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ORIGINAL ARTICLE

Purchase of prophylactic topical corticosteroids is associated with improved survival in NSCLCs treated with EGFR TKI: real-world cohort study

Virve Alanen[a], Sanna Iivanainen[a], Martti Arffman[b] and Jussi P. Koivunen[a]

[a]Department of Medical Oncology and Radiotherapy and Medical Research Center Oulu, Oulu University Hospital and University of Oulu, Oulu, Finland; [b]Health and Social Systems Research Unit, Finnish Institute for Health and Welfare, Helsinki, Finland

ABSTRACT

Background: With the first- and second-generation epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs), clinical benefit and rash correlate together. EGFR TKI-induced rash can be alleviated with topical corticosteroids and tetracyclines. This study investigates whether prophylaxis with topical corticosteroids is associated with improved survival among the EGFR TKI-treated non-small cell lung cancers (NSCLCs).

Material and methods: We collected all the patients ($n = 1271$) who had received reimbursement for the first- or second-generation EGFR TKIs in Finland 2011–2016, had purchased TKIs, and had data available at the Finnish Cancer Registry (FCR). Survival was analyzed from the first EGFR TKI purchase to death or the end of follow-up, and patients were stratified according to the TKIs, purchases of topical corticosteroids, and their timing.

Results: A total of 270 (21%) patients had corticosteroid purchases −14 to +200 d (all), and 196 (15%) had purchased corticosteroids as prophylaxis (−14 to +14 d) from the first EGFR TKI purchase. Corticosteroid purchases were associated with improved survival in all (0.64 95% CI 0.56–0.74) and prophylactic (0.78, 95% CI 0.66–0.92) groups when compared to non-purchasers, although these results were limited to the erlotinib users only. The survival benefit of prophylactic corticosteroids among the erlotinib users remained in multivariate analysis including sex, stage, histology, and tetracycline prophylaxis (HR 0.78, 95% CI 0.64–0.95). The prophylactic use of corticosteroids was associated with a longer erlotinib treatment duration (HR 0.75, 95% CI 0.64–0.90).

Conclusions: Prophylactic topical corticosteroids may improve the survival of NSCLC patients treated with EGFR TKIs, and they should be considered as prophylaxis when initiating EGFR TKIs with a high incidence of rash.

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KEYWORDS
EGFR TKI; NSCLC; rash; corticosteroids; tetracyclines

Introduction

Targeted therapy directed at the epidermal growth factor receptor (EGFR) is one of the treatment options for non-small cell lung cancer (NSCLC). EGFR TKIs were initially used in the treatment of NSCLCs without molecular selection [1,2]. Later, molecular characterization led to the identification of *EGFR*-mutated NSCLC in which EGFR TKIs yield a superior response rate, progression-free survival (PFS), and high quality-of-life scores when compared to chemotherapy [3–5]. Recent studies with a mutation-specific EGFR TKI, osimertinib, have shown that this agent can improve PFS compared to the first-generation TKIs and chemotherapy in T790M+ resistance mutation patients [6,7].

EGFR TKIs are generally well tolerated, and permanent treatment discontinuations because of treatment-related adverse events (TRAEs) seldom occur. Acneiform rash is the most frequent TRAE (~50–80%) of EGFR TKIs, and it usually presents early, commonly at 2–4 weeks after the therapy initiation [8–10]. The frequency and severity of the rash are higher with the first- and second-generation TKIs compared to the third-generation TKI osimertinib [6,7,10,11]. TKI-induced rash has been found to be an independent prognostic factor for survival among the first- and second-generation EGFR TKI users [12–14]. TKI rash can be alleviated by the use of moisturizer, tetracycline-class antibiotics, and topical corticosteroids. Preemptive treatment strategy on the management of dermatological toxicity seems to be more effective in limiting the incidence and severity of the rash [15,16] but has not been linked to an improved survival in prospective trials [17–19]. We have previously shown using a retrospective nationwide registry that the prophylactic use of tetracyclines is associated with improved survival of EGFR TKI-treated NSCLC patients. The benefit of tetracycline prophylaxis was only seen with erlotinib, a TKI characterized by a high incidence of rash, and the findings were probably explained by longer TKI exposure among the prophylactic tetracycline users [20].

In this study, we exploited the same retrospective cohort previously used to study the role of the tetracyclines in the

CONTACT Jussi P. Koivunen jussi.koivunen@ppshp.fi Department of Oncology and Radiotherapy, Oulu University Hospital, PB22, Oulu 90029, Finland
Supplemental data for this article can be accessed here.

EGFR TKI-treated NSCLCs. Our aim was to explore whether the prophylactic topical corticosteroids would have similar effects on survival and TKI treatment duration, and if they would have synergy with tetracyclines.

Material and methods

We collected all the patients who had received entitlement to special reimbursement for EGFR TKIs (gefitinib, erlotinib, and afatinib) in the Special Reimbursement Register of the Social Insurance Institution (SII) of Finland in 2011–16 ($n = 1541$). In Finland, reimbursement for gefitinib and afatinib is based on the advanced disease and the presence of activating tumor *EGFR* mutations. On the other hand, the reimbursement for erlotinib is available for patients in an advanced disease setting with either 1) progression on first-line chemotherapy or 2) tumors with the *EGFR*-activating mutations. With erlotinib, the patients are registered under the same reimbursement number and cannot be separated by the mutational status. Furthermore, the registries do not include information on the treatment line. Drug purchases (date of purchase, strength, and number of purchased units) from the prescription database of SII, cancer data from the Finnish Cancer Registry (FCR), and dates of death from Statistics Finland were linked using personal identity codes. Pseudonymization was carried out before the data analysis. Finally, patients having purchases for EGFR TKIs and data available at FCR ($n = 1271$) were included in the study. Due to the adjustments, the cohort had only missing information for some of the patients for the primary stage (21.2%). The formation of the cohort is described in more detail in our previous publication [20].

Survival was analyzed from the first EGFR TKI purchase date to death or end of follow-up, and death counted as an event. Patients were stratified according to the purchase of the first EGFR TKI (gefitinib, erlotinib, or afatinib), the purchase of topical corticosteroids (anatomical therapeutic chemical [ATC] class D07) or tetracycline (ATC J01AA), and the timing of the corticosteroid and tetracycline purchases. The timing of corticosteroid and tetracycline purchases was analyzed from the first EGFR TKI purchase date and grouped into overall (−14 to +200 d) or prophylactic use (−14 to +14 d). The prophylactic use of medications was used as a primary stratification factor to limit biases caused by 1) EGFR TKI rash and its association to improved survival and 2) survival time-dependent exposure risks. An EGFR TKI treatment break was characterized as a treatment break of >30 d during the first 200 d of TKI use, defined by the TKI purchase dates and the quantity of tablets purchased. The EGFR TKI treatment length was analyzed from the date of the first EGFR TKI purchase to the last purchase date plus days on the treatment, according to the number of tablets in the last purchase; treatment discontinuation before 31 December 2017 was counted as an event. However, a gap of 10 d between purchases was allowed to account for a continuation of treatment.

Data collection was carried out according to the national legislation and under a permit from the Ethical Board of Oulu University Hospital (study no.43/2017), the Social Insurance Institution of Finland (study no.48/522/2017), the Finnish Institute of Health and Welfare (study no. THL/1391/5.05.00/2017), and Statistics Finland (study no.TK-53-1277-17). Informed consent was not required due to the register nature of the study.

Comparisons between groups were assessed using chi-square analysis. Survival was analyzed by using the Kaplan–Meier method with the log-rank test. In univariate and multivariate analysis, Cox regression was used. In multivariate analysis, Cox proportional hazard models were used to adjust for sex, initial stage (local, advanced, or unknown), tumor histology (adenocarcinoma or other), and the use of prophylactic tetracyclines. Patients with no purchases were used as a reference category. The results are reported with 95% confidence level. IBM SPSS Statistics version 24.0.0.0 (SPSS Inc, IBM, Chicago, IL, USA) for Windows was applied for statistical analysis.

Results

Topical corticosteroids and survival

Demographics of the patient cohort ($n = 1271$) are presented as a supplement. In the cohort, purchases for topical corticosteroids were present in 270 patients (21.2%), whereas 196 patients (15.4%) had prophylactic purchases (Supplementary Table 1). The median follow-up time of for the patients in the cohort was 300 d and 1087 of the patients (85.5%) had died at study closure (31 December 2017). In univariate analysis, the purchase of topical corticosteroids (−14 to +200 d) was associated with an improved survival compared to those with no purchases (HR 0.64, 95% CI 0.55–0.74; Table 1; Figure 1(A)). The survival benefit was also seen with the prophylactic purchases (−14 to +14 d) for the topical corticosteroids (HR 0.78, 95% CI 0.66–0.92); Table 2; Figure 1(B)).

Topical corticosteroids, different EGFR TKIs, and synergy with tetracyclines

Next, we carried out an analysis on the benefit of topical corticosteroids to survival according to the first EGFR TKI purchased (gefitinib, erlotinib, or afatinib) since EGFR TKIs have different risks for rash. The benefit of topical corticosteroids was limited to erlotinib only (HR 0.62, 95% CI 0.52–0.73) while there was no difference among the gefitinib users (HR 0.76 95% CI 0.49–1.2; Table 2, Figure 2). Afatinib-treated patients were excluded from further analysis because of the low patient number ($n = 29$).

For the erlotinib users, univariate analysis showed improvement for survival among the overall (−14 to +200 d)

Table 1. Univariate analysis for survival according to the topical corticosteroids and timing purchases.

	HR	CI (95%)
Topical corticosteroid purchases −14 to + 200 d		
Yes *vs.* No	0.635	0.545–0.739
Topical corticosteroid purchases −14 to + 14 d		
Yes *vs.* No	0.777	0.656–0.920

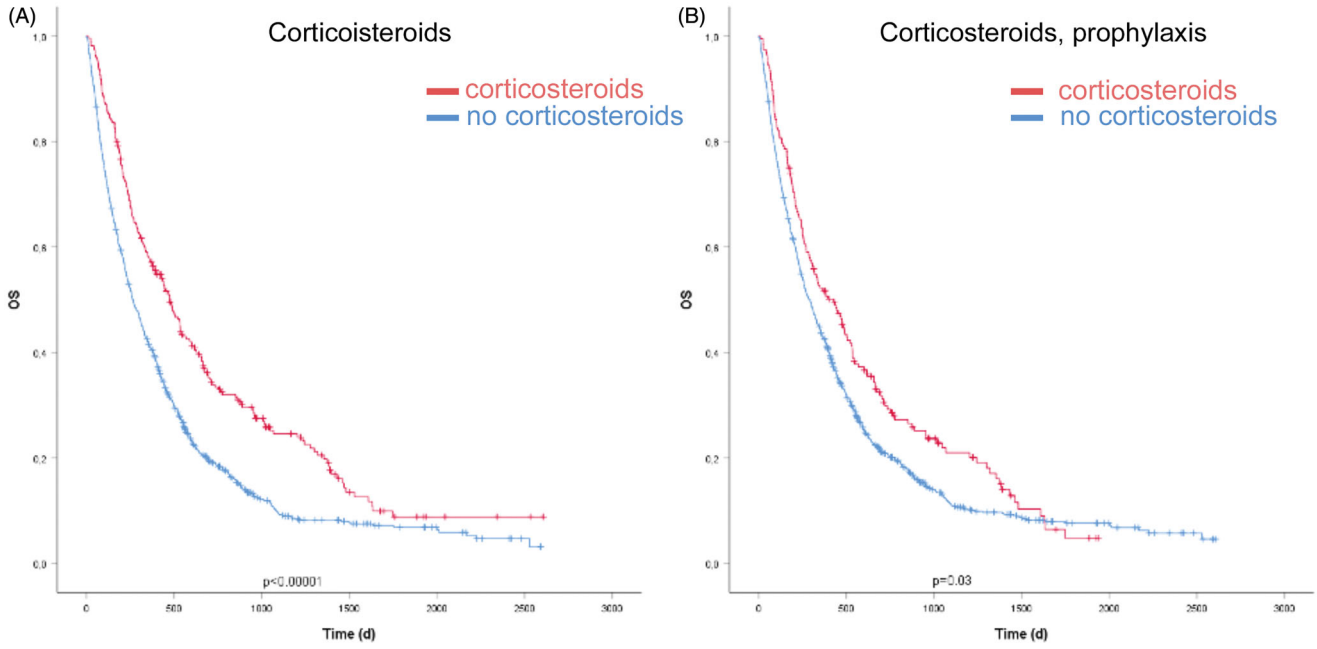

Figure 1. Kaplan–Meier analysis for the survival in the whole cohort according to the purchases of topical corticosteroids and timing of purchases in concordance to the first EGFR TKI purchase. (A) purchases of corticosteroids (red) *vs.* no purchases (blue); (B) prophylactic (−14 to +14 d) corticosteroid purchases (red) *vs.* no prophylactic corticosteroid purchases (blue). Crosses indicate censored events.

Table 2. Univariate and multivariate analysis for survival according to topical corticosteroids and EGFR TKI.

	Univariate		Multivariate	
	HR	CI (95%)	HR	CI (95%)
Sex				
Female *vs.* male	0.754	0.668–0.850	–	–
Stage				
Localized *vs.* advanced	0.642	0.503–0.819	–	–
Histology				
Adenocarcinoma *vs.* other	0.800	0.706–0.906	–	–
Tetracyclines −14 *to* + 14 d				
Yes *vs.* no	0.737	0.618–0.880	–	–
Topical corticosteroid purchases −14 *to* + 200 d				
Yes *vs.* no	0.635	0.545–0.739	0.673	0.568–0.796
Gefitinib				
Yes *vs.* no	0.764	0.493–1.184	–	–
Erlotinib				
Yes *vs.* no	0.616	0.524–0.726	0.665	0.556–0.796
Topical corticosteroid purchases −14 *to* + 14 d				
Yes *vs.* no	0.777	0.656–0.920	0.801	0.663–0.966
Gefitinib				
Yes *vs.* no	0.772	0.450–1.327	–	–
Erlotinib				
Yes *vs.* no	0.761	0.637–0.910	0.781	0.641–0.951

and prophylactic (−14 to + 14 d) purchasers of topical corticosteroids compared to patients without purchases (Table 2). Next, we carried out a multivariate analysis for the survival including sex, initial stage, tumor histology, and the use of the prophylactic tetracyclines, all statistically significant baseline factors in univariate analysis. The effect of topical corticosteroids on survival was retained in multivariate analysis for the whole population and for the erlotinib users, regardless of the timing of the corticosteroid purchases (Table 2).

We also conducted an analysis on synergy between topical corticosteroids and tetracycline prophylaxis in erlotinib users. In this cohort, 257 patients (24.0%) had prophylactic purchases of either corticosteroids or tetracyclines, and 38 patients (3.5%) had purchased for both drugs. In the Kaplan–Meier analysis, there were significant survival benefits for purchasers of both drugs (HR 0.51, 95% CI 0.35–0.75) and single agents (HR 0.78, 95% CI 0.66–0.90) compared to non-purchasers (Figure 3).

The effect of topical corticosteroids prophylaxis on erlotinib dose reductions, treatment breaks, and treatment duration

The effect of the prophylactic topical corticosteroids was analyzed for dose reductions and treatment breaks among the erlotinib users. In the analyses restricted to the first 200 d of erlotinib use, topical corticosteroid prophylaxis was not associated with erlotinib dose reductions, but there was a higher frequency of erlotinib treatment breaks (19.4% *vs.* 11.3%, $p = .004$) (Supplementary Table 2).

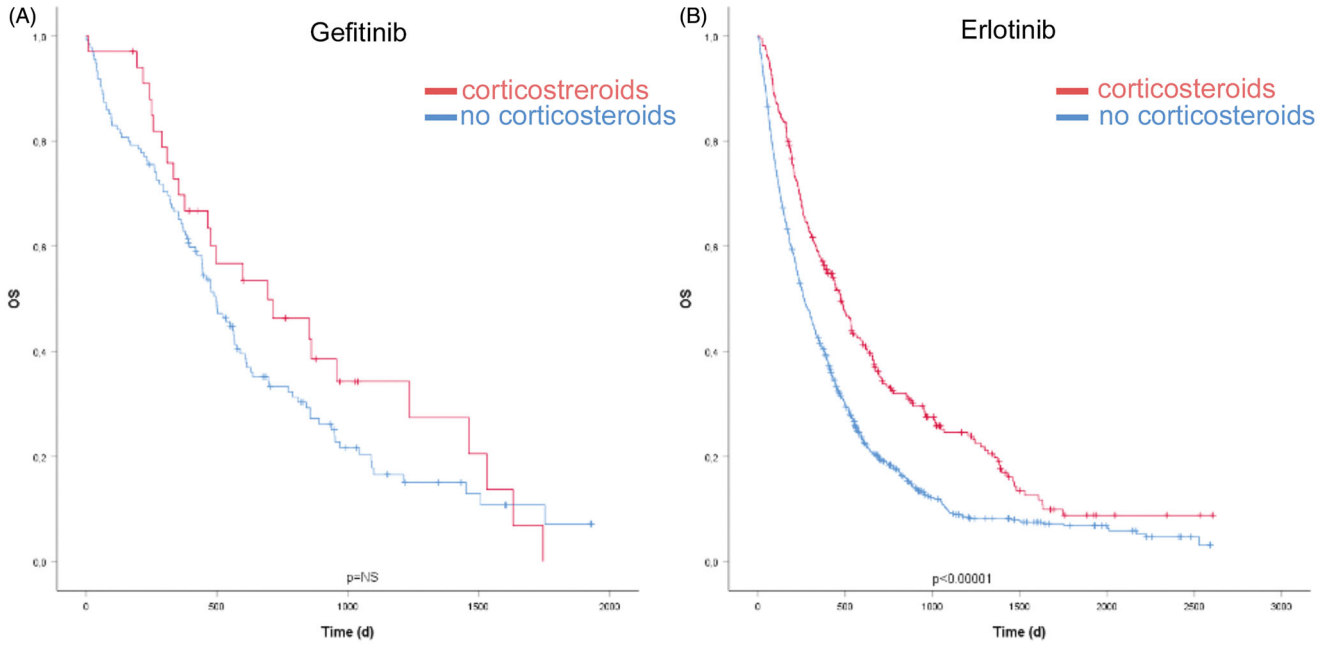

Figure 2. Kaplan–Meier analysis for the survival according to the purchases of the topical corticosteroids and first EGFR TKI. (A) Survival analysis for the gefitinib users, topical corticosteroid purchases (red) *vs.* no purchases (blue); (B) survival analysis for the erlotinib user, topical corticosteroid purchases (red) *vs.* no purchases (blue). Crosses indicate censored events.

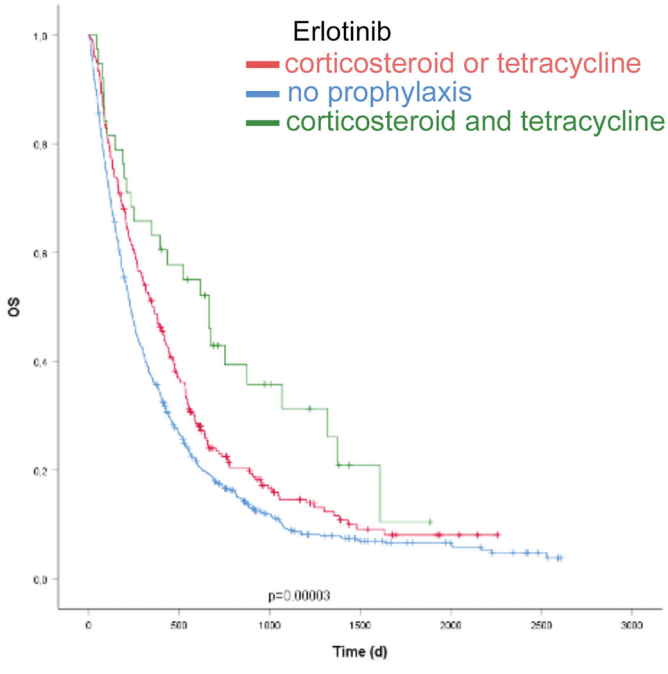

Figure 3. Kaplan–Meier analysis for the survival among the erlotinib users according to the prophylactic purchases for corticosteroids or tetracyclines (red), for both (green), or no prophylactic purchases (blue). Crosses indicate censored events.

Since the date of the progression on the EGFR TKI treatment is unavailable in our registry data, PFS cannot be analyzed. However, the registry data enables analysis for the EGFR TKI treatment duration, and since the permanent treatment discontinuations are mostly related to cancer progression, the endpoint of treatment duration closely reflects PFS. Kaplan–Meier analysis showed that the use of the prophylactic topical corticosteroids was associated with a longer treatment duration compared to no prophylaxis (HR 0.75, 95% CI 0.64–0.90) with a median treatment duration of 135 *vs.* 90 d. Furthermore, the use of both topical corticosteroids and tetracycline prophylaxis was associated with an even longer erlotinib treatment duration (HR 0.60, 95% CI 0.42–0.86) with a median of 164 d (Supplementary Table 3).

Discussion

EGFR TKIs are used in the treatment of the advanced *EGFR* mutant and wild-type lung cancers. With the first- and second-generation EGFR TKIs, rash and diarrhea are the most important side effects that can lead to a decline in the quality of life (QoL), TKI dose reductions, and treatment breaks, all of which compromise the treatment efficiency and adherence [8,11]. In NSCLC, EGFR TKI-induced rash has been linked to an improved prognosis [12–14,21,22]. The rash can be alleviated by the use of topical moisturizer, tetracycline-class antibiotics, and topical corticosteroids. Guidelines often recommend a preemptive strategy on the management of the dermatological toxicity since this decreases the incidence and severity of the rash [23,24]. We have previously shown, using a large, retrospective nationwide NSCLC cohort, that the use of the prophylactic tetracyclines is linked to an improved survival in patients treated with the first- or second-generation EGFR TKIs [20]. In this study, we investigated whether the use of the topical corticosteroids would result in comparable survival benefits to tetracyclines.

The results of this study suggest that topical corticosteroid prophylaxis may relate to improved survival in NSCLCs treated with EGFR TKIs. We saw an increase in the EGFR TKI treatment duration among prophylactic corticosteroid purchasers, suggesting that PFS benefit could have a relation to the observed survival difference. As in our previous study investigating the role of the concurrent tetracyclines with

EGFR TKIs, the survival benefit with topical corticosteroids was only seen among the erlotinib users [20]. This is probably due to the dosing of erlotinib with the maximal tolerated dose. Maximal tolerated dosing of erlotinib is associated with a higher frequency and severity of rash compared to gefitinib [25,26].

One of the main goals of the study was to investigate whether prophylactic measures with tetracyclines or topical corticosteroids would have an independent prognostic value. The hypothesis of the independent prognostic value was evident based on the survival and treatment duration analysis. It would be interesting to see whether topical moisturizers, often recommended as an EGFR TKI rash prophylaxis, would bear similar survival benefits to tetracyclines and topical corticosteroids [16]. The current cohort, however, does not enable investigating this, since these agents are rarely reimbursed in Finland and, therefore, are not registered in the national prescription database.

The prophylactic measures for the EGFR TKI side effects have previously been investigated in small to medium-sized prospective clinical trials. These studies have shown that prophylactic measures can decrease the severity of adverse events, but none have shown a survival benefit for the prophylaxis [17–19]. Due to the large number of subjects, our cohort enables survival analysis with an adequate power. However, the retrospective nature of the study is inevitably susceptible to bias compared to the randomized trials. The use of the prophylactic measures with EGFR TKIs is a clinically relevant issue and due to the lack of prospective evidence, we feel that our retrospective study adds value to current clinical knowledge.

We aimed to control the uncertainties of the retrospective approach by focusing the analysis on the patients with the prophylactic purchases (−14 to +14 d) of the topical corticosteroids and tetracyclines and using multivariate analysis that controls some of the baseline confounding factors for survival. Since the EGFR TKI-induced rash usually develops >14 d after the treatment initiation [27], and rash is linked to improved survival, the later purchases of supportive medications (+15 to +200 d) are more prone to bias. Furthermore, the later purchases have survival time-related selection bias, thus we excluded this measure from the further analysis. This study is based on drug purchases, and this might differ from the drug exposure. In cancer care, however, the patient adherence to purchased medications is generally good, and it is likely that the patients are exposed to the purchased drugs with a high frequency. Exposure to the topical agents is very difficult investigate since they do not have a standard dose or dosing frequency and this cannot be further investigated within the cohort. Both the topical corticosteroids and tetracyclines can be used in other indications than EGFR TKI rash prophylaxis or treatment and these cannot be ruled out in the current cohort. However, the effects of these drugs on the EGFR TKI-induced rash are likely to be independent from the indication of use.

The positive results from the first line studies with osimertinib (FLAURA) are likely to result in the declined use of the first- and second-generation EGFR TKIs in NSCLC [7,27,28]. However, these first- and second-generation EGFR TKIs will still be used in the countries without the first line reimbursement for osimertinib, in cases of osimertinib toxicity, and other indications; therefore, we feel that our results still have a meaningful clinical value. Furthermore, the osimertinib registration trial compared the agent to gefitinib or erlotinib, and it should be noted that the trial did not allow prophylactic measures for the comparator arm. Considering our results, one could question whether the results of the FLAURA trial would have been similar if the prophylactic tetracyclines and corticosteroids had permitted in the comparator arm.

Our study suggests that topical corticosteroid prophylaxis in EGFR TKI-treated NSCLC could lead to improved survival and highlights the importance of prophylactic approaches for EGFR TKI rash. Furthermore, the study reveals the possibilities of using large, real-world registries in investigating clinically important issues that are out of the scope of commercially funded clinical trials.

Ethics approval and consent to participate

All data collection was carried out according to national legislation and under a permit from the Ethical Board of Oulu University Hospital (study no.43/2017), Social Insurance Institution of Finland (study no.48/522/2017), Finnish Institute of Health and Welfare (study no. THL/1391/5.05.00/2017), and Statistics Finland (study no.TK-53-1277-17). Pseudonymization was carried out before data analysis. Informed consent was not required due to the register nature of the study.

Author contributions

VA, SI, JPK, and MA designed and coordinated the work. MA combined the data from different registries. MA, SI, and JPK, carried out statistical analysis. All the authors participated in analysis and interpretation of the data, and drafted, read, and approved the final version of the manuscript.

Consent for publication

All the authors have read and approved the final version of the manuscript.

Disclosure statement

VA and MA declare no conflict of interest. SI reports personal fees and other from MSD, grants from Roche, personal fees from BMS, grants from AstraZeneca, personal fees from Novartis, personal fees from Boehringer-Ingelheim all outside the submitted work. JPK reports grants and personal fees from Roche, grants and personal fees from AstraZeneca, grants and personal fees from Boehringer-Ingelheim, personal fees from Takeda, personal fees from BMS, personal fees from Merck all outside the submitted work.

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Data availability statement

Owing to data protection legislation in Finland, individual-level data on the study subjects cannot be released.

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