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ARTICLE

Adverse event profiles of epidermal growth factor receptor-tyrosine kinase inhibitors in cancer patients: A systematic review and meta-analysis

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Abstract

The efficacy of agents targeting epidermal growth factor receptor (EGFR) in patients with various cancers was well elucidated. However, the safety profile of EGFR tyrosine kinase inhibitors (EGFR-TKIs) has not been systematically investigated. This meta-analysis aimed to evaluate the safety profile of EGFR-TKIs in patients with cancer. A systematic search of PubMed, EMBASE, Cochrane Library databases, ASCO, and ESMO abstracts were conducted. Randomized controlled trials (RCTs) that compared safety profile of EGFR-TKIs with placebo were included. The end points included treatment-related adverse events (AEs), treatment discontinuation, and toxic death. Twenty-eight RCTs containing 17,800 patients were included. The analyses showed that the most frequently observed all-grade AEs in patients treated with EGFR-TKIs were diarrhea (53.7%), rash (48.6%), mucositis (46.5%), alanine aminotransferase (ALT) increased (38.9%), and skin reaction (35.2%). The most common high-grade (grade ≥3) AEs were mucositis (14.8%), pain (8.2%,), metabolism and nutrition disorders (7.4%), diarrhea (6.2%), dyspnea (6.1%), and hypertension (6.1%). The incidence of serious AEs, treatment discontinuation, and toxic death due to AEs were 18.2%, 12.36%, and 3.0%, respectively. Pooled risk ratio (RR) showed that the use of EGFR-TKIs was associated with an increased risk of developing AEs. Subgroup analysis indicated that the risk of AEs varied significantly according to tumor type, generation line, and drug type. Our meta-analysis indicates EGFR-TKIs was associated with a significant increased risk of a series of unique AEs. Early detection and proper management of AEs are important to reduce morbidity, avoid treatment discontinuation, and improve patient quality of life.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

The safety profile of epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitors (TKIs) varied in different trials, and has not been systemically investigated.

Xiaonan Yin and Zhou Zhao contributed equally to this work.

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WHAT QUESTION DID THIS STUDY ADDRESS?

We conducted this meta-analysis of randomized control trials (RCTs) to provide a comprehensive evaluation of adverse event in patients with cancer receiving EGFR-TKIs.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

Our meta-analysis indicates EGFR-TKIs was associated with a significant increased risk of a series of unique adverse events (AEs).

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

The integrated understanding of safety profile of EGFR-TKIs will help in the future design of new EGFR-TKIs with a better safety profile.

INTRODUCTION

Epidermal growth factor receptor (EGFR) pathway is an important therapeutic target for the treatment of cancer, which plays a critical role in regulating tumor angiogenesis, cell survival, differentiation, and migration through its downstream signaling pathways including phosphatidylinositol-3-kinase (PI3 K)/AKT pathway, mitogen-activated protein kinase (MAPK) pathway, and Janus kinase/signal transducers and activators of transcription (JAK/STAT) pathway.[1–3] Indeed, many small molecule tyrosine kinase inhibitors (TKIs) that target the EGFR, such as erlotinib and gefitinib, have been approved for the treatment of a range of solid tumors including non-small cell lung cancer (NSCLC), head and neck cancer, pancreatic carcinoma, and esophageal cancer.[4–7]

In contrast with traditional chemotherapy agents, EGFR-TKIs are associated with a new set of toxicity profile, such as diarrhea, rash, mucositis, and fatigue.[8,9] Although most EGFR-TKIs-related adverse events (AEs) are manageable and not life-threatening, they can significantly affect patients' physical function and quality of life, leading to the nonadherence and the increase of treatment costs. In addition, the toxicity profiles of EGFR-TKIs varied in different trials. However, to the best of our knowledge, comprehensive meta-analysis focusing on the AE profile of EGFR-TKIs has not been investigated. Therefore, we conducted a comprehensive search and meta-analysis of randomized control trials (RCTs) to fully investigate the AE profile of EGFR-TKIs in patients with cancer.

METHODS

Search strategy and selection of the studies

The study was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. A systematic search of PubMed, EMBASE, and Cochrane Library databases was conducted until October 1, 2020. Search terms included "afatinib," "erlotinib," "gefitinib," "osimertinib," "dacomitinib," "lapatinib," "neratinib," "vandetanib," "icotinib," "tumor," "cancer," "controlled clinical trial," and "randomized controlled trial." The searches were limited to human RCTs and the language was restricted to English. Additionally, abstracts from the American Society of Clinical Oncology (ASCO) annual meetings and European Society of Medical Oncology (EMSO) were also searched to retrieve additional trials that may not have been published. Only the most complete, recent report of a trial was included when multiple publications of the same clinical trials were identified.

Trials that met the following criteria were included: (a) randomized controlled phase 2 and 3 trials in patients with cancer, (b) EGFR-TKIs (afatinib or erlotinib or gefitinib or osimertinib or dacomitinib or lapatinib or neratinib or vandetanib or icotinib) were applied as the only therapy in the experimental arm, and the control arm includes placebo, best supportive care, no therapy, or observation, and (c) available data on AEs.

Data extraction and clinical outcomes

For each study that met inclusion criteria, the following information was extracted: the first author's name, year of publication, trial phase, underlying malignancy, sample size, treatment and number of patients in the experimental and control arms, median age, name and dosage of the EGFR-TKIs, median treatment duration, types and numbers of all-grade and high-grade (grade $\geq$3) AEs assessed by the National Cancer Institute Common Terminology for Adverse Events (NCI-CTCAE) in the experimental and control arms, numbers of serious AEs, treatment discontinuation, and toxic death due to AE in the experimental and control arms. AEs reported in no more than two studies were excluded. Data extraction was conducted independently by two reviewers (Y.X.N. and Z.Z.), and any disagreements were resolved by consensus.

Quality assessment

The quality of the included trials was independently assessed by two reviewers (Y.X.N. and Z.Z.) using the revised Cochrane Risk of Bias Tool for Randomized Trials (RoB version 2.0).[10]

Discrepancies between authors were resolved by consensus. We assessed the following five major domains of bias: (a) bias arising from the randomization process, (b) bias due to deviations from intended interventions, (c) bias due to missing outcome data, (d) bias in measurement of the outcome, and (e) bias in selection of the reported result. Finally, the overall risk-of-bias in each study was classified into three types: (1) low risk of bias, (2) some concerns, or (3) high risk of bias.

Statistical analysis

The primary end point of this meta-analysis was the incidence and risk ratio (RR) of all-grade and high-grade (grade ≥3) AEs, serious AEs, treatment discontinuation, and toxic death associated with EGFR-TKIs treatment. For calculation of incidence, the number of all-grade and high-grade AEs, serious AEs, treatment discontinuations, and toxic deaths were extracted from the EGFR-TKI group from each trial. For calculation of RR, end point events of patients assigned to the EGFR-TKI group were compared with those assigned to the control group in the same trial. The pooled incidence or RR and the corresponding 95% confidence interval (CI) were calculated using a fixed or random effects model, depending on heterogeneity. Heterogeneity was quantified with the I^2 statistic. I^2 values less than 30% was considered low, values between 30 and 50% were considered low to moderate, values between 50 and 75% were considered moderate to high, and values greater than 75% were considered high. Significance heterogeneity was set at I^2 value greater than 50%. A random-effect model was used when I^2 greater than 50%, otherwise, a fixed-effect model was used. Subgroup analysis was conducted to examine whether the RRs of AE varied by type of drug, type of cancer (NSCLC vs. non-NSCLC), and generation line of EGFR-TKI (first-generation, second-generation, or third-generation). The χ^2 statistic was used to assess the subgroup analysis. A p value of less than 0.05 was considered statistically significant. Potential publication bias was conducted using funnel plots (plots of study results against precision). All analyses were performed using the comprehensive meta-analysis program (version 2.0; Biostat, Englewood, NJ).

RESULTS

The initial search yielded 767 potentially relevant studies. At the initial screening, studies were excluded for at least one of the following reasons: reviews, letters, commentaries, case reports, non-randomized trials, and RCTs with combination therapies in the treatment arm. Full-text review was performed at the remaining 121 trials, 93 trials were excluded for overlapping data, not Phase 2 or 3 trials, or containing chemotherapy or hormonal therapy in control arm. In total, 28 trials with 17,800 patients were included in our analysis.[4–7,11–34] Figure 1 displays the selection process.

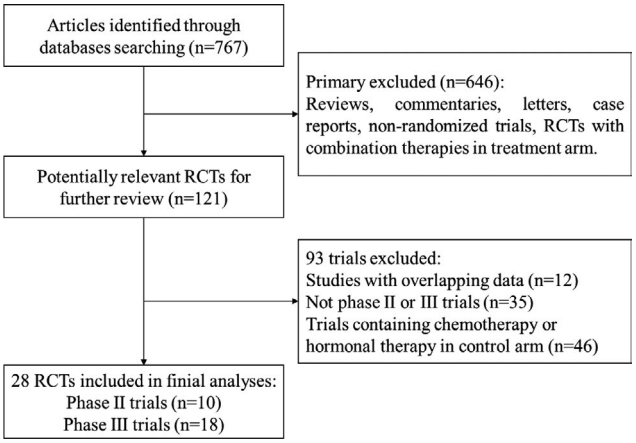

FIGURE 1 The flow chart of study selection. RCT, randomized controlled trial

Characteristics of included studies

The characteristics of the included studies were summarized in Table 1. A total of 28 trials with 17,800 patients were identified for this meta-analysis. The underlying malignancies included were NSCLC (14 trials), breast cancer (4 trials), head and neck cancer (4 trials), thyroid cancer (2 trials), bladder cancer (1 trial), hepatocellular carcinoma (1 trial), esophageal cancer (1 trial), and pancreatic carcinoma (1 trial). Among these trials, lapatinib was investigated in 7 trials, vandetanib in 6 trials, erlotinib in 5 trials, gefitinib in 5 trials, afatinib in 2 trial, dacomitinib in 1 trial, neratinib in 1 trial, and osimertinib in 1 trial, and median treatment duration ranged from 2 weeks to 19.5 months. All trials were open-label, randomized trials, including 10 Phase 2 and 18 Phase 3 trials. In 28 trials, the AEs were recorded and graded according to the CTCAE version 2.0, 3.0, or 4.0.

Incidence of adverse event

A pooled incidence of all-grade and high-grade (grade ≥3) AEs were performed on the 28 RCTs (Table 2). In the analysis of all-grade AEs of EGFR-TKIs treatment, diarrhea (53.7%, 95% CI: 45.5–61.6), rash (48.6%, 95% CI: 40.2–57.0), mucositis (46.5%, 95% CI: 27.8–66.2), alanine aminotransferase (ALT) increased (38.9%, 95% CI: 19.9–62.0), and skin reactions (35.2%, 95% CI: 13.8–64.7) were most common. The most common high-grade AEs were mucositis (14.8%, 95% CI: 4.6–38.7), pain (8.2%, 95% CI: 4.9–13.4), metabolism and nutrition disorders (7.4%, 95% CI: 7.4%, 95% CI: 5.8–9.3), diarrhea (6.2%, 95% CI: 3.8–9.9), dyspnea (6.1%, 95% CI:

TABLE 1 Characteristics of the included studies

Author(year)	Trial phase	Jadad scale	Tumor type	Line of therapy	NCI-CTCAE version	No. of patients	Treatment comparison	Patients per arm	Median age	Treatment duration median (range)
Miller, V. A. (2012)[12]	Phase 2b/3	5	NSCLC	≥Second line	3	585	Afatinib 50 mg/day	390	58	10.5 months
							Placebo	195	59	11 months
Burtness, B. (2019)[13]	Phase 3	5	Head and neck cancer	Adjuvant	3	617	Afatinib 50 mg/day	411	58	300 days
							Placebo	206	57	455.5 days
Ellis, P. M. (2014)[15]	Phase 3	5	NSCLC	≥Second line	4	720	Dacomitinib 45 mg/day	477	63.5	NR
							Placebo	239	66.5	NR
Shepherd, F. A. (2005)[19]	Phase 3	3	NSCLC	≥Second line	2	731	Erlotinib 150 mg/day	485	62	7.9 months
							Placebo	242	59	NR
Propper, D. (2014)[6]	Phase 2	3	Pancreatic carcinoma	Second line	3	207	Erlotinib 150 mg/day	104	62	6.95 months
							Placebo	103	57	8.77 months
Lee, S. M. (2012)[20]	Phase 3	5	NSCLC	First-line	3	670	Erlotinib 150 mg/day	334	77	NR
							Placebo	313	77	
Kelly, K. (2015)[4]	Phase 3	5	NSCLC	Adjuvant	3	973	Erlotinib 150 mg/day	611	62	NR
							Placebo	343	62	
Cappuzzo, F. (2010)[18]	Phase 3	4	NSCLC	Maintenance	3	889	Erlotinib 150 mg/day	433	60	NR
							Placebo	445	60	
Zhang, L. (2012)[22]	Phase 3	5	NSCLC	Maintenance	3	296	Gefitinib 250 mg/day	147	55	148 days
							Placebo	148	55	73 days
Thatcher, N. (2005)[21]	Phase 3	5	NSCLC	≥Second line	2	1682	Gefitinib 250 mg/day	1126	62	2.9 months
							Placebo	562	61	2.7 months
Goss, G. (2009)[29]	Phase 2	5	NSCLC	First-line	3	201	Gefitinib 250 mg/day	100	74	NR
							Placebo	101	76	NR
Gaafar, R. M. (2011)[16]	Phase 3	3	NSCLC	Second-line	2	173	Gefitinib 250 mg/day	85	61	115 days
							Placebo	86	62	85 days
Dutton, S. J. (2014)[5]	Phase 3	5	Esophageal cancer	Second-line	4	450	Gefitinib 500 mg/day	224	64.7	44 days
							Placebo	225	64.9	35 days
Powles, T. (2017)[27]	Phase 3	4	Bladder Cancer	Maintenance	3	232	Lapatinib 1500 mg/day	116	70.7	6 months
							Placebo	116	71.1	6 months
Leary, A. (2015)[14]	Phase 2	4	Breast cancer	Neoadjuvant	3	121	Lapatinib 1500 mg/day	94	53	2 weeks
							Placebo	27	57	2 weeks

(Continues)

TABLE 1 (Continued)

Author(year)	Trial phase	Jadad scale	Tumor type	Line of therapy	NCI-CTCAE version	No. of patients	Treatment comparison	Patients per arm	Median age	Treatment duration median (range)
Harrington, K. (2015)[7]	Phase 3	5	Head and neck cancer	Maintenance	3	688	Lapatinib 1500 mg/day	346	54	62.9 weeks
							Placebo	342	55	62.9 weeks
Harrington, K. (2013)[28]	Phase 2	4	Head and neck cancer	Maintenance	NR	67	Lapatinib 1500 mg/day	35	56	392 days
							Placebo	31	57	241 days
Goss, P. E. (2014)[11]	Phase 3	5	Breast cancer	Maintenance	3	3147	Lapatinib 1500 mg/day	1571	51	NR
							Placebo	1576	52	NR
Del Campo, J. M. (2012)[17]	Phase 2	3	Head and neck cancer	First-line	3	108	Lapatinib 1500 mg/day	71	58	4 weeks
							Placebo	36	55	4 weeks
Decensi, A. (2011)[23]	Phase 2b	3	Breast cancer	Neoadjuvant	3	58	Lapatinib 1500 mg/day	27	53.6	3 weeks
							Placebo	31	52.6	3 weeks
Martin, M. (2017)[24]	Phase 3	5	Breast cancer	Adjuvant	3	2840	Neratinib 240 mg/day	1420	52	353 days
							Placebo	1420	52	360 days
Thornton, K. (2012)[31]	Phase 3	3	Thyroid Cancer	First-line	3	330	Vandetanib 300 mg/day	231	50.7	90.1 weeks
							Placebo	99	53.4	39.9 weeks
Lee, J. S. (2012)[34]	Phase 3	4	NSCLC	Second-line	3	922	Vandetanib 300 mg/day	619	60	165 days
							Placebo	303	50	152 days
Hsu, C. (2012)[33]	Phase 2	4	Hepatocellular carcinoma	First-line	3	42	Vandetanib 300 mg/day	19	54	39 days
							Placebo	23	56	30 days
Leboulleux, S. (2012)[32]	Phase 2	5	Thyroid Cancer	First-line	3	145	Vandetanib 300 mg/day	73	63	18.9 months
							Placebo	72	64	19.5 months
Ahn, J. S. (2014)[30]	Phase 2	4	NSCLC	Maintenance	3	117	Vandetanib 300 mg/day	75	61	59 days
							Placebo	42	60.5	54 days
Arnold, A. M. (2007)[26]	Phase 2	3	NSCLC	Maintenance	2	107	Vandetanib 300 mg/day	53	56.9	7 weeks
							Placebo	54	62.4	12 weeks
Wu, Y. L. (2020)[25]	Phase 3	5	NSCLC	Adjuvant	3	682	Osimertinib 80 mg/day	339	64	22.5 months
							Placebo	343	62	18.7 months

Abbreviations: NCI-CTCAE, National Cancer Institute Common Terminology for Adverse Events; NSCLC, non-small cell lung cancer.

TABLE 2 Top 20 all- and high-grade AEs for EGFR-TKIs group

AEs	Model	Studies	Event rate (%)	Lower limit	Upper limit	*Z* value	*p* value
Toxicity outcome							
Serious AE	Random	17	18.24	12.71	25.47	−6.894	<0.001
Treatment discontinuation	Random	16	12.36	8.37	17.90	−8.825	<0.001
Toxic death	Random	18	3.01	1.84	4.90	−13.450	<0.001
All grade							
Diarrhea	Random	25	53.7	45.5	61.6	0.884	0.377
Rash	Random	23	48.6	40.2	57.0	−0.328	0.743
Mucositis	Random	4	46.5	27.8	66.2	−0.343	0.732
ALT increased	Random	3	38.9	19.9	62.0	−0.941	0.347
Skin reaction	Random	2	35.2	13.8	64.7	−0.984	0.325
Acne	Random	5	28.5	13.2	51.2	−1.860	0.063
Pain	Random	2	27.3	10.3	55.2	−1.617	0.106
Hypertension	Random	6	24.0	13.6	38.7	−3.253	0.001
Fatigue	Random	15	23.7	16.9	32.0	−5.492	<0.001
Nausea	Random	20	23.6	17.7	30.7	−6.341	<0.001
Prolonged QTC	Fixed	2	20.3	14.1	28.4	−6.086	<0.001
Decreased appetite	Random	19	17.6	14.7	20.9	−14.280	<0.001
Neutropenia	Random	4	17.1	8.3	32.0	−3.741	<0.001
Radiation skin injury	Fixed	2	16.1	12.8	19.9	−12.394	<0.001
Dry skin	Random	11	16.1	10.5	23.8	−6.638	<0.001
Dry mouth	Random	4	15.9	7.8	29.9	−4.012	<0.001
Stomatitis	Random	8	15.4	9.4	24.3	−5.891	<0.001
Asthenia	Random	9	15.1	9.3	23.5	−6.180	<0.001
Vomiting	Random	16	14.9	10.4	20.9	−8.323	<0.001
Cough	Random	9	14.4	8.9	22.5	−6.430	<0.001
High grade (grade ≥3)							
Mucositis	Random	3	14.8	4.6	38.7	−2.657	0.008
Pain	Fixed	2	8.2	4.9	13.4	−8.635	<0.001
Metabolism and nutrition disorders	Fixed	2	7.4	5.8	9.3	−19.199	<0.001
Diarrhea	Random	21	6.2	3.8	9.9	−10.532	<0.001
Dyspnea	Random	9	6.1	2.9	12.3	−6.965	<0.001
Hypertension	Fixed	4	6.1	4.7	7.8	−19.969	<0.001
Vascular disorders	Fixed	2	6.0	4.6	7.8	−18.860	<0.001
Rash	Random	18	4.9	2.9	8.1	−10.678	<0.001
Neutropenia	Random	3	4.7	1.2	17.2	−4.102	<0.001
ECG QT prolonged	Random	2	4.5	1.0	18.8	−3.770	<0.001
Gastrointestinal disorders	Random	2	4.3	0.7	22.6	−3.248	0.001
Aminotransferases increased	Random	2	4.0	0.7	20.1	−3.466	0.001
Fatigue	Random	16	3.7	2.1	6.4	−11.062	<0.001
ALT increased	Random	3	3.3	0.9	12.2	−4.735	<0.001
Alkaline phosphatase increased	Fixed	2	2.6	0.8	7.7	−6.194	<0.001
Bilirubin increased	Fixed	2	2.6	0.8	7.7	−6.194	<0.001
Asthenia	Random	6	2.6	1.0	6.3	−7.584	<0.001
Photosensitivity reaction	Fixed	2	2.5	1.2	5.2	−9.557	<0.001
Infection	Random	6	2.4	0.9	6.1	−7.347	<0.001
Hypocalcemia	Fixed	3	2.2	1.1	4.5	−10.499	<0.001

Abbreviations: AEs, adverse events; ALT, alanine aminotransferase; ECG, electrocardiogram; EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor.

2.9–12.3), and hypertension (6.1%, 95% CI: 4.7–7.8). Toxic outcomes, such as serious AEs, treatment discontinuation, and toxic death due to AE, are also important aspects of the drug's safety profile. Seventeen trials (7527 patients) reported serious AEs and 1130 cases were identified. The risk of serious AEs was 18.2% (95% CI: 12.7–25.5). Eighteen trials (8626 patients) reported treatment discontinuation due to AEs, and 1339 patients were identified. The risk of treatment discontinuation was 12.36% (95% CI: 8.4–17.9). Sixteen trials (5752 patients) reported toxic death and 239 cases were identified. The risk of toxic death was 3.0% (95% CI: 1.8–4.9).

Risk ratio of adverse event

To determine the specific contribution of EGFR-TKIs and exclude confounding factors, we calculate the RRs of AEs in patients assigned to EGFR-TKIs versus controls (Table 3). A meta-analysis of the RRs of top 20 all-grade AEs was performed. The results indicated that patients treated with EGFR-TKIs had a significant increased risk of prolonged QTC (RR = 24.56, 95% CI: 3.37–179.05, $p = 0.002$), hypertension (RR = 5.99, 95% CI: 3.98–9.02, $p < 0.001$), acne (RR = 3.58, 95% CI: 1.94–6.60, $p < 0.001$), diarrhea (RR = 3.32, 95% CI: 2.82–3.92, $p < 0.001$), dry skin (RR = 3.19, 95% CI: 2.41–4.23, $p < 0.001$), stomatitis (RR = 3.19, 95% CI: 2.33–4.37, $p < 0.001$), rash (RR = 3.18, 95% CI: 2.68–3.77, $p < 0.001$), ALT increased (RR = 2.74, 95% CI: 2.01–3.75, $p < 0.001$), mucositis (RR = 1.71, 95% CI: 1.10–2.65, $p = 0.017$), vomiting (RR = 1.37, 95% CI: 1.11–1.69, $p = 0.003$), and nausea (RR = 1.31, 95% CI: 1.10–1.58, $p = 0.003$). However, patients treated with EGFR-TKI had a significant decreased risk of radiation skin injury (RR = 0.69, 95% CI: 0.52–0.92, $p = 0.012$). A meta-analysis of the RR of high-grade AEs showed that patients treated with EGFR-TKIs had a significant increased risk of electrocardiogram (ECG) QT prolonged (RR = 9.90, 95% CI: 1.94–50.48, $p = 0.006$), rash (RR = 7.34, 95% CI: 4.34–12.16, $p < 0.001$), diarrhea (RR = 7.32, 95% CI: 5.05–10.61, $p < 0.001$), hypertension (RR = 6.69, 95% CI: 1.91–23.51, $p = 0.003$), gastrointestinal disorders (RR = 1.85, 95% CI: 1.06–3.25, $p = 0.031$), and mucositis (RR = 1.42, 95% CI: 1.08–1.85, $p = 0.012$). In addition, patients treated with EGFR-TKI had a significant increased risk of serious AEs (RR = 1.20, 95% CI: 1.05–1.37, $p = 0.008$) and treatment discontinuation (RR = 3.68, 95% CI: 3.25–4.17, $p < 0.001$).

Subgroup analysis

Subgroup analysis according to the tumor type

In order to explore the relationship between EGFR-TKIs associated AEs and tumor types, we further analyzed the RRs of AEs in patients with NSCLC and non-NSCLC (Table 4). For all-grade mucositis ($p < 0.001$), nausea ($p = 0.016$), and high-grade vascular disorders ($p = 0.002$), there were significant differences in the RRs by type of cancer. All-grade mucositis and high-grade vascular disorders were more likely to occur in patients with NSCLC than with non-NSCLC, whereas all-grade nausea was more likely to occur in patients with non-NSCLC than with NSCLC.

Subgroup analysis according to the generation line

Studies were further stratified according to the generation line of EGFR-TKIs (first-, second-, or third-generation; Table 5). Erlotinib and gefitinib were first-generation EGFR-TKIs, afatinib, dacomitinib, lapatinib, neratinib, and vandetanib were second-generation EGFR-TKIs, and osimertinib was third-generation EGFR-TKI. There were significant differences in the RRs by generation line of EGFR-TKIs for all-grade fatigue ($p = 0.020$), nausea ($p = 0.030$), and high-grade diarrhea ($p = 0.029$), vascular disorders ($p = 0.002$), and fatigue ($p = 0.001$). Patients treated with second-generation EGFR-TKIs were more likely to occur all-grade fatigue, nausea, and high-grade vascular disorders and fatigue when compared with patients treated with first-generation EGFR-TKIs. Furthermore, second-generation EGFR-TKIs were associated with the highest risk of high-grade diarrhea compared with first- or third-generation EGFR-TKIs.

Subgroup analysis according to the agent used

In order to explore the impact of individual agents on the RRs of AEs, we calculated RRs based on the type of agent used (Table 6). For all-grade AEs, there were significant differences in the RRs by type of drug for diarrhea ($p < 0.001$), mucositis ($p < 0.001$), acne ($p < 0.001$), nausea ($p = 0.004$), decreased appetite ($p = 0.035$), dry skin ($p < 0.001$), dry mouth ($p = 0.003$), and vomiting ($p < 0.001$). Afatinib was associated with the highest risk of all-grade diarrhea (RR = 38.88) and dry mouth (RR = 6.89), dacomitinib was associated with the highest risk of all-grade mucositis (RR = 40.27), acne (RR = 16.72), dry skin (RR = 5.97), and vomiting (RR = 14.61), whereas neratinib was associated with the highest risk of all-grade nausea (RR = 2.75) and decreased appetite (RR = 4.67). Erlotinib was associated with the lowest risk of all-grade diarrhea (RR = 3.43), nausea (RR = 0.99), dry skin (RR = 1.54), and vomiting (RR = 0.86), lapatinib was associated with the lowest risk of all-grade mucositis (RR = 1.13), decreased appetite (RR = 0.94), and dry mouth (RR = 1.15), osimertinib was associated with the lowest risk of all-grade acne (RR = 2.52). For high-grade AEs, there were

TABLE 3 Summary RR of AEs with EGFR-TKIs

Outcome	Model	Number of studies	RR	Lower limit	Upper limit	*Z* value	*p* value
Toxic outcomes							
Serious AE	Random	17	1.20	1.05	1.37	2.653	0.008
Treatment discontinuation	Fixed	16	3.68	3.25	4.17	20.468	<0.001
Toxic death	Fixed	18	1.18	0.96	1.46	1.580	0.114
All grade							
Prolonged QTC	Fixed	2	24.56	3.37	179.05	3.158	0.002
Hypertension	Fixed	6	5.99	3.98	9.02	8.569	<0.001
Acne	Random	5	3.58	1.94	6.60	4.088	<0.001
Diarrhea	Random	25	3.32	2.82	3.92	14.312	<0.001
Dry skin	Random	11	3.19	2.41	4.23	8.067	<0.001
Stomatitis	Random	8	3.19	2.33	4.37	7.234	<0.001
Rash	Random	23	3.18	2.68	3.77	13.334	<0.001
ALT increased	Fixed	3	2.74	2.01	3.75	6.312	<0.001
Skin reaction	Random	2	1.91	0.83	4.38	1.532	0.125
Mucositis	Random	4	1.71	1.10	2.65	2.387	0.017
Dry mouth	Random	4	1.59	0.99	2.58	1.906	0.057
Vomiting	Random	16	1.37	1.11	1.69	2.947	0.003
Nausea	Random	20	1.31	1.10	1.58	2.966	0.003
Fatigue	Random	15	1.10	0.90	1.35	0.973	0.330
Asthenia	Fixed	9	1.06	0.91	1.24	0.794	0.427
Pain	Fixed	2	0.99	0.75	1.31	−0.076	0.939
Neutropenia	Fixed	4	0.91	0.72	1.16	−0.739	0.460
Cough	Fixed	9	0.91	0.81	1.04	−1.408	0.159
Radiation skin injury	Fixed	2	0.69	0.52	0.92	−2.513	0.012
High grade							
ECG QT prolonged	Fixed	2	9.90	1.94	50.48	2.757	0.006
Rash	Random	18	7.34	4.43	12.16	7.748	<0.001
Diarrhea	Random	21	7.32	5.05	10.61	10.516	<0.001
Hypertension	Fixed	4	6.69	1.91	23.51	2.967	0.003
Aminotransferases increased	Fixed	2	6.17	0.75	50.53	1.697	0.090
Photosensitivity reaction	Fixed	2	5.16	0.65	40.92	1.553	0.120
ALT increased	Fixed	3	3.32	0.94	11.76	1.862	0.063
Hypocalcemia	Fixed	3	2.87	0.55	15.00	1.246	0.213
Bilirubin increased	Fixed	2	2.11	0.28	16.14	0.721	0.471
Gastrointestinal disorders	Fixed	2	1.85	1.06	3.25	2.160	0.031
Vascular disorders	Random	2	1.55	0.68	3.56	1.043	0.297
Asthenia	Fixed	6	1.51	0.98	2.34	1.855	0.064
Metabolism and nutrition disorders	Fixed	2	1.42	0.90	2.23	1.524	0.127
Mucositis	Fixed	3	1.42	1.08	1.85	2.527	0.012
Fatigue	Random	16	1.24	0.89	1.72	1.265	0.206
Neutropenia	Fixed	3	1.23	0.84	1.81	1.057	0.290
Pain	Fixed	2	1.19	0.56	2.55	0.450	0.653
Infection	Fixed	6	1.05	0.71	1.55	0.235	0.814
Dyspnea	Fixed	9	0.92	0.82	1.04	−1.354	0.176

Abbreviations: AEs, adverse events; ALT, alanine aminotransferase; ECG, electrocardiogram; EGFR, epidermal growth factor receptor; RR, risk ratio; TKI, tyrosine kinase inhibitor.

TABLE 4 Summary RR of AEs with EGFR-TKIs in the subgroup analysis according to the tumor type

Outcomes	RR [95% CI]		*p* value for group difference
	Non-NSCLC	NSCLC	
Toxicity outcome			
Serious AE	1.15 [0.97, 1.37]	1.28 [1.03, 1.58]	0.470
Treatment discontinuation	3.95 [3.40, 4.60]	3.16 [2.54, 3.94]	0.102
Toxic death	1.27 [0.81, 2.00]	1.16 [0.92, 1.47]	0.719
All-grade			
Diarrhea	3.23 [2.56, 4.07]	3.40 [2.74, 4.23]	0.745
Rash	2.91 [2.18, 3.88]	3.47 [2.63, 4.58]	0.384
Mucositis	1.04 [0.94, 1.15]	24.30 [9.14, 64.60]	<0.001
ALT increased	2.66 [1.74, 4.07]	2.85 [1.79, 4.54]	0.834
Acne	2.95 [1.16, 7.52]	4.32 [1.59, 11.77]	0.586
Hypertension	5.67 [2.43, 13.26]	5.52 [2.46, 12.38]	0.965
Fatigue	1.34 [0.97, 1.84]	0.91 [0.66, 1.26]	0.099
Nausea	1.56 [1.28, 1.91]	1.10 [0.90, 1.35]	0.016
Prolonged QTC	34.53 [2.12, 563.53]	17.32 [1.03, 292.59]	0.734
Decreased appetite	1.63 [1.05, 2.52]	1.70 [1.15, 2.50]	0.894
Neutropenia	0.88 [0.68, 1.13]	1.36 [0.63, 2.95]	0.292
Dry skin	3.84 [2.08, 7.08]	3.02 [2.01, 4.55]	0.523
Dry mouth	1.42 [0.70, 2.88]	4.01 [1.05, 15.30]	0.180
Stomatitis	2.36 [0.82, 6.81]	5.14 [2.12, 12.47]	0.269
Asthenia	1.13 [0.90, 1.42]	1.02 [0.83, 1.25]	0.508
Vomiting	1.31 [0.89, 1.94]	1.44 [0.94, 2.21]	0.756
Cough	0.97 [0.56, 1.67]	0.91 [0.80, 1.04]	0.836
High-grade			
Mucositis	1.39 [1.06, 1.82]	14.56 [0.87, 243.05]	0.103
Pain	1.70 [0.64, 4.50]	0.68 [0.20, 2.31]	0.247
Metabolism and nutrition disorders	1.07 [0.55, 2.06]	1.84 [0.99, 3.42]	0.240
Diarrhea	5.94 [2.44, 14.67]	7.77 [3.28, 18.41]	0.671
Dyspnea	0.66 [0.11, 3.82]	0.93 [0.83, 1.04]	0.704
Hypertension	8.57 [1.17, 62.99]	5.69 [1.13, 28.66]	0.754
Vascular disorders	0.67 [0.31, 1.46]	4.90 [1.77, 13.56]	0.002
Rash	6.58 [2.19, 19.75]	13.66 [4.72, 39.51]	0.349
Neutropenia	1.25 [0.84, 1.86]	1.02 [0.22, 4.82]	0.806
ECG QT prolonged	7.71 [1.04, 56.99]	16.18 [0.97, 268.80]	0.674
Aminotransferases increased	7.47 [0.40, 138.58]	5.03 [0.24, 103.96]	0.854
Fatigue	2.03 [1.01, 4.07]	1.09 [0.66, 1.79]	0.153
ALT increased	3.88 [0.21, 71.38]	3.21 [0.79, 13.04]	0.908
Asthenia	1.59 [0.70, 3.58]	1.48 [0.88, 2.49]	0.888
Infection	1.15 [0.57, 2.33]	1.01 [0.63, 1.61]	0.760
Hypocalcemia	5.16 [0.65, 40.92]	1.01 [0.06, 15.92]	0.354

Abbreviations: AEs, adverse events; ALT, alanine aminotransferase; CI, confidence interval; ECG, electrocardiogram; EGFR, epidermal growth factor receptor; NSCLC, non-small cell lung cancer; RR, risk ratio; TKI, tyrosine kinase inhibitor.

significant differences in the RRs by type of drug for diarrhea ($p < 0.001$), vascular disorders ($p = 0.002$), rash ($p = 0.002$), and fatigue ($p = 0.001$). Dacomitinib was associated with the highest risk of high-grade diarrhea (RR = 68.10), vandetanib was associated with the highest risk of high-grade vascular disorders (RR = 5.16), erlotinib was associated with the highest risk of rash (RR = 54.09), and neratinib was associated with the highest risk of fatigue (RR = 3.88). In addition,

TABLE 5 Summary RR of AEs with EGFR-TKI in the subgroup analysis according to the generation line

Outcomes	RR [95% CI]			*p* value for group difference
	First-generation	Second-generation	Third-generation	
Toxicity outcome				
Serious AE	1.29 [0.99, 1.68]	1.16 [0.98, 1.38]	1.30 [0.75, 2.24]	0.779
Treatment discontinuation	3.24 [2.50, 4.20]	3.82 [3.31, 4.42]	3.74 [1.89, 7.41]	0.548
Toxic death	1.70 [1.15, 2.51]	1.03 [0.81, 1.32]	0.34 [0.01, 8.25]	0.078
All-grade				
Diarrhea	2.73 [2.04, 3.65]	3.74 [3.07, 4.55]	2.34 [1.20, 4.55]	0.120
Rash	3.96 [2.80, 5.61]	2.87 [2.25, 3.65]	–	0.133
ALT increased	2.60 [1.39, 4.86]	2.79 [1.95, 4.01]	–	0.847
Acne	3.96 [2.80, 5.61]	2.87 [2.25, 3.65]	–	0.133
Fatigue	0.70 [0.46, 1.09]	1.27 [1.00, 1.62]	–	0.020
Nausea	1.01 [0.76, 1.33]	1.44 [1.22, 1.71]	–	0.030
Decreased appetite	1.32 [0.81, 2.14]	1.78 [1.25, 2.53]	3.45 [1.01, 11.75]	0.304
Dry skin	2.52 [1.45, 4.36]	3.65 [2.38, 5.59]	3.66 [1.49, 8.97]	0.554
Stomatitis	3.31 [0.93, 11.84]	3.97 [1.41, 11.21]	4.29 [0.53, 34.45]	0.969
Asthenia	1.06 [0.82, 1.39]	1.08 [0.87, 1.34]	–	0.946
Vomiting	1.06 [0.64, 1.74]	1.55 [1.10, 2.18]	–	0.217
Cough	0.88 [0.72, 1.08]	0.89 [0.74, 1.07]	1.11 [0.80, 1.54]	0.457
High-grade				
Pain	0.68 [0.20, 2.31]	1.70 [0.64, 4.50]	–	0.247
Metabolism and nutrition disorders	1.07 [0.55, 2.06]	1.84 [0.99, 3.42]	–	0.240
Diarrhea	2.65 [1.12, 6.26]	11.47 [5.97, 22.05]	8.14 [0.61, 108.04]	0.029
Dyspnea	0.92 [0.82, 1.04]	0.93 [0.59, 1.48]	–	0.975
Vascular disorders	0.67 [0.31, 1.46]	4.90 [1.77, 13.56]	–	0.002
Rash	20.73 [4.68, 91.77]	7.34 [3.08, 17.50]	–	0.237
Gastrointestinal disorders	0.34 [0.01, 8.16]	1.96 [1.11, 3.46]	–	0.287
Aminotransferases increased	5.03 [0.24, 103.96]	7.47 [0.40, 138.58]	–	0.854
Fatigue	0.73 [0.48, 1.11]	2.17 [1.37, 3.42]	–	0.001
ALT increased	7.05 [0.37, 135.25]	2.81 [0.69, 11.37]	–	0.581
Alkaline phosphatase increased	3.04 [0.13, 73.47]	5.09 [0.25, 103.62]	–	0.817
Bilirubin increased	1.01 [0.06, 15.92]	5.09 [0.25, 103.62]	–	0.438
Asthenia	1.27 [0.72, 2.26]	1.92 [0.98, 3.78]	–	0.362
Infection	0.89 [0.42, 1.89]	1.11 [0.70, 1.76]	–	0.626
Hypocalcemia	1.01 [0.06, 15.92]	5.16 [0.65, 40.92]	–	0.354

Abbreviations: AEs, adverse events; ALT, alanine aminotransferase; CI, confidence interval; EGFR, epidermal growth factor receptor; RR, risk ratio; TKI, tyrosine kinase inhibitor.

gefitinib was associated with the lowest risk of high-grade diarrhea (RR = 1.12), vascular disorders (RR = 0.65), and fatigue (RR = 3.09), lapatinib was associated with the lowest risk of high-grade rash (RR = 0.66).

Quality of the studies and publication bias

The trials included in this study were assessed using the Jadad scoring system. Overall, the Jadad scores for each trial are listed in Table 1, and the median score was 4, indicating that the quality of the studies was satisfactory. Furthermore, the funnel plots of AEs profile identified in the current meta-analysis were relatively symmetrical, indicating that there is no significant publication bias.

DISCUSSION

With the discovery of EGFR pathway, a new set of effective and relatively safe EGFR-TKIs have been introduced for the treatment of patients with NSCLC, breast cancer, thyroid

TABLE 6 Summary RR of AEs with EGFR-TKI in the subgroup analysis according to the drug type

Outcomes	RR [95% CI]								*p* value for group difference
	Vandetanib	Afatinib	Dacomitinib	Erlotinib	Gefitinib	Lapatinib	Neratinib	Osimertinib	
Toxicity outcome									
Serious AE	1.83 [0.98, 3.43]	1.16 [0.53, 2.54]	1.13 [0.50, 2.53]	1.70 [0.93, 3.09]	1.24 [0.70, 2.19]	1.11 [0.70, 1.78]	1.23 [0.55, 2.73]	1.36 [0.58, 3.21]	0.922
Treatment discontinuation	3.80 [1.96, 7.37]	2.77 [1.09, 7.06]	11.74 [2.38, 57.99]	4.25 [2.43, 7.44]	2.36 [1.21, 4.60]	2.62 [1.43, 4.79]	6.65 [3.10, 14.27]	4.08 [1.48, 11.25]	0.341
Toxic death	1.04 [0.56, 1.95]	0.75 [0.26, 2.13]	0.95 [0.64, 1.41]	1.98 [0.76, 5.10]	1.69 [1.08, 2.64]	1.50 [0.80, 2.81]	–	0.34 [0.01, 8.28]	0.348
All-grade									
Diarrhea	6.12 [3.82, 9.82]	38.88 [19.21, 78.69]	19.74 [7.65, 50.92]	3.43 [2.07, 5.69]	3.79 [2.12, 6.79]	7.62 [4.80, 12.10]	37.64 [15.39, 92.07]	3.49 [1.39, 8.73]	<0.001
Rash	5.52 [2.96, 10.30]	16.60 [6.50, 42.39]	3.81 [0.93, 15.65]	8.91 [4.53, 17.53]	6.13 [2.76, 13.62]	4.11 [2.25, 7.51]	2.29 [0.64, 8.23]	–	0.125
Mucositis	–	–	40.27 [14.74, 110.03]	–	–	1.13 [0.84, 1.51]	–	–	<0.001
ALT increased	4.60 [2.84, 7.45]	–	–	–	3.03 [1.49, 6.17]	–	–	–	0.340
Acne	4.61 [2.58, 8.23]	–	16.72 [10.00, 27.94]	–	–	–	–	2.52 [1.37, 4.63]	<0.001
Fatigue	1.02 [0.44, 2.35]	1.93 [0.63, 5.97]	2.10 [0.43, 10.26]	0.70 [0.27, 1.79]	0.63 [0.12, 3.42]	1.25 [0.49, 3.21]	1.49 [0.32, 6.87]	–	0.792
Nausea	1.57 [1.12, 2.20]	1.33 [0.83, 2.11]	2.58 [1.37, 4.88]	0.99 [0.68, 1.45]	1.01 [0.68, 1.50]	1.46 [1.11, 1.93]	2.75 [1.79, 4.21]	–	0.004
Decreased appetite	1.66 [0.97, 2.86]	3.58 [1.63, 7.83]	3.34 [1.16, 9.61]	1.37 [0.79, 2.37]	1.28 [0.61, 2.67]	0.94 [0.48, 1.85]	4.67 [1.75, 12.45]	3.81 [1.25, 11.64]	0.035
Neutropenia	1.65 [0.82, 3.31]	–	–	–	–	0.79 [0.56, 1.10]	–	–	0.061
Dry skin	3.88 [1.55, 9.71]	2.92 [1.85, 4.60]	5.97 [3.46, 10.28]	1.54 [1.08, 2.20]	3.76 [2.42, 5.86]	5.53 [3.98, 7.68]	–	4.47 [2.71, 7.37]	<0.001
Dry mouth	–	6.89 [1.62, 29.31]	4.28 [1.67, 11.00]	–	–	1.15 [0.86, 1.54]	–	–	0.003
Stomatitis	–	20.17 [4.55, 89.52]	–	5.66 [1.13, 28.37]	1.58 [0.20, 12.18]	1.75 [0.42, 7.33]	–	4.99 [0.63, 39.67]	0.156
Asthenia	1.16 [0.83, 1.64]	–	–	1.26 [0.77, 2.05]	0.99 [0.73, 1.34]	1.09 [0.76, 1.58]	–	–	0.841
Vomiting	1.24 [0.75, 2.05]	1.46 [0.86, 2.49]	14.61 [4.80, 44.50]	0.86 [0.55, 1.33]	1.48 [0.92, 2.37]	1.29 [0.92, 1.81]	4.11 [2.46, 6.87]	–	<0.001
Cough	0.96 [0.71, 1.30]	0.64 [0.40, 1.02]	–	0.98 [0.71, 1.37]	0.73 [0.51, 1.03]	0.80 [0.30, 2.12]	–	1.13 [0.76, 1.68]	0.387
High-grade									
Mucositis	–	–	14.99 [0.89, 252.28]	–	–	1.53 [1.08, 2.16]	–	–	0.115
Pain	–	–	–	–	0.66 [0.18, 2.42]	1.78 [0.62, 5.11]	–	–	0.244
Metabolism and nutrition disorders	1.90 [0.99, 3.65]	–	–	–	1.07 [0.53, 2.18]	–	–	–	0.244
Diarrhea	8.94 [3.18, 25.13]	30.04 [5.16, 175.05]	68.10 [3.61, 1286.19]	10.59 [3.51, 31.91]	1.12 [0.46, 2.72]	7.74 [3.44, 17.42]	40.00 [14.41, 111.07]	8.32 [0.85, 81.45]	<0.001
Dyspnea	0.95 [0.52, 1.75]	0.90 [0.41, 1.98]	–	0.81 [0.60, 1.10]	0.95 [0.60, 1.50]	–	–	–	0.935
Vascular disorders	5.16 [1.83, 14.57]	–	–	–	0.65 [0.29, 1.49]	–	–	–	0.002

(Continues)

TABLE 6 (Continued)

Outcomes	RR [95% CI]								*p* value for group difference
	Vandetanib	Afatinib	Dacomitinib	Erlotinib	Gefitinib	Lapatinib	Neratinib	Osimertinib	
Rash	5.96 [1.87, 18.93]	43.92 [8.72, 221.13]	11.81 [0.69, 201.24]	54.09 [13.31, 219.84]	7.68 [1.43, 41.27]	3.09 [1.76, 5.40]	11.04 [0.61, 199.83]	–	0.002
Neutropenia	0.62 [0.16, 2.41]	–	–	–	–	1.36 [0.86, 2.15]	–	–	0.281
Gastrointestinal disorders	2.05 [1.12, 3.75]	–	–	–	0.33 [0.01, 8.30]	–	–	–	0.276
Aminotransferases increased	–	–	–	–	5.10 [0.24, 107.21]	8.32 [0.41, 168.45]	–	–	0.823
Fatigue	1.36 [0.74, 2.51]	3.03 [1.02, 8.96]	1.65 [0.53, 5.10]	0.79 [0.58, 1.07]	0.66 [0.37, 1.16]	3.02 [1.09, 8.36]	3.88 [1.58, 9.56]	–	0.001
ALT increased	2.98 [0.69, 12.84]	–	–	–	7.19 [0.37, 140.51]	–	–	–	0.601
Alkaline phosphatase increased	5.30 [0.25, 113.04]	–	–	–	3.07 [0.12, 76.45]	–	–	–	0.810
Bilirubin increased	5.30 [0.25, 113.04]	–	–	–	1.01 [0.06, 16.45]	–	–	–	0.433
Asthenia	2.41 [1.02, 5.70]	–	–	2.82 [0.33, 24.25]	1.20 [0.65, 2.22]	1.36 [0.43, 4.31]	–	–	0.572
Infection	1.10 [0.65, 1.88]	–	–	0.50 [0.12, 2.10]	1.12 [0.45, 2.82]	1.22 [0.35, 4.23]	–	–	0.769
Hypocalcemia	5.30 [0.66, 42.82]	–	–	–	1.01 [0.06, 16.45]	–	–	–	0.352

Abbreviations: AEs, adverse events; ALT, alanine aminotransferase; CI, confidence interval; EGFR, epidermal growth factor receptor; RR, risk ratio; TKI, tyrosine kinase inhibitor.

cancer, head and neck cancer, and other types of cancers. In recent years, EGFR-TKIs have been extensively studied in patients with various cancer and approved as first line, greater than or equal to second line, maintenance, or adjuvant therapy.[18,35–38] Drug-related AEs are an essential problem for patients treated with EGFR-TKIs in clinical practice, which may lead to treatment discontinuation and poor patient adherence. To the best of our knowledge, accurate analysis of EGFR-TKIs-related AEs has not yet been fully investigated. Hence, in this systematic review, we summarize the safety profile of EGFR-TKIs in patients with cancer.

Our results suggested a significantly increased risk of a variety of AEs with the use of EGFR-TKIs compared with placebo. Among EGFR-TKI-related AEs of all grades, diarrhea (53.7%), rash (48.6%), mucositis (46.5%), ALT increase (38.9%), and skin reaction (35.2%) were the most common. The most common grade 3 or more AEs were mucositis (14.8%), pain (8.2%), metabolism and nutrition disorders (7.4%), diarrhea (6.2%), dyspnea (6.1%), and hypertension (6.1%). For all-grade AEs, EGFR-TKIs significantly increased the risk of prolonged QTC, hypertension, acne, diarrhea, dry skin, stomatitis, rash, and ALT. For high-grade AEs, ECG QT prolonged, rash, diarrhea, and hypertension had a higher occurrence in patients receiving EGFR-TKIs versus placebo. EGFR is a receptor tyrosine kinase that is expressed on almost all normal cell surfaces, especially on those of epithelial origin, such as digestive tract, skin, and liver, which might be the reasons that EGFR-TKIs are commonly associated with rash, diarrhea, mucositis, and ALT increase.[39,40]

In order to identify the potential risk factors, we performed subgroup analysis according to tumor types. Patients with NSCLC showed a significantly increased risk of all-grade mucositis and high-grade vascular disorders compared with patients with non-NSCLC, whereas all-grade nausea was more likely to occur in patients with non-NSCLC than with NSCLC. This could be attributed to the reason that different tumors have distinct pathogeneses and different responses for EGFR-TKIs treatment. However, the RRs of some common AEs, such as all-grade diarrhea, rash, high-grade mucositis, and pain did not vary differently according to tumor types. These results were inconsistent with the findings from previous meta-analysis conducted by Li et al.[40] In their study, all-grade diarrhea was more likely to occur in patients with NSCLC (RR = 4.01) than with non-NSCLC (RR = 2.81). The discrepancy can be explained by the differences in the numbers of patients enrolled. Our study included more patients than previous meta-analysis, and could provide more precisive information for the risk of EGFR-TKIs related AEs. When stratified by generation line, our results showed that second-generation EGFR-TKIs were associated with the highest risk of all-grade fatigue, nausea, and high-grade diarrhea, vascular disorders, and fatigue. The possible explanation was that first-generation EGFR-TKIs were reversible inhibitors, whereas second-generation EGFR-TKIs were irreversible inhibitors that had higher affinity for the kinase domain of EGFR, which may lead to the higher risk of AEs.

In addition, subgroup analysis was performed to examine whether the RRs of AEs varied by the type of drug. The risk of AEs varied significantly according to drug types. It was noteworthy that afatinib was associated with the highest risk of all-grade diarrhea and dry mouth, dacomitinib was associated with the highest risk of all-grade mucositis, acne, dry skin, vomiting, and high-grade diarrhea, neratinib was associated with the highest risk of all-grade nausea, decreased appetite, and high-grade fatigue, vandetanib was associated with the highest risk of vascular disorders, and erlotinib was associated with the highest risk of high-grade rash. One proposed theory is that different EGFR-TKIs have different structure and pharmacokinetics, and target different receptors, which may lead to different risk of AEs. The differences in the safety profile of different EGFR-TKIs may have an impact on the clinical decision making, and clinicians must pay attention when using these EGFR-TKIs.

This study has several limitations. First, the data analyzed in this study were extracted from published clinical trials and were not on the patient level. Second, CTCAE versions for recording AEs from the incorporated trials were different, which may contribute to the change in some AEs grading, such as hypertension and rash, leading to the heterogeneity among different studies. Third, the top 20 all-grade and high-grade AEs determined by our meta-analysis were not reported by all included trials, which may lead to reduced power of subgroup analysis to reach a definitive conclusion. Fourth, the present study mainly included RCTs concerning lapatinib, vandetanib, erlotinib, gefitinib, with only two trials concerning afatinib, one trial concerning dacomitinib, one trial concerning neratinib, and one trial concerning osimertinib. Hence, afatinib-, dacomitinib-, neratinib-, and osimertinib-related AEs may not be fully reviewed in our study.

CONCLUSION

In conclusion, our study showed a unique safety profile of EGFR-TKIs, which is characterized mainly by diarrhea, rash, and mucositis. This finding will provide clinicians and patients a comprehensive recognition of the risk of EGFR-TKI-related AEs. Early detection and proper management of AEs are important to reduce morbidity, avoid treatment discontinuation, and improve patient quality of life. In addition, the integrated understanding of toxicity profile of EGFR-TKIs will help in the future design of new EGFR-TKIs with a better safety profile.

CONFLICTS OF INTERESTS

The other authors declared no competing interests for this work.

AUTHOR CONTRIBUTION

X.Y. and Z.Z. wrote the manuscript. Y.Y. and B.Z. designed the research. Z.Z., Z. Cai, J.W., and Z. Chen performed the research. X.Y., Y.Y., C.S., and X.C. analyzed the data.

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