	-
	2. Dose reduction EGFRi	4	7	0.804
	3. Hold EGFRi	0	21	<0.001
	4. Topical steroids	7	21	0.021
	5. Topical antibiotics	7	16	0.231
	6. Topical retinoid	4	2	-
	7. Benzoyl peroxide	6	1	-
	8. Doxycycline	10	14	0.782
	9. Minocycline	5	18	0.019
	10. Isotretinoin	12	3	<0.001
	11. Acitretin	2	2	-

Chapter Three: A Systematic Review of Oral Retinoids for Treatment of Acneiform Eruptions Induced by Epidermal Growth Factor Receptor Inhibitors

In the majority of clinical guidelines published in Europe, United States and Canada, tetracyclines are recommended as first line systemic therapy for management of acneiform eruptions. Systemic retinoids are listed as an alternative systemic therapy, in most cases third line after trial with systemic steroids. Although tetracyclines are generally considered to be a safe and effective medication to manage acneiform eruptions, it is important for clinicians to have alternate options for patients with contraindications or who do not respond to therapy. Further, with advanced knowledge of the importance of the gut microbiome in health and disease, there are recent concerns regarding the use of tetracyclines due to their effect on the gut microbiome's diversity. (45) Therefore, in this chapter, we systematically reviewed the literature to summarize available data on the use of systemic retinoids for management of acneiform eruptions. The objective of the study was to pool together available published clinical experience on the use of systemic retinoids for management of acneiform eruptions, for clinicians to use when deciding optimal systemic therapy for management of a patient's acneiform eruption.

A Systematic Review of Oral Retinoids for Treatment of Acneiform Eruptions Induced by Epidermal Growth Factor Receptor Inhibitors

Authors: Bierbrier Rachel[1] MD, Lam Megan[2] BSc, Pehr Kevin MD[1,3]

Affiliations:

1. Department of Dermatology, McGill University, Montreal, Canada
2. DeGroote School of Medicine, McMaster University, Hamilton, Canada
3. Lady Davis Institute, Jewish General Hospital, McGill University, Montreal Canada

Abstract

Epidermal growth factor receptor inhibitors (EGFRi) are now standard of care in patients with EGFR mutations in non-small cell lung cancer (NSCLC) and are increasingly being used in other EGFR mutated cancers, including gastrointestinal, and head and neck. However, EGFRi are well known to cause acneiform eruptions, which are shown to positively correlate with tumor response to treatment, but may be severe enough to cause interruption of their treatment. Although most guidelines call for the use of tetracyclines to treat these acneiform eruptions, there is mounting evidence for the use of systemic retinoids instead. The objective of this review is to summarize available data on the use of systemic retinoids for management of acneiform eruptions on EGFRi. This study was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. MEDLINE and EMBASE were searched from database inception until December 10th, 2021. All articles were screened and relevant data extracted independently in duplicate by two reviewers. In total, sixteen case reports, case series and retrospective reviews were included. Forty-three patients were treated with retinoids for their acneiform eruption due to EGFRi. The majority (77%) noted moderate to significant improvement after treatment initiation with minimal adverse events (16%). The findings of this systematic review suggest that systemic retinoids are a safe and effective therapy for the management of acneiform eruptions induced by EGFRi.

Background and Introduction

Epidermal growth factor receptor inhibitors (EGFRi) are now standard of care in patients with EGFR mutations in non-small cell lung cancer (NSCLC) and are increasingly being used in other EGFR mutated cancers, including gastrointestinal, and head and neck. (1)

EGFRi are well-known to cause cutaneous adverse events (AE), most commonly an acneiform eruption. (2) This is unsurprising given that EGFR is expressed in the skin and adnexal structures and is shown to be important in keratinocyte proliferation and differentiation. (3) Although the precise mechanism of action underlying this AE eruption is yet to be completely elucidated, current consensus is that EGFRi's affect keratinocyte proliferation by up regulation of p27, which leads to hyperkeratinisation and abnormal desquamation, ultimately resulting in follicular plugging. (4) Other cutaneous AE include xerosis, and hair and nail changes. Acneiform eruptions are estimated to occur in up to 100% of patients. (5) There is evidence to suggest that these changes may be associated with a favorable response to therapy, however, they adversely affect the quality of life of patients and may be severe enough to lead to premature discontinuation of life saving cancer treatment. (6)

The onset of an acneiform eruption is usually within two weeks of treatment initiation. It begins with erythema and edema, followed by papules and pustules but no comedones; the distribution of the rash follows that of acne, favouring the face, neck, chest and upper back. (7)
Papules crust over and develop into areas of post inflammatory hyperpigmentation. The eruption usually resolves within 6 weeks with treatment. (8) Most authors grade the severity using the CTCAE criterion, with Grade 1 representing a mild reaction and a Grades 2-4 representing a moderate to severe reaction. (9) It is important to note that, although we base our treatments for EGFRi-induced acneiform eruptions on treatment regiments for acne vulgaris, they are not the same condition. (10)

Systemic retinoids bind to nuclear receptors, altering gene expression, and ultimately altering cellular pathways involved in inflammation, apoptosis, sebaceous gland activity and cellular differentiation. (11) Isotretinoin is approved for use in severe acne vulgaris, and more recently

for acne with severe impact on quality of life. Acitretin, another systemic retinoid, is used for treatment of disease with altered keratinocyte proliferation and differentiation such as psoriasis. Bexarotene and alitretinoin are systemic retinoids used for the treatment of cutaneous malignancy; cutaneous T cell lymphoma and Kaposi sarcoma, respectively. (12)

The majority of guidelines for the treatment of acneiform eruptions are based on the treatment of acne vulgaris. Oral tetracyclines are named in most guidelines as the only recommended systemic therapy for patients with moderate to severe acneiform eruptions. However, this recommendation is primarily described in case reports and case series, and the total improvement is only modest (43% average by lesion count) and not durable (improvement peaked by 4 weeks of treatment, then worsened by 8 weeks). (13) This had therefore prompted exploration of use of alternate systemic therapies for the treatment of this skin eruption. There is mounting evidence for using isotretinoin for the treatment of acneiform eruptions induced by EGFRi. (14) (15) (16) (17) (18) However, there are concerns with the use of isotretinoin given overlapping side effects with tyrosine kinase inhibitors, specifically xerosis, dermatitis, cheilitis and the development of pyogenic granulomas. Therefore, the objective of this review is to summarize the current published literature on the use of systemic retinoids in acneiform eruptions caused by EGFRi.

Methods

This study was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

We searched Embase and MEDLINE electronic databases for any study that examined the use of retinoids, alone or in combination, for acneiform eruptions induced by EGFRi in patients from inception of those databases until December 10th, 2021. We included observational studies, prospective trials, and case reports, as well as abstracts. We excluded studies where EGFRi were used in non-oncology patients, and non-English studies if no translation was available. The search was conducted with input from an experienced research librarian, and comprised of all currently available EGFRi, all currently approved systemic retinoids and “acneiform eruptions”. (19) (12) Complete search history details are presented in Figure 1.

Two investigators (R.B. and M.L.) screened titles and abstracts, followed by an assessment of full texts based on our inclusion and exclusion criteria. R.B and M.L also manually searched the reference list of review articles included in the initial search for potentially relevant studies. At each stage of study screening, discrepancies between reviewers were highlighted and resolved by senior author (K.P) if not resolved between reviewers.

The same 2 investigators (R.B. and M.L.) used a standardized form to independently extract the following information from each study: patient demographics, timing of acneiform eruption, timing of retinoid treatment initiation, use of concurrent topical or systemic treatment, dose and duration of retinoid therapy, timing to effect of retinoid, measurement of response to treatment, adverse events, and cancer outcomes.

Data were summarized quantitatively in tables. Given that all published reports were case reports, no risk of bias assessment was performed.

Results

Study Characteristics

We retrieved 123 records from the literature. After five duplicates were removed, 96 articles were screened by title and abstract for relevancy. 41 full text articles were assessed for eligibility (Figure 2). Fifteen texts remained eligible for inclusion after full text review and an additional paper was included after reference screening in review articles. In total, sixteen papers were included in this review. Five were from USA, four from Germany, four from Italy, one from Spain, one from Portugal and one from Poland. All included papers were case reports, case series or retrospective chart reviews. There were no controlled trials. (Table 1)

Participant characteristics

A total of 43 patients were reported treated with a systemic retinoid after developing an acneiform eruption secondary to EFGRi. Five of the patients were female (16%) and the average

patient age was 56 years. The majority of the reported study participants were white; however, most studies did not report ethnicity.

Acneiform eruption

Nine patients were diagnosed with colorectal cancer, three with NSCLC, one with pancreatic cancer, one with laryngeal cancer, one with clear cell sarcoma, and the remainder were not reported. The majority of patients were treated with cetuximab, only a few each with other agents (Table 2). On average, the acneiform eruption occurred within two weeks of the start of the EGFRi. For the majority of studies, the rash was graded using a physician general assessment and photographs. Two studies used the CTCAE grading criterion, one study used the EGFRI induced rash severity score and one study used percentage of body surface area improvement.

Treatment characteristics

40 patients were treated with isotretinoin and three were treated with acitretin, none with the other retinoids. One patient received isotretinoin then acitretin sequentially. In addition to systemic retinoids, eight patients were also treated with concurrent topical therapy. The majority of physicians (77%) reported a moderate to significant improvement with isotretinoin. Of the three patients treated with acitretin, one patient had a complete response, one gradually improved, and one had minimal improvement. The patient with sequential systemic retinoid therapy had significant improvement with isotretinoin then minimal improvement with acitretin. AE associated with isotretinoin included xerosis (3 patients), cheilitis (2 patient), paronychia (1 patient) and retinoid dermatitis (1 patient). One patient on isotretinoin developed xerosis of the skin and lips, epistaxis, photosensitivity, and impaired healing. Small transient elevations in liver function tests and triglycerides was noted in one study. One patient on acitretin significant reddening, exfoliation of skin and recurrent whitlow. The other two patients on acitretin developed no AE. (Table 3)

Cancer outcomes

The majority of papers did not report cancer outcome of reported cases. Of those that were reported, three had stable disease, two had partial remission, one had no effect on cancer therapy and one patient died.

Discussion

In this systematic review, we compiled the available data on the use of systemic retinoids for the treatment of acneiform eruptions secondary to EGFRi. In total, 43 patients were published in case reports and case series. There are no published controlled trials analyzing the effect of isotretinoin or acitretin for this off label indication, and no publications on the use of bexarotene or alitretinoin.

In all patients, the acneiform eruption started early after initiation of EGFRi therapy and persisted despite conventional topical therapy. The majority of patients demonstrated a significant improvement with isotretinoin and minimal, dose related adverse events. The response to acitretin was more variable, and may be less effective, however this conclusion is limited based on the small sample size.

The acneiform eruption is found to be a positive predictor of cancer response to systemic therapy and is associated with favourable patient outcomes, although with a potential severe impact of quality of life. (20) (6) Therefore, effective treatment of the acneiform eruption is an important adjunctive therapy to prevent cancer therapy discontinuation.

In the European Society for Medical Oncology (ESMO) published guidelines, for moderate to severe eruptions, only oral tetracyclines are recommended for systemic therapy, with isotretinoin being mentioned but not clearly recommended. (21) On the other hand, guidelines from the MASCC Skin Toxicity Study Group in the United States as well as from experts in oncodermatology in Brazil and Italy include both doxycycline and isotretinoin in the treatment of acneiform eruptions caused by EGFRi. (22) (23) (24) However, all recommendations are of low grade given insufficient data.

Recently, there are concerns with the use of tetracyclines for treatment of acneiform eruptions in cancer patients, namely due to the effects of the antibiotic on the gut microflora, especially in the context of colorectal cancer. (25) Therefore, it is important that alternate systemic therapy is

available for physicians to provide to patients. Further, isotretinoin is currently being explored for other targeted cancer therapies known to cause acneiform eruptions including MEK inhibitors and immune checkpoint inhibitors (26) (27)

The excellent response of patients to oral retinoids for this cutaneous eruption supports this class of medication's mechanism of action. Given isotretinoin's action on the pilosebaceous unit, it is of most interest to reverse the papules and pustules caused by EGFRi. Acitretin's mechanism of action also correct abnormal keratinocyte proliferation. Taken together, these two systemic retinoids most directly target the dysregulated pathway underlying the development of acneiform eruptions in patients on EGFRi. It is unsurprising that no data is available for the use of bexarotene or alitretinoin for acneiform eruptions, given their cellular effects differ from other systemic retinoids. (12)

Some providers hesitate to incorporate systemic retinoids, for the treatment of acneiform eruptions secondary to EGFRi. There are concerns regarding the synergistic AE of isotretinoin and EGFRi in the development of cutaneous side effects such as xerosis, dermatitis, cheilitis and pyogenic granulomas. In this study, 16% patients developed a known cutaneous AE of isotretinoin or EGFRi including xerosis, cheilitis, pyogenic granulomas/paronychia and photosensitivity. These AE generally responded to either dose reduction or symptomatic management. Only one patient on isotretinoin, and one patient on acitretin had to discontinue their retinoid due to cutaneous AE. In a systematic review on cutaneous AEs of EGFRi, xerosis occurs in 16% patients, nail changes in 17% patients, pruritus in 16% patients. (28) (29) Therefore, rates of cutaneous AEs of combined systemic retinoids and EGFRi in this study are similar to what is reported in the literature for EGFRi monotherapy and no synergistic effect was observed.

There is theoretical concern regarding the effect of isotretinoin on tumor response to EGFRi. (30) There is some evidence to suggest that isotretinoin may increase mortality in lung cancer patients who smoke. (31) (32) On the other hand, systemic retinoids, in combination with traditional chemotherapy for non-small cell lung cancer, improve response rate and progression free survival. (33) Isotretinoin may be used as chemoprevention for cutaneous and head and neck

squamous cell carcinomas. (34) (35) On a molecular level, Carter et al demonstrate down regulation of EGFR signaling in endometrial adenocarcinoma cell lines treated with isotretinoin. (36)

In conclusion, published reports demonstrate that isotretinoin provides an effective systemic therapy for patients with acneiform eruption triggered by EGFRi, with few, dose dependent side effects. There is limited evidence use of acitretin in the treatment of acneiform eruptions, where a variable clinical response is demonstrated. No data is available for bexarotene or alitretinoin. The major limitation of this review is the lack of controlled prospective trials to assess the efficacy and safety of systemic retinoids in the treatment of the acneiform eruption. As many more new targeted therapies emerge for the treatment of malignancy, research into management of cutaneous AE is critical to improve the patient's quality of life and minimize cancer therapy discontinuation due to adverse events.

References

1. Ettinger DS, Wood DE, Aisner DL, Akerley W, Bauman J, Chirieac LR, et al. Non–Small Cell Lung Cancer, Version 5.2017, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw. 2017 Apr;15(4):504–35.

2. Annunziata MC, Ferrillo M, Cinelli E, Panariello L, Rocco D, Fabbrocini G. Retrospective Analysis of Skin Toxicity in Patients under Anti-EGFR Tyrosine Kinase Inhibitors: Our Experience in Lung Cancer. Open Access Maced J Med Sci. 2019 Mar 27;7(6):973–7.

3. Lacouture ME. Mechanisms of cutaneous toxicities to EGFR inhibitors. Nat Rev Cancer. 2006 Oct;6(10):803–12.

4. DeWitt CA, Siroy AE, Stone SP. Acneiform eruptions associated with epidermal growth factor receptor–targeted chemotherapy. J Am Acad Dermatol. 2007 Mar;56(3):500–5.

5. Melosky B, Leighl NB, Rothenstein J, Sangha R, Stewart D, Papp K. Management of egfr tki–induced dermatologic adverse events. Curr Oncol. 2015 Jan 8;22(2):123.

6. Giovannini M, Gregorc V, Belli C, Roca E, Lazzari C, Viganò MG, et al. Clinical Significance of Skin Toxicity due to EGFR-Targeted Therapies. J Oncol. 2009;2009:1–8.

7. Hirsh V. Managing treatment-related adverse events associated with egfr tyrosine kinase inhibitors in advanced non-small-cell lung cancer. Curr Oncol. 2011 Jun 8;18(3):126–38.

8. Melosky B. Supportive care treatments for toxicities of anti-EGFR and other targeted agents. Curr Oncol. 2012 Jun 25;19(0):S59-63.

9. U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES. Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. 2017.

10. Bolognia, Jean., Jorizzo, Joseph L.Schaffer, Julie V., eds. Dermatology. [Philadelphia] :: Elsevier Saunders, 2018. Print.

11. Landis MN. Optimizing Isotretinoin Treatment of Acne: Update on Current Recommendations for Monitoring, Dosing, Safety, Adverse Effects, Compliance, and Outcomes. Am J Clin Dermatol. 2020 Jun;21(3):411–9.

12. Wolverton, S., 2020. Comprehensive Dermatologic Drug Therapy. 4th ed. Elsevier, pp.Chapters 9, 22. In.

13. Scope A, Agero ALC, Dusza SW, Myskowski PL, Lieb JA, Saltz L, et al. Randomized Double-Blind Trial of Prophylactic Oral Minocycline and Topical Tazarotene for Cetuximab-Associated Acne-Like Eruption. J Clin Oncol. 2007 Dec 1;25(34):5390–6.

14. Bidoli P, Cortinovis DL, Colombo I, Crippa A, Cicchiello F, Villa F, et al. Isotretinoin Plus Clindamycin Seem Highly Effective Against Severe Erlotinib-Induced Skin Rash in Advanced Non-small Cell Lung Cancer. J Thorac Oncol. 2010 Oct;5(10):1662–3.

15. Vezzoli P, Marzano A, Onida F, Alessi E, Galassi B, Tomirotti M, et al. Cetuximab-induced Acneiform Eruption and the Response to Isotretinoin. Acta Derm Venereol. 2008;88(1):84–6.

16. Gutzmer R, Werfel T, Mao R, Kapp A, Elsner J. Successful treatment with oral isotretinoin of acneiform skin lesions associated with cetuximab therapy. Br J Dermatol. 2005 Oct;153(4):849–51.

17. Andrews ED, Garg N, Patel AB. A retrospective chart review on oral retinoids as a treatment for epidermal growth factor receptor inhibitor– and mitogen-activated protein kinase kinase inhibitor–induced acneiform eruptions. J Am Acad Dermatol. 2020 Apr;82(4):998–1000.

18. Costello CM, Hill HE, Brumfiel CM, Yang YW, Swanson DL. Choosing between isotretinoin and acitretin for epidermal growth factor receptor inhibitor and small molecule tyrosine kinase inhibitor acneiform eruptions. J Am Acad Dermatol. 2021 Mar;84(3):840–1.

19. Roskoski R. Properties of FDA-approved small molecule protein kinase inhibitors: A 2021 update. Pharmacol Res. 2021 Mar;165:105463.

20. Journagan S, Obadiah J. An acneiform eruption due to erlotinib: Prognostic implications and management. J Am Acad Dermatol. 2006 Feb;54(2):358–60.

21. Lacouture ME, Sibaud V, Gerber PA, van den Hurk C, Fernández-Peñas P, Santini D, et al. Prevention and management of dermatological toxicities related to anticancer agents: ESMO Clinical Practice Guidelines☆. Ann Oncol. 2021 Feb;32(2):157–70.

22. MASCC Skin Toxicity Study Group, Lacouture ME, Anadkat MJ, Bensadoun R-J, Bryce J, Chan A, et al. Clinical practice guidelines for the prevention and treatment of EGFR inhibitor-associated dermatologic toxicities. Support Care Cancer. 2011 Aug;19(8):1079–95.

23. Cury-Martins J, Eris APM, Abdalla CMZ, Silva G de B, Moura VPT de, Sanches JA. Management of dermatologic adverse events from cancer therapies: recommendations of an expert panel. An Bras Dermatol. 2020 Mar;95(2):221–37.

24. Pinto C, Barone CA, Girolomoni G, Russi EG, Merlano MC, Ferrari D, et al. Management of Skin Toxicity Associated with Cetuximab Treatment in Combination with Chemotherapy or Radiotherapy. The Oncologist. 2011 Feb;16(2):228–38.

25. Mihai MM, Ion A, Giurcăneanu C, Nițipir C, Popa A-M, Chifiriuc M-C, et al. The Impact of Long-Term Antibiotic Therapy of Cutaneous Adverse Reactions to EGFR Inhibitors in Colorectal Cancer Patients. J Clin Med. 2021 Jul 21;10(15):3219.

26. O'Connor C, Power D, Gleeson C, Heffron C. Pembrolizumab-induced follicular eruption and response to isotretinoin. Immunotherapy. 2021 Nov 17;imt–2021–0001.

27. Caruana M, Hatami A, Marcoux D, Perreault S, McCuaig CC. Isotretinoin for the treatment of severe acneiform eruptions associated with the MEK inhibitor trametinib. JAAD Case Rep. 2020 Oct;6(10):1056–8.

28. Lacouture ME, Anadkat M, Jatoi A, Garawin T, Bohac C, Mitchell E. Dermatologic Toxicity Occurring During Anti-EGFR Monoclonal Inhibitor Therapy in Patients With Metastatic Colorectal Cancer: A Systematic Review. Clin Colorectal Cancer. 2018 Jun;17(2):85–96.

29. Garden BC, Wu S, Lacouture ME. The risk of nail changes with epidermal growth factor receptor inhibitors: A systematic review of the literature and meta-analysis. J Am Acad Dermatol. 2012 Sep;67(3):400–8.

30. Gerber PA, Meller S, Eames T, Buhren BA, Schrumpf H, Hetzer S, et al. Management of EGFR-inhibitor associated rash: a retrospective study in 49 patients. Eur J Med Res. 2012 Dec;17(1):4.

31. Lee JJ, Feng L, Reshef DS, Sabichi AL, Williams B, Rinsurongkawong W, et al. Mortality in the Randomized, Controlled Lung Intergroup Trial of Isotretinoin. Cancer Prev Res (Phila Pa). 2010 Jun;3(6):738–44.

32. Lippman SM, Lee JJ, Karp DD, Vokes EE, Benner SE, Goodman GE, et al. Randomized Phase III Intergroup Trial of Isotretinoin to Prevent Second Primary Tumors in Stage I Non-Small-Cell Lung Cancer. JNCI J Natl Cancer Inst. 2001 Apr 18;93(8):605–18.

33. Arrieta O, González-De la Rosa CH, Aréchaga-Ocampo E, Villanueva-Rodríguez G, Cerón-Lizárraga TL, Martínez-Barrera L, et al. Randomized Phase II Trial of All- *Trans* -Retinoic Acid With Chemotherapy Based on Paclitaxel and Cisplatin As First-Line Treatment in Patients With Advanced Non–Small-Cell Lung Cancer. J Clin Oncol. 2010 Jul 20;28(21):3463–71.

34. Hong WK, Lippman SM, Itri LM, Karp DD, Lee JS, Byers RM, et al. Prevention of Second Primary Tumors with Isotretinoin in Squamous-Cell Carcinoma of the Head and Neck. N Engl J Med. 1990 Sep 20;323(12):795–801.

35. Kraemer KH, DiGiovanna JJ, Moshell AN, Tarone RE, Peck GL. Prevention of Skin Cancer in Xeroderma Pigmentosum with the Use of Oral Isotretinoin. N Engl J Med. 1988 Jun 23;318(25):1633–7.

36. Carter CA, Shaw BL. Retinoic Acid Affects the EGF-R Signaling Pathway during Differentiation Induction of Human Endometrial Adenocarcinoma Cells. Exp Mol Pathol. 2000 Jun;68(3):170–86.

37. Chiang HC, Anadkat MJ. Isotretinoin for high-grade or refractory epidermal growth factor receptor inhibitor-related acneiform papulopustular eruptions. J Am Acad Dermatol. 2013 Oct;69(4):657–8.

38. de Noronha e Menezes NMBV, Lima R, Moreira A, Varela P, Barroso A, Baptista A, et al. Description and management of cutaneous side effects during erlotinib and cetuximab treatment in lung and colorectal cancer patients: A prospective and descriptive study of 19 patients. Eur J Dermatol. 2009 May;19(3):248–51.

39. Esposito L, Barbareschi M. LOW DOSE ISOTRETINOIN FOR THE TREATMENT OF ACNEIFORM ERUPTION INDUCED BY EGFR INHIBITOR (AFATINIB). In Milan; 2019.

40. Homey B, Gerber PA, Wollenberg A, Dirschka T, Hassel JC, Bölke E, et al. Escalating therapy of cutaneous side effects of EGFR inhibitors: experience of German reference centers. JDDG J Dtsch Dermatol Ges. 2012 Aug;10(8):559–62.

41. Wollenberg A, Moosmann N, Kroth J, Heinemann V, Klein E. Therapie schwerer akneiformer Cetuximab-Exantheme mit oralem Retinoid, topischem Antibiotikum und Steroidexternum. Hautarzt. 2007 Jul;58(7):615–8.

42. Requena C, Llombart B, Sanmartín O. Acneiform eruptions induced by epidermal growth factor receptor inhibitors: treatment with oral isotretinoin. Cutis. 2012 Aug;90(2):77–80.

43. Pomerantz RG, Chirinos RE, Falo LD, Geskin LJ. Acitretin for Treatment of EGFR Inhibitor–Induced Cutaneous Toxic Effects. Arch Dermatol [Internet]. 2008 Jul 1 [cited 2021 Dec 12];144(7). Available from: http://archderm.jamanetwork.com/article.aspx?doi=10.1001/archderm.144.7.949

44. Korzycka M, Osmola-Mańkowska AJ, Bowszyc-Dmochowska M, Żaba RW, Adamski Z. Dermatological adverse effects in a cancer patient treated with an EGFR inhibitor. Case report and literature review. Dermatol Rev. 2018;105(5):632–8.

45. Gisondi P, Geat D, Mattiucci A, Lombardo F, Santo A, Girolomoni G. Incidence of Adverse Cutaneous Reactions to Epidermal Growth Factor Receptor Inhibitors in Patients with Non-Small-Cell Lung Cancer. Dermatology. 2021;237(6):929–33.

Table 1: Study Characteristics

Authors	***Year of Publication***	***Country***	***Study design***	***Measurement of response***	***Frequency of follow-up***
Andrews et al.(17)	2020	USA	Retrospective chart review	CTCAE grading	1 month
Bidoli et al. (14)	2010	Italy	Case series	CTCAE grading + photos	Days 0, 15, and 30
Chiang et al. (37)	2013	USA	Retrospective chart review	Global physician assessment (GPA) + photographs	1, 2 months
Costello et al. (18)	2021	USA	Retrospective chart review	Percent improvement in body surface area	NR
Menezes et al. (38)	2009	Portugal	Prospective case series	CTCAE grading	4 weeks
DeWitt et al. (4)	2007	USA	Case series	GPA	4 weeks
Esposito et al. (39)	2019	Italy	Case report	GPA	NR
Gerber et al. (30)	2012	Germany	Retrospective review	EGFRI induced rash severity score (ERSS or WoMoScore)	3 weeks
Gutzmer et al. (16)	2005	Germany	Case report	GPA + photos	4 weeks
Homey et al. (40)	2012	Germany	Case series	GPA + photos	8 weeks
Wollenberg et al. (41)	2007	Germany	Case report	GPA + photos	1 week, 3 weeks
Requena et al. (42)	2012	Spain	Case series	GPA + photos	1 month
Vezzoli et al. (15)	2007	Italy	Case report	GPA	20 days
Pomerantz et al. (43)	2008	USA	Case report	GPA	1 month
Korzycka et al (44)	2018	Poland	Case report	GPA	NR
Gisondi et al (45)	2021	Italy	Retrospective review	GPA	2 months

NR: not reported, GPA: global physician assessment

Table 2: Participant Characteristics

Authors	***No. of patients***	***Female, n(%)***	***Mean age***	***Ethnicity (% black)***	***Systemic medication***	***Concurrent topical therapy***	***Type of cancer***	***Name of EGFRi***	***Timing of rash***
Andrews et al. (17)	1	0	39	white (0)	Isotretinoin 30-40mg die	TCS	clear cell sarcoma	erlotinib	6 days
Bidoli et al (14)	7	NR	NR	NR	oral clindamycin (450mg/d, days 1–10; 300	none	NSCLC	erlotinib	14 days

					mg/d, days 11–20) plus oral isotretinoin (20 mg/d, days 11–20)				
Chiang et al (37)	11	NR	NR	NR	Isotretinoin	NR	NR	NR	NR
Costello et al (18)	1	1	70	NR	Isotretinoin 20mg die	None	NR	erlotinib	NR
Costello et al (18)	1	0	59	NR	Isotretinoin 20mg die	None	NR	cetuximab	NR
Costello et al (18)	1	0	62	NR	Isotretinoin 60mg die	None	NR	cetuximab	NR
Costello et al (18)	1	0	37	NR	Isotretinoin 10mg die	None	NR	cetuximab	NR
Costello et al (18)	1	0	73	NR	Isotretinoin 40mg die then acitretin 25mg die	None	NR	erlotinib then cetuximab	NR
Costello et al (18)	1	0	67	NR	Acitretin 10-25mg die	None	NR	afatinib	NR
Menezes et al. (38)	1	0	47	NR	Isotretinoin 20mg die, previously on minocycline with no response	Sunscreen, mild skin cleanser, oatmeal cream	NR	erlotinib	13 days
DeWitt et al (4)	1	0	30	M	isotretinoin 20 mg die then every other day after 1 month	None	colon ca	cetuximab	few days after second infusion
Esposito et al (39)	1	0	36	white (0)	Isotretinoin 20mg die	NR	NSCLC	afatinib	NR
Gerber et al (30)	5	NR	NR	NR	Isotretinoin 10-20mg die	Nadifloxacin 1% cream (1x/d) plus prednicarbate 0.25% cream	nr	erlotinib or cetuximab	NR

Gutzmer et al (16)	1	0	63	white (0)	Isotretinoin 30mg die	topical metronizadole gel	colon ca	cetuximab	after 2 cycles
Gutzmer et al (16)	1	1	37	white (0)	Isotretinoin 40mg die	topical metronizadole gel, then 1% erythromycin, 2% triclosan	laryngeal cancer	cetuximab	3 days
Homey et al 38)	1	1	41	white (0)	Isotretinoin 10mg die	octenidine solution (2 3/day), followed by prednicarbate cream or nadifloxacin cream	NSCLC	erlotinib	5 days
Wollenberg et al (41)	1	0	37	white (0)	Isotretinoin 20mg die	nadifloxacin and prednicarbate cream	colon ca	cetuximab	4 days
Wollenberg et al (41)	1	0	59	white (0)	Isotretinoin 20mg die	nadifloxacin and prednicarbate cream	rectal	cetuximab	1 week
Requena et al (42)	1	0	77	nr	Isotretinoin 10mg die	None	colon ca	cetuximab	9 days
Requena et al (42)	1	1	70	white (0)	Isotretinoin 10mg die	None	colon ca	cetuximab	nr
Requena et al (42)	1	0	65	white (0)	Isotretinoin 10mg die	None	colon ca	cetuximab	1 month
Vezzoli et al (15)	1	0	64	nr	Isotretinoin 30mg die	boric acid solution 2%, mupirocin	colon ca	cetuximab	NR
Pomerantz et al (43)	1	1	57	NR	Acitretin 10mg	None	pancreatic ca	erlotinib	4 days
Korzycka et al (44)	1	0	51	white (0)	Acitretin 50mg die	none, ceftriaxone IV, dexamethasone 16mg IV	rectal	panitumumab	2 weeks
Gisondi et al (45)	NR	NR	NR	NR	Isotretinoin 0.2-0.3mg/kg DIE	NR	lung	variable: afatinib, erlotinib, gefitinib, osimertinib	within 4-14 weeks

Table 3: Study Results

Authors	*Baseline vs final result*	*Durability of response*	*Cancer outcomes*	*% deaths*	*Adverse events*
Andrews et al. (17)	3-4 to 1	NR	NR	NR	Small, transient elevations in liver enzyme and triglyceride levels
Bidoli et al (14)	3/4 - 1/0	NR	No effect on cancer outcomes	NR	None
Chiang et al (37)	Eight of the 11 patients showed at least moderate response to isotretinoin. 4/8 complete clearance, 4/8 improvement in rash severity without complete clearance. 1 patient's rash worsened despite treatment. In 2 patients, responses to isotretinoin could not be assessed because medication was discontinued before formal assessment at follow-up.	NR	NR	NR	Xerosis of the skin and lips, epistaxis, photosensitivity, and impaired healing. Severe xerosis in one patient led to treatment discontinuation.
Costello et al (18)	moderate improvement	7-8 months	NR	NR	Retinoid dermatitis
Costello et al (18)	significant improvement	6 months	NR	NR	None
Costello et al (18)	significant improvement	3 months	NR	NR	None
Costello et al (18)	significant improvement	1-2 months	NR	NR	None
Costello et al (18)	significant improvement then minimal improvement	10mo then 6 months	NR	NR	None
Costello et al (18)	minimal improvement	7 months	NR	NR	None
Menezes et al. (38)	Slight improvement but did not live long enough for full assessment	NR	death	100	NR
DeWitt et al (4)	dramatic clearing of pustules	6 months	remission	0	xerosis
Esposito et al (39)	total progressive resolution	6 months	NR	0	NR
Gerber et al (30)	average a reduction of the ERSS from 59.2 to 43.8	NR	NR	NR	Adverse effects of our management strategies were generally rare and in line with the potential common adverse effects reported for each drug in the literature.
Gutzmer et al (16)	marked improvement	6 months	partial remission	0	paronychia
Gutzmer et al (16)	marked improvement	4 months	stable disease	0	none

Homey et al 38)	significant improvement	NR	NR	0	NR
Wollenberg et al (41)	improvement	4.5 months	partial remission	0	lip dryness
Wollenberg et al (41)	significant improvement	6 months	stable disease	0	slight dryness of the mucous membranes, paronychia
Requena et al (42)	remarkable improvement	6 months	NR	NR	none
Requena et al (42)	complete response	3 months	NR	NR	none
Requena et al (42)	complete response	NR	NR	NR	none
Vezzoli et al (15)	good improvement of acneiform lesions	NR	NR	0	NR
Pomerantz et al (43)	complete response	6 months	stable disease	NR	none
Korzycka et al (44)	gradual improvement	NR	NR	0	Significant reddening, exfoliation of skin, recurrent whitlow
Gisondi et al (45)	response noted	NR	NR	NR	NR

Figure 1: Search Strategies

MEDLINE and EMBASE were searched for EGFRi's (cetuximab, erlotinib, afatinib, gefitinib, osimertinib, panitumumab, mobocertinib, amivantamab, dacomitinib, lapatinib), systemic retinoids (isotretinoin, acitretin, bexarotene and alitretinoin) and keywords for acneiform eruption (acne vulgaris, folliculitis, acneiform, papulopustular, cutaneous adverse effect) from date of inception until Dec 10th, 2021.

MEDLINE
https://proxy.library.mcgill.ca/login?url=http://ovidsp.ovid.com/ovidweb.cgi?T=JS&NEWS=N&PAGE=main&SHAREDSEARCHID=3dewLHotlg7ZiRCM7qAgulY7eEem4W5lJ1cQENaz4GXkDL2DNL6FmSY81vr1cwPux

Ovid MEDLINE(R) ALL <1946 to December 10, 2021>

1 Cetuximab/ 4919
2 cetuximab.mp,rn. 8027
3 (cetuximab or Cetuximab Liquid Injection or Cetuximab Sarotalocan or cetuximab Injection or cetuximab 2 MG ML or cetuximab Injectable Product or cetuximab Injection Erbitux or cetuximab 2 MG ML Erbitux or 50 ML cetuximab 2 MG ML Injection or 100 ML cetuximab 2 MG ML Injection or 100 ML cetuximab 2 MG ML Injection Erbitux or 50 ML cetuximab 2 MG ML Injection Erbitux).mp,rn. 8027
4 Erlotinib Hydrochloride/ 4153
5 erlotinib.mp,rn. 7384
6 (erlotinib or erlotinib hydrochloride or erlotinib Oral Tablet or erlotinib Pill or erlotinib 25 MG Oral Tablet or Gemcitabine Erlotinib Regimen or erlotinib Oral Tablet Tarceva or erlotinib 150 MG or erlotinib 25 MG or erlotinib 100 MG or erlotinib 100 MG Tarceva or

erlotinib 150 MG Tarceva or erlotinib 25 MG Tarceva or erlotinib Oral Product or erlotinib 150 MG Oral Tablet or erlotinib 100 MG Oral Tablet or erlotinib 100 MG Oral Tablet Tarceva or erlotinib 150 MG Oral Tablet Tarceva or erlotinib 25 MG Oral Tablet Tarceva).mp,rn. 7384
7 Afatinib/ 828
8 afatinib.mp,rn. 1727
9 (afatinib or afatinib Oral Tablet or afatinib dimaleate or afatinib Pill or afatinib 40 MG Gilotrif or afatinib 30 MG Gilotrif or afatinib 20 MG Gilotrif or afatinib Oral Tablet Gilotrif or afatinib 40 MG or afatinib 30 MG or afatinib 20 MG or afatinib Oral Product or afatinib 40 MG Oral Tablet or afatinib 30 MG Oral Tablet or afatinib 20 MG Oral Tablet or afatinib 40 MG Oral Tablet Gilotrif or afatinib 30 MG Oral Tablet Gilotrif or afatinib 20 MG Oral Tablet Gilotrif).mp,rn. 1727
10 Gefitinib/ 4752
11 gefitinib.mp,rn. 7798
12 (gefitinib or gefitinib Pill or gefitinib 250 MG or gefitinib Oral Tablet or gefitinib Oral Tablet Iressa or gefitinib 250 MG Iressa or gefitinib Oral Product or gefitinib 250 MG Oral Tablet or gefitinib 250 MG Oral Tablet Iressa).mp,rn. 7798
13 osimertinib.mp,rn. 1748
14 (panitumumab or Panitumumab Liquid Injection or panitumumab Injection or panitumumab 20 MG ML or panitumumab Injectable Product or panitumumab Injection Vectibix or panitumumab 20 MG ML Vectibix or 5 ML panitumumab 20 MG ML Injection or 20 ML panitumumab 20 MG ML Injection or 5 ML panitumumab 20 MG ML Injection Vectibix or 20 ML panitumumab 20 MG ML Injection Vectibix).mp,rn. 1971
15 Panitumumab/ 1079
16 mobocertinib.mp,rn. 16
17 amivantamab.mp,rn. 21
18 (amivantamab or amivantamab vmjw or amivantamab Injection or amivantamab Injection Rybrevant or amivantamab Injectable Product or amivantamab vmjw 50 MG ML or 7 ML amivantamab vmjw 50 MG ML Injection or amivantamab vmjw 50 MG ML Rybrevant or 7 ML amivantamab vmjw 50 MG ML Injection Rybrevant).mp,rn. 21
19 epidermal growth factor receptor kinase inhibitor*.ti,ab,kf. 67
20 Dacomitinib.mp,rn. 271
21 (dacomitinib or dacomitinib anhydrous or dacomitinib Pill or dacomitinib 15 MG or dacomitinib Oral Product or dacomitinib Oral Tablet or dacomitinib 15 MG Vizimpro or dacomitinib Oral Tablet Vizimpro or dacomitinib 30 MG or dacomitinib 30 MG Vizimpro or dacomitinib 45 MG or dacomitinib 45 MG Vizimpro or dacomitinib 15 MG Oral Tablet or dacomitinib 30 MG Oral Tablet or dacomitinib 45 MG Oral Tablet or dacomitinib 15 MG Oral Tablet Vizimpro or dacomitinib 30 MG Oral Tablet Vizimpro or dacomitinib 45 MG Oral Tablet Vizimpro).mp,rn. 271
22 Lapatinib/ 1685
23 (lapatinib or lapatinib ditosylate or lapatinib Oral Tablet or lapatinib Pill or lapatinib 250 MG or lapatinib 250 MG Tykerb or lapatinib Oral Tablet Tykerb or lapatinib Oral Product or lapatinib 250 MG Oral Tablet or lapatinib 250 MG Oral Tablet Tykerb).mp,rn. 2988
24 epidermal growth factor inhibitor.ti,ab,kf. 32
25 Isotretinoin/ 3771
26 isotretinoin.mp,rn. 4885

27 (isotretinoin or isotretinoin Oral Capsule or isotretinoin Pill or isotretinoin 10 MG or isotretinoin 40 MG or isotretinoin 20 MG or isotretinoin 5 MG or isotretinoin Oral Capsule Accutane or isotretinoin Oral Capsule Amnesteem or isotretinoin Oral Capsule Claravis or isotretinoin 30 MG or isotretinoin Oral Capsule Sotret or isotretinoin 10 MG Amnesteem or isotretinoin 10 MG Sotret or isotretinoin 20 MG Amnesteem or isotretinoin 20 MG Sotret or isotretinoin 40 MG Amnesteem or isotretinoin 40 MG Sotret).mp,rn. 4885
28 acitretin/ 1223
29 acitretin.mp,rn. 1909
30 (13-cis-acitretin or "54757-46-9 (cpd w/o isomeric designation)" or "55079-83-9 (acitretin)" or "69427-46-9 ((z,e,e,e)-isomer)" or acitretin or "acitretin, (z,e,e,e)-isomer" or etretin or isoacitretin or isoetretin or lch760e9t7 or neotigason or ro 10-1670 or ro 101670 or ro 13-7652 or ro 137652 or ro-10-1670 or ro-13-7652 or ro101670 or ro137652 or soriatane).mp,rn. 3145
31 Bexarotene/ 551
32 bexarotene.mp,rn. 822
33 Alitretinoin/ 769
34 alitretinoin.mp,rn. 854
35 Acneiform Eruptions/ or Acne Vulgaris/ 12783
36 ((cutaneous or skin) adj2 (event* or eruption* or toxicity or side effect* or rash*)).ti,ab,kf. 15623
37 Folliculitis/ 2157
38 (acneiform or acne or pustul* or papulopustular or papular or folliculitis).ti,ab,kf. 32425
39 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 2425211
40 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 9273
41 35 or 36 or 37 or 38 50070
42 39 and 40 and 41 10

EMBASE
https://proxy.library.mcgill.ca/login?url=http://ovidsp.ovid.com/ovidweb.cgi?T=JS&NEWS=N&PAGE=main&SHAREDSEARCHID=2JS3oTDnCDedKk51alqF0xMrKDDUf4UxmbVND34J6rULrlNn9jXvy77x8kdcYh5xp

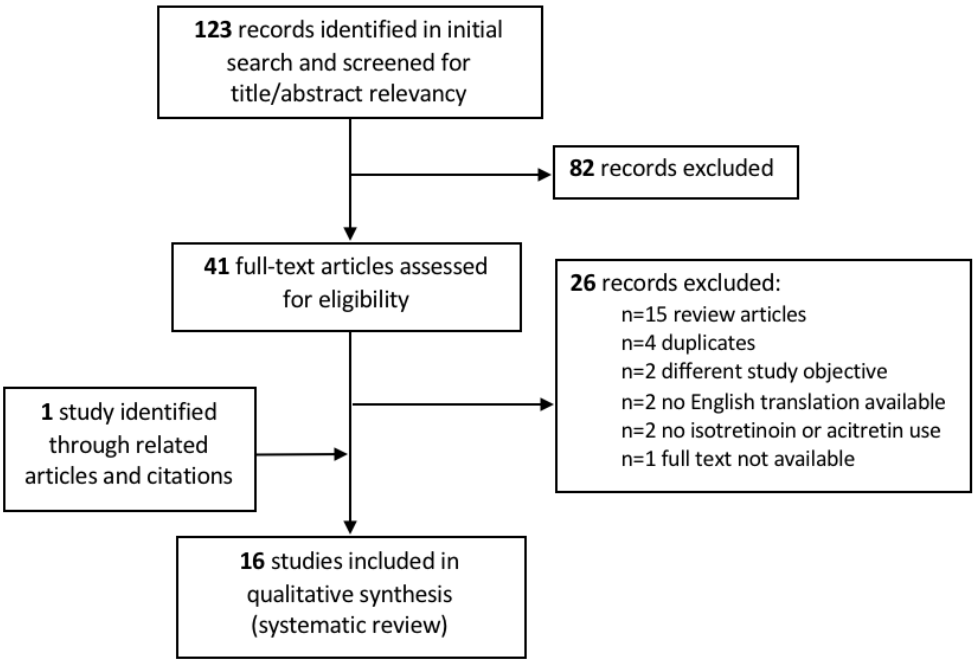
Embase Classic+Embase <1947 to 2021 Week 48>

1 cetuximab/ 30497
2 cetuximab.mp,rn. 31515
3 (cetuximab or Cetuximab Liquid Injection or Cetuximab Sarotalocan or cetuximab Injection or cetuximab 2 MG ML or cetuximab Injectable Product or cetuximab Injection Erbitux or cetuximab 2 MG ML Erbitux or 50 ML cetuximab 2 MG ML Injection or 100 ML cetuximab 2 MG ML Injection or 100 ML cetuximab 2 MG ML Injection Erbitux or 50 ML cetuximab 2 MG ML Injection Erbitux).mp,rn. 31515
4 erlotinib/ 29180
5 erlotinib.mp,rn. 30131
6 (erlotinib or erlotinib hydrochloride or erlotinib Oral Tablet or erlotinib Pill or erlotinib 25 MG Oral Tablet or Gemcitabine Erlotinib Regimen or erlotinib Oral Tablet Tarceva or erlotinib 150 MG or erlotinib 25 MG or erlotinib 100 MG or erlotinib 100 MG Tarceva or

erlotinib 150 MG Tarceva or erlotinib 25 MG Tarceva or erlotinib Oral Product or erlotinib 150 MG Oral Tablet or erlotinib 100 MG Oral Tablet or erlotinib 100 MG Oral Tablet Tarceva or erlotinib 150 MG Oral Tablet Tarceva or erlotinib 25 MG Oral Tablet Tarceva).mp,rn. 30131
7 afatinib/ 6483
8 afatinib.mp,rn. 6706
9 (afatinib or afatinib Oral Tablet or afatinib dimaleate or afatinib Pill or afatinib 40 MG Gilotrif or afatinib 30 MG Gilotrif or afatinib 20 MG Gilotrif or afatinib Oral Tablet Gilotrif or afatinib 40 MG or afatinib 30 MG or afatinib 20 MG or afatinib Oral Product or afatinib 40 MG Oral Tablet or afatinib 30 MG Oral Tablet or afatinib 20 MG Oral Tablet or afatinib 40 MG Oral Tablet Gilotrif or afatinib 30 MG Oral Tablet Gilotrif or afatinib 20 MG Oral Tablet Gilotrif).mp,rn. 6706
10 gefitinib.mp,rn. 27304
11 (gefitinib or gefitinib Pill or gefitinib 250 MG or gefitinib Oral Tablet or gefitinib Oral Tablet Iressa or gefitinib 250 MG Iressa or gefitinib Oral Product or gefitinib 250 MG Oral Tablet or gefitinib 250 MG Oral Tablet Iressa).mp,rn. 27304
12 osimertinib/ 4866
13 osimertinib.mp,rn. 5055
14 Panitumumab/ 8789
15 (panitumumab or Panitumumab Liquid Injection or panitumumab Injection or panitumumab 20 MG ML or panitumumab Injectable Product or panitumumab Injection Vectibix or panitumumab 20 MG ML Vectibix or 5 ML panitumumab 20 MG ML Injection or 20 ML panitumumab 20 MG ML Injection or 5 ML panitumumab 20 MG ML Injection Vectibix or 20 ML panitumumab 20 MG ML Injection Vectibix).mp,rn. 9165
16 mobocertinib.mp,rn. 61
17 amivantamab.mp,rn. 60
18 (amivantamab or amivantamab vmjw or amivantamab Injection or amivantamab Injection Rybrevant or amivantamab Injectable Product or amivantamab vmjw 50 MG ML or 7 ML amivantamab vmjw 50 MG ML Injection or amivantamab vmjw 50 MG ML Rybrevant or 7 ML amivantamab vmjw 50 MG ML Injection Rybrevant).mp,rn. 60
19 Dacomitinib.mp,rn. 1355
20 (dacomitinib or dacomitinib anhydrous or dacomitinib Pill or dacomitinib 15 MG or dacomitinib Oral Product or dacomitinib Oral Tablet or dacomitinib 15 MG Vizimpro or dacomitinib Oral Tablet Vizimpro or dacomitinib 30 MG or dacomitinib 30 MG Vizimpro or dacomitinib 45 MG or dacomitinib 45 MG Vizimpro or dacomitinib 15 MG Oral Tablet or dacomitinib 30 MG Oral Tablet or dacomitinib 45 MG Oral Tablet or dacomitinib 15 MG Oral Tablet Vizimpro or dacomitinib 30 MG Oral Tablet Vizimpro or dacomitinib 45 MG Oral Tablet Vizimpro).mp,rn. 1355
21 Lapatinib/ 12994
22 (lapatinib or lapatinib ditosylate or lapatinib Oral Tablet or lapatinib Pill or lapatinib 250 MG or lapatinib 250 MG Tykerb or lapatinib Oral Tablet Tykerb or lapatinib Oral Product or lapatinib 250 MG Oral Tablet or lapatinib 250 MG Oral Tablet Tykerb).mp,rn. 13390
23 epidermal growth factor receptor kinase inhibitor/ 9196
24 epidermal growth factor receptor kinase inhibitor*.ti,ab,kf. 76
25 (isotretinoin or isotretinoin Oral Capsule or isotretinoin Pill or isotretinoin 10 MG or isotretinoin 40 MG or isotretinoin 20 MG or isotretinoin 5 MG or isotretinoin Oral Capsule Accutane or isotretinoin Oral Capsule Amnesteem or isotretinoin Oral Capsule Claravis or

isotretinoin 30 MG or isotretinoin Oral Capsule Sotret or isotretinoin 10 MG Amnesteem or isotretinoin 10 MG Sotret or isotretinoin 20 MG Amnesteem or isotretinoin 20 MG Sotret or isotretinoin 40 MG Amnesteem or isotretinoin 40 MG Sotret).mp,rn. 13829
26 isotretinoin/ 13487
27 isotretinoin.mp,rn. 13829
28 acitretin.mp,rn. 2698
29 (13-cis-acitretin or "54757-46-9 (cpd w/o isomeric designation)" or "55079-83-9 (acitretin)" or "69427-46-9 ((z,e,e,e)-isomer)" or acitretin or "acitretin, (z,e,e,e)-isomer" or etretin or isoacitretin or isoetretin or lch760e9t7 or neotigason or ro 10-1670 or ro 101670 or ro 13-7652 or ro 137652 or ro-10-1670 or ro-13-7652 or ro101670 or ro137652 or soriatane).mp,rn. 7490
30 bexarotene/ 2859
31 bexarotene.mp,rn. 2938
32 alitretinoin/ 2507
33 alitretinoin.mp,rn. 2521
34 acne/ 25946
35 acne vulgaris/ 13028
36 ((cutaneous or skin) adj2 (event* or eruption* or toxicity or side effect* or rash*)).ti,ab,kf. 28295
37 folliculitis/ 6684
38 (acneiform or acne or pustul* or papulopustular or papular or folliculitis).ti,ab,kf. 50571
39 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 23 or 24 76634
40 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 24364
41 34 or 35 or 36 or 37 or 38 93693
42 39 and 40 and 41 120

Figure 2: Study Selection



Discussion

In this thesis, we discussed complimentary features of the acneiform eruption, the most common cutaneous adverse event in patients on EGFRi therapy. Given that the acneiform eruption is common in patients on EGFRi but is not universal, identifying those at risk of developing an adverse event allows for advanced medical planning and initiation of prophylactic therapy. In Chapter one, we investigated multiple demographic and clinical parameters to identify risk factors for development of acneiform eruptions in our cohort. However, we were unable to find any baseline demographic features that were statistically significantly associated with an increased risk of acneiform eruption. This finding remains an important contribution to the literature because it confirms the uncertainty that exists for potential risk factors for the development of acneiform eruptions. Together with previously published work, our findings support the notion that because no clear-cut risk factors exist, all patients must be counselled this potential cutaneous adverse event and managed promptly should they go onto develop an acneiform eruption. Future work in this field is required to elucidate risk factors associated with the development of acneiform eruptions.

When a patient develops an acneiform eruption secondary to EGFRi, effective management to maintain quality of life and prevent early treatment discontinuation is key. In the second chapter of this thesis, we performed a cross sectional study to assess management strategies of acneiform eruptions by dermatologists and oncologists across Canada. Interestingly, we were able to identify statistically significant differences in treatments offered between the two specialties. Where oncologists are more likely to follow recommendations from organizations such as ESMO and MASCCC, dermatologists are more likely to use treatment ladders used in acne vulgaris. Given that there is no robust data to support the effectiveness of therapies for management of acneiform eruptions, more investigation into the optimal treatment is required. Importantly, in our survey, no dermatologists recommended EGFRi discontinuation for management of severe acneiform eruptions. This finding reinforces the important role that dermatologists have in co-managing oncology patients, to maintain lifesaving cancer therapy while effectively managing cutaneous adverse events.

In the third chapter of this thesis, we systematically summarized available published clinical experience on the use of systemic retinoids for management of acneiform eruptions. Current guidelines heavily favor the use of tetracycline antibiotics as first line systemic therapy. However, there is no evidence-based data to support tetracyclines for management of acneiform eruptions, and their durability is questioned in the literature. Therefore, there is a need for physicians to have suitable alternate therapies to offer to patients, should they have a contraindication or not respond to therapy. The information gathered in this review can therefore be used for clinicians to discuss the risks and benefits of the use of systemic retinoids for management of acneiform eruptions with patients. It provides a succinct summary of the available clinical experience with retinoids for clinicians to use when searching the literature. Another key finding from this investigation was the lack of prospective data on the use of systemic retinoids for management of acneiform eruptions. Our paper provides a call to action for more research into the optimal management of cutaneous adverse events of targeted cancer therapy, which currently primarily relies on expert opinion and management of similar cutaneous disease. In the era of evidence-based medicine, higher quality data in this important and emerging field is required to provide the best care to patients.

Conclusions

Acneiform eruptions remain a common cutaneous adverse event of EGFRi therapy. The tyrosine kinase pathway is recognized as an important driving mutation in cancer and remains a desirable target for new therapy, with many new medications in the development stages. Elucidating risk factors for cutaneous adverse events, as well as optimal management of such events may be applicable to future tyrosine kinase blocking agents, and thus remains an important field in cancer research. No demographic risk factors were elucidated as risk factors for the development of acneiform eruptions. Notably, we demonstrate that the generation of the EGFRi is important as a risk factor. Overall, the results of our investigation in Chapter one contributes to the literature by maintaining the uncertainty regarding demographic risk factors for the development of acneiform eruptions. Our data also hints to possible new unexplored associations with abnormal baseline bloodwork. In Chapter two, our study describes the current Canadian landscape for management of acneiform eruptions by oncologists and dermatologists. A pertinent finding is that dermatologists are unlikely to recommend discontinuation of EGFRi therapy, which may improve patient survival. The differences in management strategies between the two specialties highlights the need for more robust evidence on optimal treatment regimens, as well as the important role dermatologists have in managing acneiform eruptions in oncology patients. In Chapter three, our thorough review of the literature on the use of systemic retinoids provides evidence into the use of this class of medications for management of acneiform eruptions as an alternate to tetracycline antibiotics, expanding the range of therapeutics available to patients.

Overall, it is my hope that the projects undertook in this thesis provide a contribution to the literature in this important field in oncology. By increasing knowledge on risk factors and management of cutaneous adverse events secondary to cancer therapy, research can aid in maintaining the quality of life of cancer patients undergoing treatment.

References

1. Herbst RS, Sandler AB. Overview of the Current Status of Human Epidermal Growth Factor Receptor Inhibitors in Lung Cancer. Clin Lung Cancer. 2004 Dec;6:S7–19.

2. El-Rayes BF, LoRusso PM. Targeting the epidermal growth factor receptor. Br J Cancer. 2004 Aug;91(3):418–24.

3. Scaltriti M, Baselga J. The Epidermal Growth Factor Receptor Pathway: A Model for Targeted Therapy: Fig. 1. Clin Cancer Res. 2006 Sep 15;12(18):5268–72.

4. Schneider MR, Wolf E. The epidermal growth factor receptor ligands at a glance. J Cell Physiol. 2009 Mar;218(3):460–6.

5. Guo G, Gong K, Wohlfeld B, Hatanpaa KJ, Zhao D, Habib AA. Ligand-Independent EGFR Signaling. Cancer Res. 2015 Sep 1;75(17):3436–41.

6. Yoon HY, Ryu JS, Sim YS, Kim D, Lee SY, Choi J, et al. Clinical significance of EGFR mutation types in lung adenocarcinoma: A multi-centre Korean study. Lee JW, editor. PLOS ONE. 2020 Feb 13;15(2):e0228925.

7. Ettinger DS, Wood DE, Aisner DL, Akerley W, Bauman JR, Bharat A, et al. NCCN Guidelines Insights: Non–Small Cell Lung Cancer, Version 2.2021: Featured Updates to the NCCN Guidelines. J Natl Compr Canc Netw. 2021 Mar;19(3):254–66.

8. Johnson JR, Cohen M, Sridhara R, Chen YF, Williams GM, Duan J, et al. Approval Summary for Erlotinib for Treatment of Patients with Locally Advanced or Metastatic Non–Small Cell Lung Cancer after Failure of at Least One Prior Chemotherapy Regimen. Clin Cancer Res. 2005 Sep 15;11(18):6414–21.

9. Shepherd FA, Rodrigues Pereira J, Ciuleanu T, Tan EH, Hirsh V, Thongprasert S, et al. Erlotinib in Previously Treated Non–Small-Cell Lung Cancer. N Engl J Med. 2005 Jul 14;353(2):123–32.

10. Soria JC, Ohe Y, Vansteenkiste J, Reungwetwattana T, Chewaskulyong B, Lee KH, et al. Osimertinib in Untreated EGFR -Mutated Advanced Non–Small-Cell Lung Cancer. N Engl J Med. 2018 Jan 11;378(2):113–25.

11. Khopkar U, Madke B, Gole P, Kumar P. Dermatological side effects of epidermal growth factor receptor inhibitors: ′Pride′ complex. Indian J Dermatol. 2014;59(3):271.

12. Yin X, Zhao Z, Yin Y, Shen C, Chen X, Cai Z, et al. Adverse event profiles of epidermal growth factor receptor-tyrosine kinase inhibitors in cancer patients: A systematic review and meta-analysis. Clin Transl Sci. 2021 May;14(3):919–33.

13. Rowinsky EK, Schwartz GH, Gollob JA, Thompson JA, Vogelzang NJ, Figlin R, et al. Safety, Pharmacokinetics, and Activity of ABX-EGF, a Fully Human Anti–Epidermal Growth Factor Receptor Monoclonal Antibody in Patients With Metastatic Renal Cell Cancer. J Clin Oncol. 2004 Aug 1;22(15):3003–15.

14. Cunningham D, Humblet Y, Siena S, Khayat D, Bleiberg H, Santoro A, et al. Cetuximab Monotherapy and Cetuximab plus Irinotecan in Irinotecan-Refractory Metastatic Colorectal Cancer. N Engl J Med. 2004 Jul 22;351(4):337–45.

15. Soulieres D, Senzer NN, Vokes EE, Hidalgo M, Agarwala SS, Siu LL. Multicenter Phase II Study of Erlotinib, an Oral Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitor, in Patients With Recurrent or Metastatic Squamous Cell Cancer of the Head and Neck. J Clin Oncol. 2004 Jan 1;22(1):77–85.

16. Uozumi S, Enokida T, Suzuki S, Nishizawa A, Kamata H, Okano T, et al. Predictive Value of Cetuximab-Induced Skin Toxicity in Recurrent or Metastatic Squamous Cell Carcinoma of the Head and NECK. Front Oncol. 2018 Dec 13;8:616.

17. Mohamed MK, Ramalingam S, Lin Y, Gooding W, Belani CP. Skin rash and good performance status predict improved survival with gefitinib in patients with advanced non-small cell lung cancer. Ann Oncol. 2005 May;16(5):780–5.

18. Petrelli F, Borgonovo K, Barni S. The predictive role of skin rash with cetuximab and panitumumab in colorectal cancer patients: a systematic review and meta-analysis of published trials. Target Oncol. 2013 Sep;8(3):173–81.

19. Tischer B, Huber R, Kraemer M, Lacouture ME. Dermatologic events from EGFR inhibitors: the issue of the missing patient voice. Support Care Cancer. 2017 Feb;25(2):651–60.

20. Bolognia, Jean., Jorizzo, Joseph L.Schaffer, Julie V., eds. Dermatology. [Philadelphia] :: Elsevier Saunders, 2018. Print.

21. Malik SN, Siu LL, Rowinsky EK, deGraffenried L, Hammond LA, Rizzo J, et al. Pharmacodynamic evaluation of the epidermal growth factor receptor inhibitor OSI-774 in human epidermis of cancer patients. Clin Cancer Res Off J Am Assoc Cancer Res. 2003 Jul;9(7):2478–86.

22. DeWitt CA, Siroy AE, Stone SP. Acneiform eruptions associated with epidermal growth factor receptor–targeted chemotherapy. J Am Acad Dermatol. 2007 Mar;56(3):500–5.

23. Mascia F, Mariani V, Girolomoni G, Pastore S. Blockade of the EGF Receptor Induces a Deranged Chemokine Expression in Keratinocytes Leading to Enhanced Skin Inflammation. Am J Pathol. 2003 Jul;163(1):303–12.

24. Pastore S, Mascia F, Mariani V, Girolomoni G. The Epidermal Growth Factor Receptor System in Skin Repair and Inflammation. J Invest Dermatol. 2008 Jun;128(6):1365–74.

25. Sharma R, Parashar A. Special considerations in paediatric burn patients. Indian J Plast Surg. 2010;43(3):43.

26. Wollenberg A, Moosmann N, Klein E, Katzer K. A tool for scoring of acneiform skin eruptions induced by EGF receptor inhibition. Exp Dermatol. 2008 Sep;17(9):790–2.

27. Hofheinz RD, Lorenzen S, Trojan J, Ocvirk J, Ettrich TJ, Al-Batran SE, et al. EVITA—a double-blind, vehicle-controlled, randomized phase II trial of vitamin K1 cream as prophylaxis for cetuximab-induced skin toxicity. Ann Oncol. 2018 Apr;29(4):1010–5.

28. Lacouture ME, Maitland ML, Segaert S, Setser A, Baran R, Fox LP, et al. A proposed EGFR inhibitor dermatologic adverse event-specific grading scale from the MASCC skin toxicity study group. Support Care Cancer. 2010 Apr;18(4):509–22.

29. Agnew T, Furber G, Leach M, Segal L. A Comprehensive Critique and Review of Published Measures of Acne Severity. J Clin Aesthetic Dermatol. 2016 Jul;9(7):40–52.

30. Wolverton, S., 2020. Comprehensive Dermatologic Drug Therapy. 4th ed. Elsevier, pp.Chapters 9, 22. In.

31. Scope A, Agero ALC, Dusza SW, Myskowski PL, Lieb JA, Saltz L, et al. Randomized Double-Blind Trial of Prophylactic Oral Minocycline and Topical Tazarotene for Cetuximab-Associated Acne-Like Eruption. J Clin Oncol. 2007 Dec 1;25(34):5390–6.

32. Jatoi A, Rowland K, Sloan JA, Gross HM, Fishkin PA, Kahanic SP, et al. Tetracycline to prevent epidermal growth factor receptor inhibitor-induced skin rashes: Results of a placebo-controlled trial from the North Central Cancer Treatment Group (N03CB). Cancer. 2008 Aug 15;113(4):847–53.

33. Jatoi A, Dakhil SR, Sloan JA, Kugler JW, Rowland KM, Schaefer PL, et al. Prophylactic tetracycline does not diminish the severity of epidermal growth factor receptor (EGFR) inhibitor-induced rash: results from the North Central Cancer Treatment Group (Supplementary N03CB). Support Care Cancer. 2011 Oct;19(10):1601–7.

34. Lacouture ME, Mitchell EP, Piperdi B, Pillai MV, Shearer H, Iannotti N, et al. Skin Toxicity Evaluation Protocol With Panitumumab (STEPP), a Phase II, Open-Label, Randomized Trial Evaluating the Impact of a Pre-Emptive Skin Treatment Regimen on Skin Toxicities and Quality of Life in Patients With Metastatic Colorectal Cancer. J Clin Oncol. 2010 Mar 10;28(8):1351–7.

35. Lacouture ME, Sibaud V, Gerber PA, van den Hurk C, Fernández-Peñas P, Santini D, et al. Prevention and management of dermatological toxicities related to anticancer agents: ESMO Clinical Practice Guidelines☆. Ann Oncol. 2021 Feb;32(2):157–70.

36. Melosky B, Burkes R, Rayson D, Alcindor T, Shear N, Lacouture M. Management of Skin Rash during egfr-Targeted Monoclonal Antibody Treatment for Gastrointestinal Malignancies: Canadian Recommendations. Curr Oncol. 2009 Jan 1;16(1):16–26.

37. MASCC Skin Toxicity Study Group, Lacouture ME, Anadkat MJ, Bensadoun RJ, Bryce J, Chan A, et al. Clinical practice guidelines for the prevention and treatment of EGFR inhibitor-associated dermatologic toxicities. Support Care Cancer. 2011 Aug;19(8):1079–95.

38. Landis MN. Optimizing Isotretinoin Treatment of Acne: Update on Current Recommendations for Monitoring, Dosing, Safety, Adverse Effects, Compliance, and Outcomes. Am J Clin Dermatol. 2020 Jun;21(3):411–9.

39. Boily G, Guédon AC, Golo KT, Qureshi S, Lehuédé C, Strumpf E, et al. Création et caractérisation d'une cohorte québécoise de patients atteints d'un cancer du poumon à l'aide de données clinico-administratives. INESSS; 2021.

40. Wheatley-Price P, Ding K, Seymour L, Clark GM, Shepherd FA. Erlotinib for Advanced Non–Small-Cell Lung Cancer in the Elderly: An Analysis of the National Cancer Institute of Canada Clinical Trials Group Study BR.21. J Clin Oncol. 2008 May 10;26(14):2350–7.

41. Jatoi A, Green EM, Rowland, Jr. KM, Sargent DJ, Alberts SR. Clinical Predictors of Severe Cetuximab-Induced Rash: Observations from 933 Patients Enrolled in North Central Cancer Treatment Group Study N0147. Oncology. 2009;77(2):120–3.

42. Luu M, Boone SL, Patel J, Sullivan P, Rademaker AW, Balagula Y, et al. Higher severity grade of erlotinib-induced rash is associated with lower skin phototype: Higher-grade erlotinib rash in patients with lighter skin phototype. Clin Exp Dermatol. 2011 Oct;36(7):733–8.

43. Hughes AN, O'Brien MER, Petty WJ, Chick JB, Rankin E, Woll PJ, et al. Overcoming CYP1A1/1A2 Mediated Induction of Metabolism by Escalating Erlotinib Dose in Current Smokers. J Clin Oncol. 2009 Mar 10;27(8):1220–6.

44. Hassel JC, Kripp M, Al-Batran S, Hofheinz RD. Treatment of Epidermal Growth Factor Receptor Antagonist-Induced Skin Rash: Results of a Survey among German Oncologists. Onkologie. 2010;33(3):94–8

45. Mihai MM, Ion A, Giurcăneanu C, Nițipir C, Popa AM, Chifiriuc MC, et al. The Impact of Long-Term Antibiotic Therapy of Cutaneous Adverse Reactions to EGFR Inhibitors in Colorectal Cancer Patients. J Clin Med. 2021 Jul 21;10(15):3219.