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

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ABSTRACT

Introduction. Folliculitis is the most common side effect of epidermal growth factor receptor (EGFR) inhibitors (EGFRIs). It is often apparent, altering patients' quality of life and possibly impacting compliance. Variations in terms of the treatment-related incidence and intensity have not been fully elucidated. Tetracyclines have been recommended for the prophylaxis and treatment of folliculitis but their efficacy is yet to be established.

Materials and Methods. We carried out two systematic literature reviews. The first assessed the preventive and curative efficacy of tetracyclines. The second assessed the incidence of grade 3–4 folliculitis in the main clinical studies published.

Results. In four randomized studies, preventive tetracycline treatment was associated with a significantly lower incidence of grade 2–3 folliculitis and a better quality of life in three of the four studies. In curative terms, tetracycline efficacy was not evaluated in any randomized study, but an improvement in grade ≥ 2 folliculitis was reported in case series. The frequency and severity of folliculitis seem to be greater with the antibodies than with the tyrosine kinase inhibitors. Analysis restricted to lung cancer studies showed a statistically greater incidence in terms of grade 3–4 folliculitis with cetuximab (9%) and erlotinib (8%) than with gefitinib (2%) ($p < .0001$).

Conclusion. Unless contraindicated, a tetracycline

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should be routinely prescribed prophylactically for patients treated with an EGFRi (level of evidence, B2). In curative therapy, the level of evidence for tetracycline

efficacy is low (level of evidence, D). The incidence of grade 3–4 folliculitis induced by EGFRis appears to be lower with gefitinib. *The Oncologist* 2012;17:555–568

INTRODUCTION

The epidermal growth factor receptor (EGFR) is expressed in numerous solid tumors, and it has become a target for certain anticancer treatments [1]. Today, EGFR inhibitors (EGFRIs) are part of the therapeutic arsenal for advanced cancers of the colon, rectum, pancreas, lungs, and upper airways [2–12]. EGFR can be inhibited by the monoclonal antibodies (mAbs) cetuximab (Erbix®; ImClone Systems, Inc., New York) and panitumumab (Vectibix®; Amgen Inc., Thousand Oaks, CA) and by the small molecule tyrosine kinase inhibitors (TKIs) erlotinib (Tarceva®; OSI Pharmaceuticals, Inc., Melville, NY) and gefitinib (Iressa®; AstraZeneca Pharmaceuticals, Wilmington, DE) [13–16].

EGFRIs are associated with dermatological side effects that affect the majority of patients. This skin toxicity has a unique, class-specific semiology [17, 18]. Folliculitis is the most common side effect of the skin, affecting more than one in two patients [1, 17–21]. The terms used in various studies and articles to describe it evolved over time, are variable, and are often inadequate and inaccurate. Thus, the folliculitis induced by EGFRIs is identified in the literature by the terms rash, acne, acne-like skin rash, acneiform skin reaction, acneiform follicular rash, maculopapular skin rash, and monomorphic pustular lesions, and its severity is listed most often using successive versions of the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) severity scale [1–21].

Folliculitis corresponds to inflammation of a pilosebaceous follicle and is clinically characterized by a pustule with a hair at the center. It develops stereotypically: early onset, maximum intensity during week 1–4, and then tending to improve spontaneously thereafter [1, 17, 19, 22]. The severity of folliculitis is dose dependent [1, 18, 19, 23] and is reported to be correlated with a better tumor response [1, 18, 24–28]. Its main aggravating factors are sun exposure, concomitant radiotherapy [29–31], and inadequate moisture levels in the skin.

More than 80% of treated patients present with no or low toxicity (grades 0–2) [17, 19, 21–23], and it is never fatal [32]. Folliculitis is, however, responsible for considerable morbidity because of its visible characteristics and related symptoms [33]. Its impact on quality of life and treatment compliance, especially for oral medication, must therefore not be overlooked [17, 19, 34, 35].

The interest in tetracyclines for acne or rosacea treatment has been established [36, 37]. Their efficacy comprises antibacterial, anti-inflammatory, and immunomodulator actions [36, 38]. These data have led certain authors to evaluate tetracyclines in the treatment of folliculitis induced by EGFRIs. The aim of prophylaxis with tetracyclines, given before EGFRi initiation, is to prevent or reduce the occurrence of folliculitis, whereas in curative management, when tetracyclines are started after its occurrence, the aim is to cure or reduce the

cutaneous side effects. Based on previous publications, several learned societies advocate tetracycline use in curative treatment, but the evidence level of these recommendations has not been established [17, 39].

The purpose of this article was to carry out a systematic review of published data relating to the efficacy of tetracyclines in the preventive and curative management of folliculitis induced by EGFRIs and to establish the level of evidence. We also carried out a systematic review to analyze whether or not the incidence of folliculitis differs depending on the type of EGFRi, that is, mAb or TKI.

METHODOLOGY

Research Strategy

Three electronic databases, PubMed, Embase, and the Cochrane central register of controlled trials, were simultaneously searched in November 2010 to identify published articles in an attempt to assess the efficacy of tetracyclines. In addition, abstracts presented at the American Society of Clinical Oncology (ASCO) and European Society for Medical Oncology congresses in 2010 were also searched. All articles and abstracts focusing on the effects of the preventive or curative treatment of folliculitis were selected.

The PubMed database was searched in order to establish the incidence of folliculitis, and all phase II and phase III studies referring to folliculitis incidence were selected. The study references were analyzed during the search for additional studies.

Searches were carried out in November 2010 and covered studies published in January 1, 2000 to September 30, 2010. Data extraction was done by J.B.B. (efficacy of tetracyclines) and L.P. (incidence of folliculitis depending on the type of EGFRi). Each author in the working group independently evaluated each selected publication. Disagreements were resolved by discussion.

Selection Criteria

Abstracts were screened to assess the relevance of the publications. Articles written in a language other than English or French and review articles or recommendations put forward by a scientific or professional society were excluded from the detailed analysis. Full-length articles of all potentially eligible studies were selected for detailed analysis.

To analyze the efficacy of tetracyclines, the searches were structured on the basis of key words relating to EGFRIs (anti-EGFR, epidermal growth factor receptor inhibitor, cetuximab, panitumumab, erlotinib, gefitinib) and the skin toxicities of EGFRIs (skin toxicity, rash, acne, folliculitis, acneiform eruption, drug eruptions). The following inclusion criteria were used to select published articles: cancer of any type, treatment with an EGFRi regardless of the type of EGFRi, administra-

tion of a tetracycline as preventive or curative therapy, and the description of folliculitis lesions and their evolution under tetracycline therapy (grade and timescale). Exclusion criteria were as follows: the onset of tetracycline treatment after the first cycle for preventive therapy and discontinuation of the EGFRi in conjunction with the introduction of curative tetracyclines (it is impossible to assess whether the improvement was a result of the tetracycline or the withdrawal of the EGFRi). To analyze the incidence of folliculitis, searches were structured on the basis of key words relating to EGFRis (anti-EGFR, epidermal growth factor receptor inhibitor, cetuximab, panitumumab, erlotinib, gefitinib) and the type of study (clinical trial, phase II; clinical trial, phase III). The following inclusion criteria were used to select published articles: cancer of any type, treatment with an EGFRi (cetuximab, panitumumab, erlotinib, gefitinib), list of skin-related side effects associated with the EGFRi, and prospective phase II study (>50 patients in the EGFRi arm in order to have a sufficiently typical incidence) or phase III or large scale, prospective, open-label study. Exclusion criteria were as follows: incidence of folliculitis not specified, additional review of previously published studies, and rationale for future studies. Regarding the meta-analysis, we subsequently excluded studies that separated reports on rash and acneiform dermatitis because both toxicity categories can refer to patients with folliculitis without being mutually exclusive.

Assessment Criteria

Regarding treatments for folliculitis, the criterion used to assess the efficacy of tetracyclines was a lower incidence and/or grade of skin toxicity with preventive therapy or a reduction in the grade and/or a cure in curative therapy. Other data were also collected to identify potential sources of heterogeneity: type of tetracycline used, dosage and duration of treatment, method used to evaluate folliculitis (quantification and time span), concomitant treatments, and quality of life.

To study the incidence of folliculitis, the assessment criterion was the incidence of folliculitis according to the type of EGFRi received. The incidence of folliculitis was initially analyzed taking all grades into account and for severe grades (3 and 4). Secondly, the meta-analyses focused solely on grade 3–4 folliculitis because of the greater comprehensiveness of the data.

Conclusions for each intervention were quoted by the working group according to the following French Federation of Cancer Centers grading system of levels of evidence, based on the methodology, the quality of the study, and the coherence of the results with other available data [40]: level A, if at least one meta-analysis of high standard or several randomized therapeutic trials of high standard provided consistent results; level B, if randomized studies (level B1), therapeutic trials, quasiexperimental trials, or comparisons of populations (level B2) provided consistent results when considered together; level C, if studies, therapeutic trials, quasiexperimental trials, or comparisons of populations had methodology that was not high quality or that provided inconsistent results when considered together; level D, if either the scientific data did not exist

or there was only a series of cases; and expert agreement, if the data did not exist for the method concerned but the experts were unanimous in their judgment.

Statistical Analysis

To assess the preventive efficacy of tetracyclines, the treatments (type of tetracycline and dosage) together with the evaluating criteria assessing grade 2–3 folliculitis were considered equivalent among the trials. The statistical analysis was carried out according to the Mantel Haenzel method using fixed effects and random effects models when appropriate.

Because of the heterogeneity of the studies for the type of cancer, the variety of skin toxicity evaluation procedures, and the diversity of therapeutic protocols used, the incidences of grade 3–4 folliculitis were analyzed using a random effects model. The homogeneity of the studies was analyzed for the various types of cancer and per treatment type. In lung cancer studies, the incidence of folliculitis was compared among the different EGFRi molecules.

The analysis was carried out with R software version 2.13.

RESULTS

Efficacy of Tetracyclines

Articles Selected

Forty-three publications were considered potentially eligible for analyzing the efficacy of tetracyclines in preventive or curative therapy and were analyzed in detail. Eighteen publications in which tetracyclines were not used as a treatment were excluded [41–59]. Two practical surveys that did not provide any efficacy data were excluded [35, 60]. Overall, 22 publications and one abstract reported on the use of tetracyclines in the preventive and/or curative therapy of folliculitis induced by EGFRis.

Among these 23 publications, nine were excluded because the criteria used to assess efficacy were considered inadequate. In one clinical case, preventive treatment with minocycline had been introduced after the first cycle of cetuximab [61]. In three clinical cases, the EGFRi was discontinued at the same time as tetracycline treatment was introduced [62–64]. In five publications (four clinical cases and one prospective series), an improvement in folliculitis was reported but there was no reference to time span and/or quantification [65–69]. Overall, 14 publications or abstracts were considered eligible (Fig. 1).

Preventive Tetracyclines

Four randomized clinical trials evaluating the use of tetracyclines in preventive therapy were reported: three publications and one abstract presented at the 2010 ASCO congress (Table 1) [70–73]. The tetracyclines used were minocycline, tetracycline, and doxycycline ($n = 2$). In these studies, the tetracyclines were either compared with placebo or with the absence of treatment. The NCI-CTCAE, version 3.0, classification was used in the four studies [70–73]. Only the Skin Toxicity Evaluation Protocol Panitumumab [STEPP] study was positive in terms of its primary objective, which was to lead to a lower

Figure 1. Flow chart: systematic literature review focusing on the efficacy of tetracyclines in the management of folliculitis induced by epidermal growth factor receptor inhibitors.
Abbreviations: ASCO, American Society of Clinical Oncology; ESMO, European Society for Medical Oncology.

Table 1. Randomized trials evaluating tetracyclines in the prophylaxis of folliculitis induced by EGFRIs								
Study	n of patients	EGFRI treatment	Type of cancer	General measures	Experimental arm versus control	Primary endpoint	Secondary endpoint	Quality of life
Scope et al. (2007) [73]	48	Cetuximab	Colorectal	Emollients, sun cream	Minocycline (100 mg/day) versus placebo	n of lesions at 8 wks: 58.5 versus 60.2 (p = .22)	Grade 2–3 toxicity at 4 wks ^a : 20% versus 42% (p = .13)	–
Jatoi et al. (2008) [71]	61	Gefitinib, cetuximab, others	Colorectal, lung, others	–	Tetracycline (500 mg twice a day) versus placebo	All grades of toxicity at 4 wks: 76% versus 70% (p = .61)	Grade 2–3 toxicity at 4 wks ^b : 17% versus 55% (p = .009)	Skindex-16 scale: ^c favorable effect at 4 wks
Lacouture et al. (2010) [70]	95	Panitumumab	Colorectal	Emollients, sun cream	Doxycycline (100 mg twice a day) ^d versus placebo	Grade 2–3 toxicity during the 6th wk: 29% versus 62%; OR, 0.3		DLQI scale: favorable effect at 3 wks
Deplanque et al. (2010) [72]	147	Erlotinib	Lung	–	Doxycycline (100 mg/day) versus placebo	All grades of toxicity for 4 mos: 71% versus 81% (p = .12)	Grade 2–3 toxicity for 4 mos: 39% versus 80%	VAS and DLQI scales: favorable effect for 4 mos

^aRead blind.

^bDoctors' evaluation.

^cQuality of life dermatological scale.

^dMore 1% hydrocortisone cream, single daily application at bedtime.

Abbreviations: DLQI, Dermatology Life Quality Index; EGFRI, epidermal growth factor receptor inhibitor; OR, odds ratio; VAS, visual analog scale.

incidence of grade 2–3 folliculitis during the first 6 weeks of treatment: 29.2% (*n* = 14 or 48) versus 61.7% (*n* = 29 of 47) (odds ratio [OR], 0.256; 95% confidence interval [CI], 0.099–0.652; *p* = .0014) [70]. In the other three studies, the primary objective was not reached but a lower incidence of grade 2–3 folliculitis was observed in the tetracycline arm in all cases

[71–73]. Figure 2 shows a combined analysis of the OR associated with the incidence of folliculitis in each study. No heterogeneity among studies was detected (Cochrane's *Q* test, *p* = .620). The combined OR was 0.19 (95% CI, 0.12–0.31; fixed effect model *p* < .0001), indicating that the administration of a tetracycline in preventive therapy was associated with

Figure 2. Meta-analysis of four randomized trials assessing the effect of tetracyclines in the prevention of folliculitis induced by epidermal growth factor receptor inhibitors.

Abbreviation: CI, confidence interval; OR, odds ratio.

a significantly lower incidence of grade 2–3 folliculitis (level of evidence, B2).

Prophylactic tetracycline treatment was also associated with an improvement in the quality of life of patients in three of the four studies in which this parameter was analyzed [70–72].

Curative Tetracyclines

Seven publications of one to four clinical cases and three nonrandomized, prospective series of 11–24 patients reported the results of curative treatment with minocycline, doxycycline, or tetracycline administered concomitantly to varying degree with different local topical agents [24, 74–82]. Most of the patients included in those studies presented with grade ≥ 2 folliculitis. Tetracycline treatment with or without local topical agents was reported to be effective and was associated with a reduction in the grade of folliculitis in the vast majority of patients. This improvement was reported after variable treatment periods of 1–4 weeks' duration, according to the publications. No randomized study investigated the efficacy of curative tetracyclines. These nonrandomized studies were too heterogeneous and the patient cohorts were too small to analyze the curative effects of tetracyclines (level of evidence, D).

Incidence of Folliculitis

Articles Selected

Seventy-seven articles were considered to be potentially eligible and were analyzed in detail (Fig. 3). Twelve articles were excluded because they reported on data additional to results already published [8, 24, 25, 83–91]. Four articles were excluded because they corresponded to the publication of study rationales [92–95]. Five studies were excluded because they involved < 50 patients treated with EGFRIs [96–100]. Six studies were excluded because they did not refer to the frequency of folliculitis [101–106]. Overall, 50 publications were initially selected and are summarized in Table 2 [2–7, 9–16, 20, 27, 107–140]. Secondly, for the meta-analysis, 10 additional studies had to be excluded because rash and acneiform dermatitis were reported separately [9, 12, 15, 20, 107–112]. Overall, 40 studies were selected for the meta-analysis [2–7, 10, 11, 13, 14, 16, 27, 113–140].

Figure 3. Flow chart: systematic literature review focusing on the incidence of folliculitis induced by epidermal growth factor receptor inhibitors.

Systematic Literature Review: Comparison of the Incidence of Folliculitis Between Anti-EGFR mAbs and EGFR TKIs

The mAbs were assessed in colorectal cancer (CRC) (10 studies), head and neck squamous cell carcinoma (HNSCC) (four studies), non-small cell lung cancer (NSCLC) (four studies), and pancreatic cancer (one study), whereas TKIs were evaluated in NSCLC (16 studies), pancreatic cancer (four studies), and HNSCC (one study).

In the studies in which it was mentioned, the frequency of folliculitis, taking all grades into account, was $> 70\%$ in 11 of the 15 mAb studies (73%), compared with just eight of the 24 TKI studies (33%) (Table 3). In the four studies focusing on mAbs and having a low incidence of folliculitis ($< 70\%$), acneiform dermatitis was reported separately from rash. Its frequency was in the range of 22%–62%, which could help to account for the low frequency of folliculitis. The frequency of severe folliculitis (grade

Table 2. Incidence of rash, acneiform dermatitis, skin toxicity, and treatment modifications (withdrawal or reduction) in phase II and phase III trials and in major open-label studies focusing on EGFR monoclonal antibodies and tyrosine kinase inhibitors

Pharmaceutical class	Concomitant chemotherapy in the EGFR arm	Target organ	n of patients	Side effects (% of patients)						Changes due to skin toxicity (% of patients)		
				Rash		Acneiform dermatitis		All forms of skin toxicity		Withdrawal	Dose reduction	CTCAE version
				All grades	Grade 3–4	All grades	Grade 3–4	All grades	Grade 3–4			
EGFR antibody												
Open-label study												
Cetuximab, 400/250 mg/m ² [12]	Irinotecan	CRC	1,690	76	13	–	3	–	–	–	–	2.0
Panitumumab, 6 mg/kg every 2 wks [112]		CRC	176	53	5	59	6	–	–	–	–	3.0
Phase II												
Cetuximab, 400/250 mg/m ² [113]	FOLFOX4	CRC	170	–	11	–	–	90	18	4	–	2.0
Cetuximab, 400/250 mg/m ² [13]	With or without irinotecan	CRC	329	77	8	–	–	84	11	–	–	2.0
Cetuximab, 400/250 mg/m ² [111]	FOLFOX6 or FOLFIRI	CRC	151	35	11	22	4	–	11	–	–	3.0
Cetuximab, 400/250 mg/m ² [114]	Platinum salt	HNSCC	131	70	4	–	–	–	–	0	–	2.0
Cetuximab, 400/250 mg/m ² [115]	Paclitaxel + carboplatin	NSCLC	167	–	12	–	–	–	–	–	–	3.0
Cetuximab, 400/250 mg/m ² [116]	Docetaxel + carboplatin	NSCLC	80	–	4	–	–	–	5	–	–	3.0
Cetuximab, 400/250 mg/m ² [117]	platinum salt	HNSCC	96	72	3	–	–	80	3	0	–	2.0
Cetuximab, 400/250 mg/m ² [118]		CRC	346	–	–	83	5	–	–	0,3	–	2.0
Panitumumab, 2.5 mg/kg per wk [14]		CRC	148	78	3	16	0	95	–	1,4	3	2.0
Phase III												
Cetuximab, 400/250 mg/m ² [119]	Oxaliplatin + fluoropyrimidine	CRC	268	84	10	–	–	–	–	–	–	3.0
Cetuximab, 400/250 mg/m ² [10]	FOLFOX6	CRC	933	–	5	–	–	–	–	–	3	3.0
Cetuximab, 400/250 mg/m ² [11]	FOLFIRI	CRC	600	–	16	–	–	–	20	–	–	2.0
Cetuximab, 400/250 mg/m ² [120]	Capecitabine + oxaliplatin + bevacizumab	CRC	192	81	26	–	–	92	38	–	–	3.0
Cetuximab, 400/250 mg/m ² [121]	Irinotecan	CRC	638	76	8	–	–	–	–	–	–	2.0
Cetuximab, 200/125 mg/m ² [122]	Cisplatin	HNSCC	57	–	16	–	–	77	23	–	–	2.0
Cetuximab, 400/250 mg/m ² [123]	Radiotherapy	HNSCC	208	87	17	–	–	–	–	4	<5	NA
Cetuximab, 400/250 mg/m ² [124]	Gemcitabine	Pancreatic cancer	361	–	7	–	–	–	8	–	–	3.0
Cetuximab, 400/250 mg/m ² [125]	Cisplatin + vinorelbine	NSCLC	548	–	10	–	–	–	–	–	–	2.0
Cetuximab, 400/250 mg/m ² [126]		CRC	288	89	12	–	–	–	–	–	–	2.0
Cetuximab, 400/250 mg/m ² [127]	Taxane + carboplatin	NSCLC	325	–	11	–	–	–	–	2	–	3.0
Panitumumab, 6 mg/kg every 2 wks [20]		CRC	229	20	1	62	7	90	14	0,4	–	3.0
Panitumumab, 6 mg/kg every 2 wks [9]	Oxaliplatin or irinotecan + bevacizumab	CRC	518	63	15	35	11	95	36	–	–	3.0

(continued)

(continued)

Table 2. (Continued)

Pharmaceutical class	Concomitant chemotherapy in the EGFRi arm	Target organ	n of patients	Side effects (% of patients)						Changes due to skin toxicity (% of patients)		
				Rash		Acneiform dermatitis		All forms of skin toxicity		Withdrawal	Dose reduction	CTCAE version
				All grades	Grade 3–4	All grades	Grade 3–4	All grades	Grade 3–4			
Tyrosine kinase inhibitors												
Phase II												
Erlotinib, 150 mg/day [16]	Platinum salt + gemcitabine	HNSCC	115	79	11	–	–	–	–	–	1	2.0
Erlotinib, 150 mg/day [128]		NSCLC	80	79	6	–	–	–	–	1	10	2.0
Erlotinib, 150 mg/day [129]		NSCLC	74	65	3	–	–	–	–	0	–	3.0
Gefitinib, 250,500 mg/day [15]		NSCLC	209	58	4	13	1	–	–	1	–	2.0
Gefitinib, 500 mg/day [130]		NSCLC	136	82	12	–	–	–	–	–	–	2.0
Gefitinib, 250 mg/day [131]	Vandetanib	NSCLC	114	22	0,9	4	0	–	–	–	–	2.0
Phase III												
Erlotinib, 100/150 mg/day [4]	Gemcitabine	Pancreatic cancer	282	72	6	–	–	–	–	–	–	2.0
Erlotinib, 100 mg/day [7]	Gemcitabine + bevacizumab	Pancreatic cancer	583	47	5	–	–	–	–	–	–	3.0
Erlotinib, 150 mg/day [107]	Carboplatin + paclitaxel	NSCLC	209	62	7	22	3	–	–	–	–	2.0
Erlotinib, 150 mg/day [2]	Gemcitabine + cisplatin	NSCLC	580	66	10		–	–	–	–	–	NA
Erlotinib, 150 mg/day [132]		NSCLC	433	60	9	–	–	62	9	–	–	3.0
Erlotinib, 150 mg/day [5]		NSCLC	485	76	9	–	–	–	–	14	12	2.0
Erlotinib, 100 mg/day[27]	Gemcitabine	pancreas	259	69	5	–	–	–	–	–	–	2.0
Erlotinib, 150 mg/day [134]	Capecitabine or gemcitabine	pancreas	114	64	8	–	–	–	–	–	–	2.0
Gefitinib, 250/500 mg/day [110]		HNSCC	324	34	2	14	2	–	–	–	–	3.0
Gefitinib, 250/500 mg/day [108]	Gemcitabine + cisplatin	NSCLC	720	51	8	23	4	–	–	yes	–	2.0
Gefitinib, 250 mg/day [135]		NSCLC	107	–	7	–	–	–	–	–	–	2.0
Gefitinib, 250 mg/day [136]		NSCLC	81	75	4	–	–	–	–	–	–	3.0
Gefitinib, 250/500 mg/day [109]	Paclitaxel + carboplatin	NSCLC	684	61	7	23	3	–	–	–	–	2.0
Gefitinib, 250 mg/day [137]		NSCLC	244	76	0,4	–	–	–	–	–	–	2.0
Gefitinib, 250 mg/day [138]	Platinum salt	NSCLC	300	–	0,3	–	–	–	–	–	–	2.0
Gefitinib, 250 mg/day [6]		NSCLC	1126	37	2	–	–	–	–	–	–	2.0
Gefitinib, 250 mg/day [3]		NSCLC	729	49	2	–	–	–	–	–	–	2.0
Gefitinib, 250 mg/day [139]		NSCLC	87	74	2	–	–	–	–	–	–	3.0
Gefitinib, 250 mg/day [140]		NSCLC	607	66	3	–	–	–	–	–	–	3.0
Gefitinib, 250 mg/day [141]		NSCLC	114	66	5	–	–	–	–	–	–	3.0

Abbreviations: CRC, colorectal cancer; CTCAE, Common Terminology Criteria for Adverse Events; EGFR, epidermal growth factor receptor inhibitor; FOLFIRI, 5-fluorouracil, leucovorin, and irinotecan; FOLFOX, 5-fluorouracil, leucovorin, and oxaliplatin; HNSCC, head and neck squamous cell carcinoma; NSCLC, non-small cell lung carcinoma; NA, not available.

Table 3. Percentage of studies with a high frequency of folliculitis, taking all grades into account and only grade 3–4, depending on the type of EGFRi studied

Agent	Frequency $\geq 70\%$ for folliculitis, taking all grades into account	Frequency $\geq 10\%$ for grade 3–4 folliculitis
Monoclonal antibodies	73% (11/15)	54% (13/24)
Cetuximab	91% (10/11)	60% (12/20)
Tyrosine kinase inhibitors	33% (8/24)	12% (3/26)
Erlotinib	36% (4/11)	18% (2/11)
Gefitinib	31% (4/13)	7% (1/15)

3–4) was $>10\%$ in 13 of 24 (54%) mAb studies and in only three of 26 (12%) TKI studies (Table 3).

The frequencies of folliculitis, taking all grades into account, and severe folliculitis (grades 3–4) are presented in detail in Table 2. Studies concerning panitumumab systematically gave separate reports for rash and acneiform dermatitis, thus precluding reliable analysis. The frequency and severity of folliculitis tended to be greater with mAbs than with TKIs. Severe folliculitis occurred more frequently with erlotinib than with gefitinib.

Meta-Analysis of All Studies Selected

Taking all studies into account, the incidence of grade 3–4 folliculitis was on the order of 7% (Table 2). Analysis of the heterogeneity in the incidence rates observed in these studies indicates some disparity for studies focusing on mAbs in CRC ($p < .0001$), HNSCC ($p < .0001$), and NSCLC ($p = .0256$) patients and for TKI studies in NSCLC ($p < .0001$) patients. The global incidence of grade 3–4 folliculitis with mAbs was 10% (95% CI, 7%–13%) in CRC, 9% (95% CI, 2%–16%) in HNSCC, and 9% (95% CI, 6%–12%) in NSCLC patients. With TKIs, this incidence was 4% (95% CI, 3%–6%) in NSCLC and 5% (95% CI, 4%–7%) in pancreatic cancer patients.

Meta-Analysis of Studies Focusing on NSCLC

Figure 4 shows the incidence of grade 3–4 folliculitis in NSCLC patients comparing the three EGFRi evaluated. There was significant heterogeneity among the studies regarding cetuximab ($p = .0256$), erlotinib ($p = .0184$), and, in particular, gefitinib ($p < .0001$). The incidence rates are estimated at 9% (95% CI, 6%–12%) for cetuximab, 8% (95% CI, 5%–10%) for erlotinib, and 2% (95% CI, 1%–3%) for gefitinib. The incidence of grade 3–4 folliculitis appears to be statistically higher with erlotinib and cetuximab than with gefitinib ($p < .0001$).

DISCUSSION

Folliculitis is a particularly troublesome side effect in patients receiving EGFRi [34, 35]. Several learned societies advocate

their use in the curative treatment of grade 2–3 folliculitis, but the level of evidence of these recommendations is not known [17, 24, 39]. In this systematic literature review, preventive tetracycline treatment led to a significantly lower incidence of grade 2–3 folliculitis, with a level of evidence of B2, and decreased the impact on the quality of life of patients receiving EGFRi [70–73]. In curative therapy, tetracycline treatment seems to be associated with an improvement in the lesions of grade 2–3 folliculitis but, in the absence of any randomized study, the level of evidence is low, namely, D. Furthermore, despite heterogeneity among studies, which makes it difficult to draw comparisons, the frequency and severity of folliculitis seem to be more intense with mAbs than with TKIs. Furthermore, in NSCLC patients, the incidence of severe folliculitis (grades 3–4) is lower with gefitinib than with cetuximab and erlotinib.

In the four randomized studies that assessed the preventive effect of tetracyclines, the patients included, the type of tetracycline, and the dose and duration of treatment were heterogeneous [70–73]. Our study was aimed at assessing the efficacy of tetracyclines in general, and the various treatments used were considered equivalent. The incidence of grade 2–3 folliculitis was used for the meta-analysis, but the date or time interval specified varied depending on the study: in the fourth week for two studies [71, 73], during the first 6 weeks for one study [70], and during the first 4 months for one study [72]. Regarding the natural course of folliculitis induced by EGFRi, heterogeneity in terms of the time for quantification of folliculitis did not constitute a bias when analyzing the results. Furthermore, all these studies were randomized studies with similar ORs calculated independently for each study. Preventive tetracycline treatment resulted in a lower grade of folliculitis (lower incidence of grade 2–3 folliculitis but higher incidence of grade 1 folliculitis) but did not affect the overall rate of folliculitis [70–73]. Thus, the best endpoint for assessing the efficacy of the preventive treatment of EGFRi folliculitis seems to be quantification of grade 2–3 folliculitis during the fourth or sixth week. This criterion should be the main endpoint for future preventive studies.

Among the studies selected, several types of tetracycline were used in both preventive and curative therapy: doxycycline (100 mg/day or 100 mg twice a day), minocycline (100 mg/day or 100 mg twice a day), tetracycline (500 mg twice a day), and lymecycline (300 mg/day) [70–82]. The data currently available cannot confirm the “best” tetracycline to be used or the optimum dose or treatment period. Overall, the safety of tetracyclines is excellent, with a low level of mainly gastrointestinal toxicity [36, 142]. However, the safety profiles vary among the molecules used. Although rare, the risk for phototoxicity is highest with doxycycline [36, 38, 141, 142]. In France, minocycline is no longer recommended as first-line treatment because it triggers rare but potentially extremely severe side effects such as systemic autoimmune reactions and hypersensitivity syndromes or drug reaction with eosinophilia and systemic symptoms [36, 38, 141–143]. These reactions are considerably more frequent in subjects with black skin, thus contraindicating minocycline in this population [144]. It has

Figure 4. Meta-analysis of the incidence of grade 3 or 4 folliculitis in non-small cell lung cancer patients comparing the three epidermal growth factor receptor inhibitors evaluated.

Abbreviation: CI, confidence interval.

nevertheless been suggested that minocycline could be more effective than the other tetracyclines [142, 145–147].

In preventive therapy, only the STEPP study was positive in terms of its primary endpoint [70]. In that study, the treatment arm comprised doxycycline at a dose of 100 mg twice a day for a period of 6 weeks. This dosage and duration of treatment should be recommended for preventive therapy, but a daily dose of 100 mg could be sufficient [70, 72]. Regarding the duration of treatment, 4 weeks of preventive therapy seems inadequate. In the NO3CB study, patients in the tetracycline arm had a significantly better quality of life than those in the placebo arm during the fourth week (83% versus 50%; $p = .005$) but the opposite was noted during the sixth week (67% versus 100%; $p = .04$) [71]. In that study, the duration of treatment was 4 weeks and this reversal in terms of quality of life during the sixth week could indicate a rebound effect for folliculitis after 4 weeks of preventive treatment, suggesting that this timescale is inadequate. Furthermore, other data suggest that the recommended treatment period could potentially exceed 6 weeks. Thus, in the STEPP study, patients in the tetracycline arm experienced significantly less paronychia than

those in the control arm (17% versus 36%) [70]. An evaluation at 6 weeks is early for ungual involvement during EGFRi treatment, but these results suggest the potential efficacy of tetracyclines with regard to the onset of paronychia. This hypothesis should be assessed in future studies.

In the curative treatment of grade 2–3 folliculitis, known differences in terms of the safety profile advocate the use of doxycycline or lymecycline as first-line therapy, bearing in mind the greater photosensitization with doxycycline. Studies are needed in order to define, more effectively, the dosage and duration of treatment for curative therapy. Among other curative treatments reported in the literature, several local treatments have been assessed. Two randomized studies [55, 73] and multiple case series with highly heterogeneous management strategies often combining local treatments or local and systemic treatments [41–42, 44–45, 47, 52, 56, 66, 69, 79–82, 148] have been published. The two randomized studies confirmed the failure of tazarotene [55] and pimecrolimus [73]. Given its resemblance to acne, benzoyl peroxide, adapalene, and topical retinoids were the first topical treatments used in the treatment of folliculitis induced by EGFRi [41, 45, 50, 54,

62, 66–68]. Nevertheless, at present, they must no longer be recommended for the treatment of EGFRi skin toxicity, given the aggravation of skin xerosis that they caused [39]. Conversely, local corticosteroids continue to be indicated given their anti-inflammatory activity.

In the STEPP study, pre-emptive treatment also comprised a local steroid (1% hydrocortisone cream) applied to the face, hands, feet, neck, back, and chest at bedtime. The concomitant use of a tetracycline and a local steroid in the only positive randomized study (for its primary objective) may be confusing. Thus, in the STEPP study, the local steroid could have played an additional role and increased the effects of the tetracycline. However, the absence of heterogeneity among studies and the fact that two of the three others studies reported a better OR than in the STEPP study suggest that the local steroid had little or no additional effects in folliculitis prophylaxis.

Regarding the study on the incidence of folliculitis depending on the type of EGFRi administered, our study essentially highlights the considerable heterogeneity among the various studies discussed. This heterogeneity can be explained by study-specific factors such as the type of EGFRi used and the type of cancer concerned as well as the lack of a really suitable severity grading scale [1, 149].

Heterogeneity nevertheless persisted within the five subgroups defined by the same type of cancer and the same type of EGFRi (mAb or TKI), with the exception of pancreatic cancer patients treated with a TKI, in which case the heterogeneity can be attributed to a straightforward sampling effect. The persistence of this heterogeneity within the same subgroups can be explained by the anticancer molecules associated with EGFRis, which can cause excessive skin toxicity, potentially reported as “rash.” Thus, for the mAbs, various therapeutic protocols have been used in the studies focusing on CRC and NSCLC patients. Conversely, in the HNSCC studies, cetuximab was always associated with a combination of a fluoropyrimidine and a platinum salt. These trigger little skin toxicity except in studies involving radiotherapy. The doses of cetuximab were not, however, identical in these four studies and could have promoted the heterogeneity observed. TKIs were used as monotherapy in three quarters of the NSCLC studies and were routinely used in conjunction with gemcitabine for pancreatic cancer. The heterogeneity observed in NSCLC patients could be explained by regrouping studies assessing gefitinib and others focusing on erlotinib, because these two molecules appear to have different toxicity profiles. This hypothesis is strengthened by the lack of significant heterogeneity observed among TKI studies in pancreatic cancer patients, all of which concerned erlotinib, which can, however, be administered at variable doses and always in combination. The lack of power associated with the small sample size (four studies) probably does not explain the absence of heterogeneity, because it was highly significant in other subgroups of the same size.

The diverse types of cancer and EGFRis used and the concomitant treatments nevertheless cannot alone account for the significance of the heterogeneity observed. This is probably also linked to classification problems. In fact, successive ver-

sions of the NCI-CTCAE that are not strictly comparable were used in these studies. Moreover, this scale is poorly adapted to this specific skin toxicity: version 2.0, which was widely used in these studies, only includes the rash generally encountered with chemotherapies, and version 3.0, which includes the “acneiform dermatitis” category, largely assesses severity on the basis of barely reproducible subjective criteria. The probability of classification bias in these studies is heightened by the use of variable terms (rash, acne, acneiform dermatitis) in the same study. Consequently, these classifications are difficult to use from both a terminology and a scoring perspective, and probably trigger reproducibility problems.

According to the literature, the incidence and severity of folliculitis are deemed to be greater with mAbs than with TKIs [1, 17–19, 22–23, 35, 39]. Adopting an original approach, our meta-analysis focusing on lung cancer studies reported a significantly lower incidence of severe folliculitis (grade 3–4) with gefitinib than with cetuximab and erlotinib. Because only one study concentrated on panitumumab, it is impossible to compare its frequency with those of the other molecules. These results have yet to be confirmed because they are based solely on NSCLC studies, and because heterogeneity nevertheless exists for each of these molecules. Folliculitis could be more severe with erlotinib than with gefitinib, given the dose prescribed: the maximum-tolerated dose for erlotinib versus one third of the maximum-tolerated dose for gefitinib. In addition, erlotinib has a lower distribution volume and therefore higher peak serum concentration. Skin toxicity could be linked to the extent of serum peaks [150]. Indications for the preventive treatment of folliculitis could differ depending on the type of EGFRi molecule prescribed if incidence levels were found to vary. Prospective, open-label studies investigating the incidence of folliculitis induced by EGFRis, in particular severe folliculitis, are therefore required in order to ensure the optimum adjustment of the recommendations.

CONCLUSION

Unless contraindicated, a tetracycline should be routinely prescribed for the prevention of folliculitis in patients treated with an EGFRi for a minimum period of 6 weeks (level of evidence, B2). A comparison of the incidence of folliculitis depending on the type of EGFRi used is compounded by the considerable heterogeneity among studies. However, the incidence and severity of folliculitis seem to be greater with mAbs than with TKIs. Furthermore, among the TKIs, grade 3–4 folliculitis seems to be more common with erlotinib than with gefitinib.

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