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Stomatitis and EGFR-Tyrosine Kinase Inhibitors: A Review of Current Literature in 4353 Patients

*Claudia Arena[1], Giuseppe Troiano[1], Khrystyna Zhurakivska[1], Riccardo Nocini[2] and Lorenzo Lo Muzio[1]**

[1]Department of Clinical and Experimental Medicine, University of Foggia, Foggia, Italy

[2]Department of Surgical Sciences, University of Verona, Italy

Abstract

Conventional chemotherapy presents a wide range of side effects including oral toxicities such as hyposalivation, dysphagia, discomfort, taste alterations and mucositis. Oral complications often cause dose delays and interruptions of cancer treatment. EGFR is a member of the receptor tyrosine kinase ErbB family and a cell surface molecule whose activation leads to an intracellular signaling cascade promoting invasion, apoptosis and angiogenesis. Recent researches led to the development of a new drug class anti-EGFR, EGFR Tyrosine Kinase Inhibitors (TKI). The following review was performed to answer to the following question "Which is the rate of stomatitis in patients treated with EGFR TKI's?" A systematic search was performed on the PubMed online database. Title and abstract of 102 potentially relevant studies were screened. Only 30 studies were included in the review. The overall incidence of stomatitis of any grade was 67.5% for erlotinib, 49.4% for afatinib, 40% for dacomitinib. These data showed a high rate of lower grade stomatitis. Indeed the rate of G1-G2 stomatitis was 59.3% in patients treated with erlotinib, 49.3% with afatinib and 35% with dacomitinib, while the rate of G3-G4 stomatitis was 15.3% in patients treated with erlotinib, 8.3% afatinib and 4.8% dacomitinib. Analysis of the reports about patients treated with EGFR-TKI showed a clear prevalence of stomatitis grade 1 or 2. These data differ from that of patients treated with conventional chemotherapy in which mucositis is predominantly of grade 3 or 4.

Keywords: Stomatitis; EGFR-TKI; Mucositis; Target therapy; Oral medicine; Oral pathology

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Correspondence:
Lorenzo Lo Muzio, Department of Clinical and Experimental Medicine, University of Foggia, Italy, Tel: 0039 0881 588090; Fax: 0039 0881 588081; E-mail: lorenzo.lomuzio@unifg.it

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Introduction

Conventional cytotoxic chemotherapy presents a wide range of side effects. These include oral toxicities such as hyposalivation/xerostomia, dysphagia, discomfort, taste alterations and mucositis. Oral complications are some of the most significant toxicities and are often a dose limiting effect causing dose delays and interruptions of cancer treatment [1]. For these reasons, research has focused on the study of new therapeutic aids. In the last 20 years there has been an explosion of knowledge in the field of tumor biology. For the first time, researchers have had at their disposal a series of increasingly sophisticated techniques for studying genes, their protein products, and the various aspects of the cell cycle. Thanks to the identification of molecules that interact with a specific defect, the approach to Antineoplastic pharmacology has radically changed, moving from a disease-based pharmacology to a guided cross-therapy on the molecular defect. The future of cancer therapy seems to be the "targeted therapy". Unlike the classic chemotherapy approach, which acts on nonspecific mechanisms linked to the characteristics of all rapidly proliferating cells, including normal ones, "targeted therapy" acts on the mechanisms linked to the expression of oncogenes and tumor suppressor genes, based on the specific tumor promotion action, which results in the transformation of the cell from normal to pathological [2,3]. The increase in understanding of carcinogenesis processes has in fact allowed to identify an ever-increasing series of mutations in the genes that express particular enzymes involved in several "cascades" of intracellular signals, alterations capable of subverting the normal mechanisms of regulation that maintain the equilibrium of the cell (homeostasis), pushing it towards uncontrolled proliferation, and making it acquire characteristics of aggressiveness for the organism. The development of a molecular type drug capable of blocking these enzymes or of humanized monoclonal antibodies, which act on the chains of signals interfering with the receptors present on the cell surface, has radically changed the prognosis of several types of cancers [4]. EGFR is a member of the receptor tyrosine kinases ErbB family and is a cell surface molecule whose activation leads to an intracellular signaling cascade affecting invasion, apoptosis and angiogenesis. The structure of the EGFR family receptor members

Table 1:

	Authors	Year	Neoplasia	N. cases	Stomatitis tot	Stomatitis G1	Stomatitis G2	Stomatitis G3	Stomatitis G4
1.	Besse et al. [1, 15]	2014	Previously treated patients with advanced non small cell lung cancer	A:66	A: 48(72.7%)	A: 27(40.9%)		A: 21(31.8%)	
			A: Everolimus 5 mg/ day+Erlotinib 150 mg/day	B:65	B: 15(23.1%)	B: 15(23.1%)		B: 0	
2.	Chiorean et al. [16]	2008	Taxane naïve malignancies						
			A:150 mg erlotinib+docetaxel 20 mg/m^2	A:3	A:1	A:1(33.3%)		A:0	
			B:150 mg erlotinib+docetaxel 25 mg/m^2	B:6	B:2	B:2(33.3%)		B:0	
			C:150 mg erlotinib+docetaxel 30 mg/m^2	C:3	C:2	C:2(66.6%)		C:0	
			D:150 mg erlotinib+docetaxel 35 mg/m^2	D:10	D:10	D:10(100%)		D:0	
3.	Francois et al. [17]	2012	Advanced pancreatic cancer						
			A:Gemcitabine 1000 mg/m^2/ week+erlotinib 50 mg/day	A:3	A:1	A: 1(33.3%)		A: 0	
			B:Gemcitabine 1000 mg/m^2/ week+erlotinib 75 mg/day	B:3	B:1	B: 1(33.3%)		B: 0	
			C:Gemcitabine 1000 mg/m^2/ week+erlotinib 100 mg/day	C:7	C:3	C: 3(43%)		C: 0	
			D:Gemcitabine 1000 mg/m^2/ week+erlotinib 125 mg/day	D:3	D:2	D: 2(66.6%)		D: 0	
4.	Hanauske et al. [18]	2007	Advanced solid tumors						
			A:Erlotinib 100 mg/ day+oxaliplatin 65 mg/m^2+ LV 200 mg/m^2+5-FU 400 mg/m^2 i.v. bolus followed by 5-FU 400 mg/m^2 continuous infusion	A:6	A: 0	A: 0		A: 0	
			B:Erlotinib 100 mg/ day+Oxaliplatin 85 mg/m^2 +LV 200 mg/m^2+5-FU 400 mg/m^2 i.v bolus followed by 5-FU 600 mg/m^2 continuous infusion	B:9	B:5	B: 5(56%)		B: 0	
			C:Erlotinib 150 mg/day +oxaliplatin 85 mg/m^2+ LV 200 mg/m^2+5-FU 400 mg/ m^2 i.v bolus followed by 5-FU 600 mg/m^2 continuous infusion	C:17	C:9	C: 9(53%)		C: 0	
5.	Heath et al. [19]	2013	Advanced squamous cell carcinoma						
			A:Erlotinib 150 mg a day concurrently with fractionated radiotherapy of 60-66 Gy for 6 weeks within 8 weeks of resection	A:15	A:13	A:10		A:3	
						*oral mucositis		*oral mucositis	
6.	Herchenhorn et al. [20]	2010	Locally advanced squamous cell carcinoma						
			A:Erlotinib 50 mg+cisplatin	A:3	A:3	A: 1(33.3%)		A: 2(66.6%)	
			B:Erlotinib 100 mg+cisplatin	B:3	B:3	B: 3(100%)		B: 0	
			C:Erlotinib 150 mg+cisplatin	C:3	C: 0	C: 0		C: 0	
7.	Irigoyen et al. [21]	2017	Metastatic pancreatic cancer						
			A:Gemcitabine 1000 mg/ m^2+Erlotinib 100 mg/day	A:60	Not reported	Not reported		A: 0	
			B:Gemcitabine 1000 mg/ m^2+Erlotinib 100 mg/day+ capecitabine 1660 mg/m^2	B:58				B: 5(9%)	
8.	Kao et al. [22]	2011	Recurrent head and neck cancer Erlotinib 150 mg either orally or by percutaneous endoscopic gastrostomy (PEG) once daily and celecoxib 200 to 600 mg orally or by PEG twice daily were started 14 days before radiation and were continued until the end of radiation	A:14	A:657	A: 507(71%)		A:150(21%	

9.	Krishnan et al. [23]	2006	Glioblastoma multiforme				
			A:100 mg-150 mg/day erlotinib for patients not on EIAC	A:11	Not reported	Not reported	A: 2(18%)
			B:100-200 mg/day for patients on EIAC	B:9			B: 1(15%)
10.	Nagai et al. [24]	2011	Previously treated non small cell lung cancer	A:48	A: 24(50%)	A: 23(49%)	A: 1(4.8%)
			A:Erlotinib 150 mg/day				
11.	Neal et al. [25]	2016	EGFR wild type advanced non small cell lung cancer				
			A:Erlotinib 150 mg	A:40	A:2	A: 2(5%)	A: 0
			B:Erlotinib 150 mg+Cabozantinib 40 mg	B:39	A:9	B: 9(24%)	B: 0
						*oral mucositis	*oral mucositis
12.	Ramalingam et al. [26]	2014	Advanced stage previously treated non small cell lung cancer				
			A:Erlotinib	A:436	A: 88(20%)	A: 86(20%)	A: 2(<1%)
13.	Soria et al. [27]	2015	Advanced squamous cell carcinoma of the lung				
			A:Erlotinib 150 mg per day	A:397	A:34	A: 34(8%)	A: 0
14.	Starling et al. [28]	2009	Advanced pancreatic cancer				
			A:Gemcitabine 1,000 mg/m^2 in days 1,8,15+bevacizumab 5 mg/kg on days 1 and 15 and erlotinib 100 mg/d every 28 days +910 mg/m^2	A:8	A:7	A: 7(87, 5%)	A: 0
			B:Gemcitabine 1,000 mg/m^2 in days 1,8,15+bevacizumab 5 mg/kg on days 1 and 15 and erlotinib 100 mg/d every 28 days +capecitabine 1,160 mg/m^2	B:3	B:2	B: 2(66,6%)	B: 0
			C:Gemcitabine 1,000 mg/m^2 in days 1,8,15+bevacizumab 5 mg/kg on days 1 and 15 and erlotinib 100 mg/d every 28 days + capecitabine 1,400 mg/m^2	C:6	C:4	C: 4(66, 6%)	C: 0
			D:Gemcitabine 1,000 mg/m^2 in days 1,8,15+bevacizumab 5 mg/kg on days 1 and 15 and erlotinib 100 mg/d every 28 days + capecitabine 1,660 mg/m^2	D:3	D:3	D: 3(100%)	D: 0
15.	Timmers et al. [29]	2015	Non small cell lung cancer				
			A:Erlotinib 150 mg/day	A:62	A: 41(22.0%)	Not reported	Not reported
16.	Yao et al. [30]	2016	Erlotinib 150 mg/day for two weeks+weekly docetaxel 20 mg/m^2+ XRT 70 Gy	A:43	A: 15(35%)	A: 0	A:15
							*oral mucositis
17.	Yoshida et al. [31]	2013	Non small cell lung cancer				
			A:Erlotinib	A:35	A: 6(17.1%)	A: 1(2.9%)	A:5
	Total			**1.497**	**1.010 (67.5%)**		
	Total with grade			**1.297**	**969 (74.7%)**	**770 (59.3%)**	**199 (15.3%)**
	Total not reporting grade*			**62**	**41 (66.1%)**	**Not reported**	**Not reported**
	Total reporting only grade >2**			**138**	**Not reported**	**Not reported**	**8 (5.7%)**

*Timmers et al. [29] did not report the grade of stomatitis.

**Irigoyen et al. [21] and Krishnan et al. [23] reported the incidence rates limited to grade 3 and 4 treatment-related toxicities, for this reason data about cases of stomatitis and stomatitis grade 1 and 2 are lower than real

includes an extra-cellular ligand binding domain. The binding to the domain receptors induces dimerization and autophosphorylation of intracellular tyrosine kinase domain which leads to the activation of downstream signaling pathways of RAS, RAF, Mitogen Activated Protein Kinase (MAPK), Phosphatidylinositol-3-Kinase (PI3K) Akt and the Signal Transduction and Activator of Transcription (STAT) pathways [5]. Targeting EGFR for cancer therapy has been the focus of several researches. In the late 1980's there was the first systematic attempts to develop anticancer agents by targeting the EGFR and researches led to the development of anti-EGFR

Table 2: Report on all papers about afanitib and stomatitis.

Authors	Year	Neoplasia	N.cases	Stomatitis tot	Stomatitis G1	Stomatitis G2	Stomatitis G3	Stomatitis G4
Awada et al. [32]	2013	Solid tumors						
		A:Afatinib doses escalated to 160 mg/day in combination with 75 mg/m² docetaxel	A:40	A:20	A: 20(50%)		A: 0	
Chu et al. [33]	2014	Advanced solid tumors						
		A:Afatinib 30 mg	A:20	A:12(60%)	Not reported		Not reported	
		B:Afatinib 40 mg	B:3	B:3(100%)				
		C: Afatinib 50 mg	C:7	C:6(85.7%)				
		D: Afatinib 60 mg	D:17	D:11(64.7%)				
		E: Afatinib 70 mg	E:6	E:5(83.3%)				
Clement et al. [34]	2016	Recurrent and/or metastatic head and neck squamous cell carcinoma						
		A:Afatinib 40 mg/day patients >65 years	A:83	A: 40(48%)	A: 40(48%)		A: 0	
		B:Afatinib 40 mg/day patients <65 years	B:239	B: 85(36%)	B: 85(36%)		B: 0	
Kato et al. [35]	2015	Advanced non small cell lung cancer						
		A:Afatinib	A:54	A: 49(90.7%)	A: 45(83.4%)		A: 47(7.4%)	
Lee et al. [36]	2017	Advanced non adenocarcinomatous non small cell lung cancer						
		A:Afatinib +Simvastatin	A:36	A: 24(66.7%)	A: 0		A: 24(66.7%)	
Machiels et al. [37]	2015	Recurrent or metastatic squamous cell carcinoma	A:322	A:144	A: 124(39%)		A: 20(7%)	
		A:Afatinib 40 mg/day						
Seiwert et al. [38]	2014	Metastatic or recurrent squamous cell carcinoma of the head and neck	A:61	A: 21(34.4%)	A:14		A: 7(11.5%)	
		A:Afatinib						
Sequist et al. [39]	2013	Metastaticlung adenocarcinoma						
		A:Afatinib	A:229	A:165(72.1%)	A: 145(63.3%)		A: 20(8.7%)	
Soria et al. [27]	2015	Advanced squamous cell carcinoma						
		A:Afatinib 40 mg/day	A:398	A:113	A: 97(25%)		A: 16(4%)	
Wu et al. [40]	2014	Advanced non small cell lung cancer						
		A:Afatinib	A:239	A: 124(51.9%)	A: 124(51.8%)		A: 0	
Total			**1.664**	**822 (49.4%)**				
Total with grade			**1.611**	**795 (49.3%)**	**694 (43.07%)**		**134 (8.3%)**	
Total not reporting grade*			**53**	**27 (50.9%)**	**Not reported**		**Not reported**	

Chu et al. [33] did not report the grade of stomatitis.

monoclonal antibodies and small molecules EGFR tyrosine kinase inhibitors [6]. This unique class of orally administered small molecule therapeutics has been employed into the standard of care treatment in a wide variety of cancer types including non small cell lung cancer, breast cancer, colon, pancreas, head and neck and GIST cancer [5]. Tyrosine kinase inhibitors may help patients to avoid some of the most common toxicities of traditional cytotoxic chemotherapy where toxicities usually involve bone marrow. Even if the Tyrosine Kinase Inhibitors are promising, they induce a variety of side effects such as diarrhea and mucositis, rash and paronychia due to the fact that epidermal growth factor is expressed on nearly all normal cells. In most cases mucositis induced by this class of inhibitor used in monotherapy corresponds to a moderate erythema with limited and superficial ulcers occurring shortly after treatment introduction. This form of mucositis sometimes has the appearance of lesions aphthous-like, although these lesions are less typical than those provoked by mTOR inhibitors. They can involve all areas of the not keratinized mucosa. When these drugs are used in combination with cytotoxic therapies they can cause deeper mucosal ulcerations [7]. The terms "oral mucositis" and "stomatitis" are often used interchangeably to indicate oral complications of anti-cancer therapy, but they do not refer to the same process. Oral mucositis is a Medical Subject Headings term that describes inflammation of the oral mucosa due to chemotherapeutic agents or ionizing radiations, while stomatitis is a less specific term used to describe any inflammatory condition of oral tissue [8].

Materials and Methods

The following review was performed to answer the following question "Which is the rate of stomatitis in patients treated with EGFR TKI's?" A systematic search was performed on the PubMed online database using a combination of MESH terms and free text words: "afatinib" (free text) OR "erlotinib" (MESH) OR "gefitinib" (free text) OR "lapatinib" (free text) combined through the Boolean operator AND with the key words "stomatitis" (MESH) OR "oral mucositis" (MESH).

Only studies fulfilling the following inclusion criteria were considered eligible for inclusion in this study:

1. Performed on human subjects.

Table 3: Report on all papers about dacomitinib and stomatitis.

Authors	Year	Neoplasia	N. cases	Stomatitis tot	Stomatitis G1	Stomatitis G2	Stomatitis G3	Stomatitis G4
Ellis et al. [41]	2014	Pretreated patients with advanced or metastatic non small cell lung cancer						
		A:Dacomitinib 45 mg once daily	A:480	A:196	A: 195(41%)		A: 1(<1%)	
Janne et al. [42]	2011	Advanced solid tumors						
		A:Dacomitinib continuously	A:111	A:60	A: 26(23.4%)		A: 34(30.6%)	
		B:Dacomitinib intermittently	B:10	B:6	B: 2(20%)		B: 4(40%)	
Janne et al. [43]	2014	EGFR mutant non small cell lung cancer						
		A:Dacomitinib	A:89	A:36	A: 32(36%)		A: 4(4%)	
Ramalingam et al. [26]	2014	Advanced stage previously treated non small cell lung cancer						
		A:Dacomitinib	A:436	A: 162(37%)	A: 147(34%)		A: 15(4%)	
Reckamp et al. [44]	2014	Advanced non small cell lung cancer after failure of prior chemotherapy and erlotinib						
		A:Dacomitinib 45 mg once daily	A:66	A: 16 (24.2%)	A: 16(24.2%)		A: 0	
total			**1.192**	**476 (40%)**	**418 (35%)**		**58 (4.8%)**	

2. Reporting about the use of an mTOR inhibitor.

3. Writ- ten in the English language.

4. Reporting about the incidence of stomatitis or oral mucositis.

5. More than 4 papers referring to a single agent.

Case reports and studies on animal model were excluded from this study. No restrictions were applied to the year of publication.

For each study, the following records were extracted: name of the first author, year of publication, number of patients enrolled, type of disease treated, number of events recorded, and grade of the events reported. To simplify the process of data extraction, an ad hoc extraction sheet was used. In addition, data were independently extracted by two authors (LLM and CA) and checked in a joint session. The paper reporting about "gefitinib" and "lapatinib" were excluded due to an insufficient number of cases of oral adverse events reported.

Results

Titles and abstracts of 102 potentially relevant studies were screened (Figure 1); 54 studies of these were excluded because they did not report the inclusion criteria. In the second round, 48 studies were read full text but only 30 were included in the review for the exclusion of papers referring to agents with few studies (<5 studies). Of the included study 17 referred to erlotinib, 10 to afatinib and 5 to dacomitinib. Of these 1 referred both to erlotinib and afatinib, 1 referred both to erlotinib and dacomitinib. For erlotinib 17 studies were analyzed (Table 1). A total of 1.497 patients were treated with erlotinib. The overall incidence of stomatitis of any grade with treatment was 67.5% (1.010 patients). Studies reported data about grade of stomatitis for 1.297 patients and 770 cases were grade 1/2 (59.3%) and 199 were grade 3/4 (15.3%). For afatinib 10 studies were analyzed (Table 2). A total of 1.664 patients were treated with afatinib. The overall incidence of stomatitis of any grade with treatment was 49.4% (822 patients). Studies reported data about grade of stomatitis for 1.611 patients and 795 cases were grade 1/2 (49.3%) and 134 were grade 3/4 (8.3%). For dacomitinib5 studies were analyzed (Table 3). A total of 1.192 patients were treated with dacomitinib. The overall incidence of stomatitis of any grade with treatment was 40% (476 patients) and 418 cases were grade 1/2 (35%) and 58 were grade 3/4 (4.8%).

Discussion

The aim of targeted therapy is to achieve a preferential localization of an antineoplastic agent directly in the region of disease and subsequently an increase in local concentration. EGFR inhibitors are a class of targeted drugs. The Epidermal Growth Factor Receptor (EGFR) is a transmembrane receptor Tyrosine Kinase of the ErbB family which is abnormally expressed in many epithelial tumors. The first attempt to target EGFR dates over 20 years ago when Mendelsohn et al. [9] proposed EGFR as a target for cancer therapy. Small molecules tyrosine kinase inhibitors compete with ATP binding to the Tyrosine Kinase domain of the receptor inhibiting Tyrosine Kinase activation and thus blocking EGFR signaling pathways. The differences between different agents of this class are mainly on their potency against the different members of the HER-receptor family and their ability to inhibit a single receptor type.

Tyrosine kinase inhibitors were considered to have non-overlapping toxicities if compared with cytotoxic chemotherapy. Studies reveal that the most common toxicities associated with tyrosine kinase inhibitors are neutropenia, thrombocytopenia, skin toxicities, hypertension, fatigue, hemorrhage and arterial thrombotic event [10].

Oral toxicities include mucositis, xerostomia, dysphagia and pharyngitis. Results of literature analysis showed that the rate of stomatitis of all grades in patients treated with erlotinib is 67.5%, in patients treated with afatinib is 49.4% and in patients treated with dacomitinib is 40%. The review of the literature showed a high rate of lower grade stomatitis (G1 to G2) while the onset of severe stomatitis (G3 to G4) was lower. Indeed in patients treated with erlotinib the rate of G1 to G2 stomatitis was 59.3%, in patients treated with afatinib

the rate of G1 to G2 stomatitis was 49.3% and in patients treated with dacomitinib the rate of G1 to G2 stomatitis was 35%. The rate of G3 to G4 stomatitis in patients treated with erlotinib was 15.3%, in patients treated with afatinib was 8.3% and in patients treated with dacomitinib was 4.8%. Due to the heterogeneity of the data collected and the different methods of classification of oral manifestations due to EGFR inhibitors it was not possible to collect data regarding the treatment modalities as we did for mIAS [11]. The main limitations of these new molecular drugs are represented by the very high cost and by the fact that these compounds are often effective on a limited percentage of patients who, in most cases, cannot yet be identified. To overcome this difficulty, it is necessary to identify valid predictive biomarkers of response, whose presence or activation is able to indicate the sensitivity to a specific therapy targeted. Moreover it must be considered the concurrence with other types of chemotherapeutic drugs associated in chemotherapeutic regimens.

Although the action specificity of these drugs causes less frequently the adverse effects of this class of drugs and a less debilitating effect on the patients than those of classical chemotherapy, there are still problems related to adverse reactions of this type of agents. The most common are those of oral/dermatological type linked to drugs with an inhibitory action on the growth factor of the epidermis (EGFR). In some cases, however quite rare, the level of these undesirable effects may be such as to force the abandonment of therapy [12]. As regards the treatment of stomatitis caused by EGFR-TKI literature reports that patient should follow a simple oral care regimen which consists of brushing the teeth and tongue with a soft-bristle brush or if unable to use a toothbrush with foam swab or a piece of gauze. Oral care should be performed every 2 hr to 3 hr in case of mild stomatitis and every 1 hr to 2 hr in case of severe stomatitis. In case of mouth sensitivity patients should gargle with benzydamine rinse 3 times daily as needed. For grade 1 stomatitis, patients can use triamcinolone in dental paste applied 2 to 3 times daily with the addition of oral erythromycin or mynocicline in case or grade 2. The triamcinolone is substituted by clobetasol ointment in case of grade 3 stomatitis [13,14].

Conclusion

The analysis of data of this review showed a clear prevalence of grade 1-2 stomatitis in patients treated with EGFR-TKI.

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