Original Article

Risk of treatment-related toxicity from EGFR tyrosine kinase inhibitors: a systematic review and network meta-analysis of randomized clinical trials in *EGFR*-mutant non-small cell lung cancer

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Background: Epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) are effective for non-small cell lung cancer (NSCLC) patients with *EGFR*-mutation, while their toxicity profiles are non-negligible and inconsistent. This study aimed to assess the toxicity intensity and profiles of different EGFR-TKIs in NSCLC patients with *EGFR*-mutation.

Methods: This random-effect Bayesian framed network meta-analysis (NMA) only included exclusively randomized clinical trials with demonstrated evidence on safety of EGFR-TKIs in NSCLC patients with EGFR-mutation. Pooled odds ratios and surface under the cumulative ranking curve (SUCRA) were calculated to depict the toxicity map of EGFR-TKIs.

Results: This review included 23 randomized clinical trials incorporating 7,006 patients and 11 treatments: erlotinib, gefitinib, icotinib, afatinib, dacomitinib, osimertinib, furmonertinib, aumolertinib, pemetrexed-free chemotherapy (PfCT), pemetrexed-based chemotherapy (PbCT) and placebo. Overall, chemotherapy and second-generation EGFR-TKIs exhibited higher toxicity. A toxicity sequence according to the likelihood of causing grade ≥3 adverse events (AEs) was identified as follows: PfCT > PbCT > afatinib > dacomitinib > erlotinib > aumolertinib > gefitinib > furmonertinib > osimertinib > placebo > icotinib. For discontinuation due to AEs, among EGFR-TKIs, icotinib and afatinib demonstrated best and second-best safety profiles according to pooled odds ratios and SUCRA. Regarding specific toxicity, EGFR-TKIs demonstrated variable toxicity intensity and different predominate toxicity spectrums.

Conclusions: This is the first study to depict the difference in toxicity of EGFR-TKIs in a population with EGFR-mutant NSCLC. In general, osimertinib and icotinib were associated with favorable safety compared with other EGFR-TKIs. Difference in safety between the third-generation EGFR-TKIs was also first investigated comprehensively. Furthermore, this review elaborated the varied predominate spectrum and

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ranked the toxicity of EGFR-TKIs for providing toxicity rationale for treatment decisions.

Keywords: Non-small cell lung cancer (NSCLC); epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs); toxicity; adverse events (AEs)

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Introduction

Lung cancer is one of the most prevalent malignant tumors and the leading cause of cancer-related mortality globally (1). Among its histological variants, non-small cell lung cancer (NSCLC) constitutes the predominant diagnostic entity (accounting for 85% of cases). Epidermal growth factor receptor (*EGFR*) mutations comprise a clinically significant proportion of targetable oncogenic drivers in NSCLC and are typically observed in never-smokers, Asians, females, and those with adenocarcinoma (2). In recent years, the treatments for patients with unresectable NSCLC have entered the precision era, in which targeted therapies have demonstrated their superiority over cytotoxic treatments both in efficacy and safety. EGFR tyrosine kinase inhibitors (TKIs), as successful molecular targeted agents, can drastically improve the overall survival and progression-free survival of patients with *EGFR*-mutant NSCLC (3-17). Thus far, three generations of EGFR-TKIs have been used in clinical practice: first-generation TKIs (erlotinib, gefitinib, icotinib), second-generation TKIs (afatinib, dacomitinib), and third-generation TKIs (osimertinib, furmonertinib, aumolertinib). A majority of these agents have been established as the standard first-line treatments of *EGFR*-mutant NSCLC (18). Furthermore, owing to their evident clinical benefits, EGFR-TKIs have extended their application range to encompass patients with resectable NSCLC as adjuvant or neoadjuvant treatments in recent years (4,11,14-16,19).

NSCLC typically occurs in the older adult population, potentially leading to a decrease in patients' physical performance and quality of life (QoL). Ensuring treatment safety, improving QoL, and increasing overall survival share equal importance in managing NSCLC. In comparison to cytotoxic treatments, EGFR-TKIs offer less treatment-related toxicity and improved QoL (3-17). Most adverse events (AEs) associated with EGFR-TKIs are of mild to moderate intensity, with dermatological and gastrointestinal effects being the most frequent toxic AEs (2). Although EGFR-TKIs are generally well tolerated, severe AEs that can impair QoL and even threaten life. In addition, on account of the differences in structure and inhibition of EGFR tyrosine kinase, EGFR-TKIs have demonstrated an inconsistent toxicity intensity and profile (2). Given this context, oncologist should carefully weigh the tradeoffs between efficacy and toxicity and recommend the most suitable EGFR-TKI based on the individual patient's circumstances.

The majority of previous randomized controlled trials (RCTs) have been conducted with chemotherapy as the control group (4-11,13-17). Consequently, there are limited head-to-head studies comparing the toxicity and QoL improvements associated with different EGFR-TKIs. In addition, the direct evidence for the different toxicity profiles between second- and third-generation TKIs is

Highlight box

Key findings

- Osimertinib and icotinib were associated with favorable safety compared with other epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs), and second-generation EGFR-TKIs were associated with elevated toxicity. A toxicity sequence according to the likelihood of causing grade ≥3 adverse events was identified as follows: aumolertinib > furmonertinib > osimertinib.

What is known and what is new?

- The randomized controlled trials provide direct evidence for the different toxicity profiles between second/third-generation EGFR-TKIs and first-generation EGFR-TKIs.
- This is the first study to depict the difference in toxicity of EGFR-TKIs in a population with EGFR-mutant non-small cell lung cancer. Difference in safety among the third-generation EGFR-TKIs was also first investigated comprehensively.

What is the implication, and what should change now?

- This review elaborated the varied predominate spectrum and ranked the toxicity of EGFR-TKIs, which could serve as reference and inform the toxicity rationale for treatment decision-making.

insufficient because most RCTs have been controlled with first-generation TKIs (20-24). Although a previous network meta-analysis (NMA) (25) attempted to characterize these profiles across all lung cancers, patients with wild-type *EGFR* were synthesized, which may not accurately meet the current clinical therapeutic scope of EGFR-TKIs. In order to provide precise and personalized care for patients with a more comprehensive benefit, a map of the evidence characterizing the toxicity profile and QoL of EGFR-TKIs is needed. To this end, we conducted a NMA that compared all available EGFR-TKIs. We present this article in accordance with the PRISMA NMA reporting checklist (26) (available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-682/rc).

Methods

This systematic review and NMA of RCTs was prospectively registered with PROSPERO (International Prospective Register of Systematic Reviews; CRD42023409589).

Study search and selection

Studies were identified from PubMed, Embase, Web of Science, and the Cochrane Central Register of Controlled Trials without language restrictions from database inception to June 17, 2023. The search terms including "NSCLC", "EGFR kinase inhibitor" and drug names were used in combination or alone (see the detailed strategy in Table S1). References of reviews or guidelines in relevant articles were manually searched. Abstracts, contents, and titles yielded from the search strategy were screened according to previously formulated criteria. Any discrepancies between reviewers (H.C. and S.H.) were discussed, and the senior reviewer (B.Q.) resolved any unsettled disagreements.

Selection of studies

This study only included phase II/III RCTs which met the following inclusion criteria.

This study only included patients with cytologically or histologically confirmed *EGFR*-mutant NSCLC; RCTs that compared EGFR-TKI monotherapy with corresponding treatment according to the clinical staging of NSCLC and metastasis status, including placebo, chemotherapy, or another EGFR-TKI monotherapy; RCTs that had one or more of the following (reporting number or percentages of patients): overall grade ≥3 AEs; discontinuation due to AEs, all-grade specific AEs including rash, anemia, elevated liver enzymes, etc.; and QoL improvement meeting the minimal clinical difference (MCD) measured by self-reported questionnaires.

Meanwhile, the exclusion criteria were as follows: RCTs that combined EGFR-TKIs with other regimens (such as chemotherapy, immunotherapy, or another EGFR-TKI) as treatment and RCTs that compared regimens without approval of any national food and drug administration.

For studies with more than one affiliated published article, the more comprehensive and updated reporting data for each outcome was utilized.

Data extraction

Relevant information of each study was noted on a standardized spreadsheet and included study ID, year of publication, demographic characteristics at baseline, and treatment information, as shown in *Table 1* (3-11,13-17, 19-24,27-29). Toxicity data including AEs (grade ≥3), discontinuation due to AEs, specific category of AEs (all grades), and QoL improvement were recorded on a predesigned list. Proportion of patients who reached clinical QoL improvement were collected for comparing QoL improvement of EGFR-TKIs. We preferred to collect data for treatment-related AEs. If not available, we collected overall AEs. In order to collect the most comprehensive and recent data, we also used ClinicalTrials.gov. Data extraction was carefully double-checked by H.C. and S.H. to ensure accuracy. Any disagreement was resolved by discussing with the third reviewer (B.Q.).

EGFR-TKIs were grouped into common treatment nodes based on the drug. The vast majority of NSCLC cases harboring *EGFR* mutations were non-squamous carcinoma, in which the efficacy of pemetrexed was proven to be better compared with other third-generation chemotherapeutic drugs (30,31). Therefore, pemetrexed-free chemotherapy (PfCT) and pemetrexed-based chemotherapy (PbCT) were synthesized into the NMA as two treatment nodes.

Data synthesis and statistical analysis

This Bayesian-framed NMA synthesized multiple available direct and indirect evidence sources for measuring toxicity. The total numbers of grade ≥3 AEs, discontinuation due to AEs, and the number of each specific AE (all grades) were synthesized for overall and specific toxicity. Statistical analyses were performed with JAGS (Just Another

Table 1 Baseline characteristics of studies included in the network meta-analysis

Study (phase, ethnicity)	Sample size (No.)	Age (median or mean, years)	Sex (female, %)	EGFR mutation			Staging (%)	Intervention arm	Control arm	Smoking status (current or former, %)	HRQoL assessment	ECOG PS 0 or 1 (%)	RoB
				Exon 19 deletion (%)	Exon 21 Leu858Arg (%)	Other (%)							
LUX-Lung 6 2014 (III, Asian) (3)	242/122	58/58	64.0/68.0	51/51	38/38	11/11	IIIB 6.0; IV 94.0	Afatinib 40 mg qd	PfCT (gemcitabine 1,000 mg/m^2 + cisplatin 75 mg/m^2 every 3 weeks)	23.1	EORTC QLQ-C30, QLQ-LC13	100	High
EVIDENCE 2021 (III, Asian) (4)	151/132	60/58	49.0/58.3	53/53	47/47	0	IIA 31.1; IIB 4.9; IIIA 64.0	Icotinib 125 mg tid	PfCT (25 mg/m^2 vinorelbine on day 1 and day 8 + 75 mg/m^2 cisplatin every 3 weeks)	31.4	FACT-L, LCS	100	Low
NEJ002 2010 (III, Asian) (5)	114/110	63.9/62.6*	63.2/64.0	51/54	43/44	6/2	IIIB 16.1; IV 76.8; others 7.1	Gefitinib 250 mg qd	PfCT (paclitaxel 200 mg/m^2 + carboplatin AUC =6, every 3 weeks)	38.8	N/A	98.7	Unclear
WJTOG3405 2010 (III, Asian) (6)	86/86	64/64	68.6/69.8	58/43	42/47	0/10	IIIB 11.0; IV 47.7; others 41.3	Gefitinib 250 mg qd	PfCT (cisplatin 80 mg/m^2 + docetaxel 60 mg/m^2 every 3 weeks)	31.4	N/A	100	High
AURA3 2017 (III, multiple) (7)	279/140	62/63	61.6/69.3	68/62	30/32	2/6	IIIB 3.8; IV 96.2	Osimertinib 80 mg qd	PbCT (pemetrexed 500 mg/m^2 + cisplatin 75 mg/m^2, every 3 weeks)	47.3	EORTC QLQ-C30, QLQ-LC13	N/A	High
EURTAC 2012 (III, non-Asian) (8)	86/87	65/65	67.0/78.0	66/67	34/33	0	IIIB 6.4; IV 92.5; others 1.1	Erlotinib 150 mg qd	PfCT (cisplatin 75 mg/m^2 + docetaxel 75 mg/m^2/gemcitabine 1,250 mg/m^2 every 3 weeks)	30.6	N/A	86.7	High
LUX-Lung 3 2013 (III, multiple) (9)	230/115	61.5/61.0	63.9/67.0	49/50	40/41	11/9	IIIB 10.7; IV 89.3	Afatinib 40 mg qd	PbCT (cisplatin 75 mg/m^2 + pemetrexed 500 mg/m^2 every 3 weeks)	31.6	EORTC QLQ-C30, QLQ-LC13	99.7	High
CONVINCE 2017 (III, Asian) (10)	148/137	56/56	70.9/69.3	50/50	43/39	7/11	IIIB 10.2; IV 89.8	Icotinib 125 mg tid	PbCT (cisplatin 75 mg/m^2 + pemetrexed 500 mg/m^2 every 3 weeks (4 cycles) + pemetrexed 500 mg/m^2 every 3 weeks)	21.4	N/A	95.1	High
IMPACT 2022 (III, Asian) (11)	116/116	64/64	61.2/62.1	55/51	45/48	0/1	IIA 31.9; IIB 3.9; IIIA 62.1; IIIB 2.1	Gefitinib 250 mg qd	PfCT (25 mg/m^2 vinorelbine on day 1 and day 8 + 75 mg/m^2 cisplatin every 3 weeks)	38.8	N/A	100	Low
ENSURE 2015 (III, Asian) (13)	110/107	57.5/56.0	61.8/60.7	52/57	48/43	0	IIIB 7.8; IV 92.2	Erlotinib 150 mg qd	PfCT (gemcitabine 1,250 mg/m^2 + cisplatin 75 mg/m^2 every 3 weeks)	29.5	N/A	94.0	High
EVAN 2018 (II, Asian) (14)	51/51	59/57	66.8/60.8	59/55	41/43	0/2	IIIA 100	Erlotinib 150 mg qd	PfCT (25 mg/m^2 vinorelbine on day 1 and day 8 + 75 mg/m^2 cisplatin every 3 weeks)	24.5	N/A	98	Low
EMERGING-CTONG 1103 2019 (II, Asian) (15)	37/35	59/58	70.3/77.1	43/51	57/49	0	IIIA 100	Erlotinib 150 mg qd	PfCT (gemcitabine 1,250 mg/m^2 + cisplatin 75 mg/m^2 every 3 weeks)	16.7	N/A	100	High
ADJUVANT 2018 (III, Asian) (16)	106/87	59/59	59.4/57.5	54/55	46/45	0	IIA 29.5; IIB 3.1; IIIA 66.8	Gefitinib 250 mg qd	PfCT (25 mg/m^2 vinorelbine on day 1 and day 8 + 75 mg/m^2 cisplatin every 3 weeks)	21.2	FACT-L, LCS	99	Low
OPTIMAL 2011 (III, Asian) (17)	83/72	57/59	59.0/60.0	52/54	48/46	0	IIIB 10.4; IV 88.6	Erlotinib 150 mg qd	PfCT (gemcitabine 1,000 mg/m^2 + cisplatin AUC =5 every 3 weeks)	29.2	FACT-L, LCS	93.5	High
ADAURA 2020 (III, multiple) (19)	339/343	64/62	67.8/72.0	55/55	45/45	0	IB 32; II 34; IIIA 34	Osimertinib 80 mg qd	Placebo	28.4	N/A	N/A	Low
ARCHER1050 2017 (III, multiple) (20)	227/225	62/61	64.0/56.0	59/59	41/41	0	IIIB 7.5; IV 81.0; others 11.5	Dacomitinib 45 mg qd	Gefitinib 250 mg qd	36	EORTC QLQ-C30, QLQ-LC13	100	High
FLAURA 2018 (III, multiple) (21)	279/277	64/64	64.0/62.0	63/63	37/37	0	IIIB 5.2; IV 94.6; others 0.2	Osimertinib 80 mg qd	Gefitinib 250 mg qd	35.7	EORTC QLQ-C30, QLQ-LC13	100	Low
				63/63	37/37				Erlotinib 150 mg qd				
FURLONG 2022 (III, Asian) (22)	178/179	59/60	65.2/62.0	51/51	49/49	0	IIIB 4.8; IV 95.2	Furmonertinib 80 mg qd	Gefitinib 250 mg qd	23.8	EORTC QLQ-C30	99.8	Low
LUX-Lung7 2016 (IIB, multiple) (23)	160/159	63/63	57.0/67.0	58/58	42/42	0	IIIB 3.4; IV 96.6	Afatinib 40 mg qd	Gefitinib 250 mg qd	33.5	EQ-VAS, EQ-5D	30.7	High
AENEAS 2022 (III, Asian) (24)	214/215	59/62	62.6/62.8	66/66	34/34	0	IIIB 6.8; IV 93.2	Aumolertinib 110 mg qd	Gefitinib 250 mg qd	30.1	N/A	98.8	Unclear
WJOG5108L 2016 (III, Asian) (27)	198/203	68/67	63.6/54.3	92/90		8/10	IIIB 8.2; IV 69.2; others 22.6	Gefitinib 250 mg qd	Erlotinib 150 mg qd	50.0	N/A	100	High
CTONG0901 2017 (III, Asian) (28)	128/128	58.5	46.9/53.1	58/58	42/42	0	IIIB 2.8; IV 97.2	Erlotinib 150 mg qd	Gefitinib 250 mg qd	22.7	N/A	97.7	Unclear
E100VG250 2020 (II, Asian) (29)	74/83	57/56	50.0/59.0	62/54	36/43	2/3	IIIB 2; IV 98	Erlotinib 100 mg qd	Gefitinib 250 mg qd	N/A	N/A	96	High

Data are expressed as intervention/control unless indicated otherwise. *, mean age was given instead of median age. EGFR, epidermal growth factor receptor; HRQoL, health-related quality of life; ECOG PS, Eastern Cooperative Oncology Group performance status; RoB, risk of bias; qd, quaque die (means once a day); PfCT, pemetrexed-free chemotherapy; PbCT, pemetrexed-based chemotherapy; AUC, area under the curve; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-core 30; EORTC QLQ-LC13, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Lung Cancer 13; FACT-L, Functional Assessment of Cancer Therapy—Lung Cancer questionnaire; LCS, Lung Cancer Symptom Scale; N/A, not available; EQ-VAS, EuroQoL visual analogue scale; EQ-5D, EuroQoL-5D health status self-assessment questionnaire.

Gibbs Sampler) 4.3.0 (https://CRAN.R-project.org/package=R2jags) and the "gemtc" package in R software version 4.2.1. The Markov chain Monte Carlo method was used to perform NMA in the Bayesian framework. The goodness of fit of the fixed and random effects models for primary outcomes (overall grade ≥3 AEs and discontinuation due to AEs) were evaluated (32) (Table S2). Random effect models were preferred due to lower deviance information criterion (DIC). The surface under the cumulative ranking curve (SUCRA) was calculated and plotted using GraphPad Prism software (version 8.0.2), in which a larger SUCRA represented more AEs, more discontinuations, or greater QoL improvement (33). Statistical heterogeneity was interpreted with the I^2 statistic.

To evaluate the robustness of results, sensitivity analysis was conducted for the primary outcomes (grade ≥3 AEs and discontinuation due to AEs). The first sensitivity analysis only involved 19 phase III randomized trials. The second sensitivity analysis involved all RCTs that included patients with advanced NSCLC.

Two important assumptions of NMA (consistency and transitivity) (34) were evaluated. Global consistency was validated by comparing the goodness of fit of the inconsistency and consistency model (35,36). The local inconsistency was examined through the node-splitting approach which compared direct and indirect estimates of the same comparison. In terms of transitivity, we only included trials with strict randomization and allocation concealment to reduce the potential bias of transitivity. In addition, the similarity of population characteristics of RCTs including the female ratio, smoking status, and *EGFR* mutation types was assessed.

Risk of bias and certainty of evidence

To assess the risk of bias of individual studies, we used the Cochrane risk of bias tool, which is based on domains of randomization, allocation concealment, blinding, attrition, reporting, and other potential bias. Two reviewers (R.L. and S.H.) independently assessed the risk of bias, and any discrepancies were resolved via discussion. In order to provide a quality rating of the estimates for specific comparisons, Grading of Recommendations Assessment Development and Evaluation (GRADE) criteria for NMA was used (37,38). As all of the included studies were RCTs, the quality rating started with high certainty and could be downrated to moderate, low, or very low certainty. Quality rating may be downgraded due to study limitation (relatively high risk of bias), imprecision (95% credible intervals include null effects), indirectness (intransitivity), or inconsistency (heterogeneity across trials assessing specific comparisons or significant differences across direct and indirect estimates) (39).

Results

Characteristics of included studies

After removing the duplicated articles, a total of 4,928 records remained from the database and manual searches (*Figure 1*). Subsequently, titles and abstracts were screened, after which the full text of 69 articles was checked. Finally, 23 RCTs (3-11,13-17,19-24,27-29) comprising 7,006 patients were assessed as being eligible for inclusion into the NMA.

Patients with NSCLC and confirmed *EGFR*-activating mutations were analyzed. Treatments included placebo, chemotherapy (PbCT and PfCT), and multiple EGFR-TKIs (erlotinib, gefitinib, icotinib, afatinib, dacomitinib, osimertinib, aumolertinib, furmonertinib). The network plot for eligible comparisons for toxicity is shown in *Figure 2*. A full description of demographic characteristics, interventions, outcomes, and study designs are presented in *Table 1*.

The transitivity was acceptable, as the included RCTs exhibited similar clinical features and population characteristics (Figure S1), and the local consistency was also acceptable. According to the node-splitting approach, there was a significant difference between the indirect estimate and direct estimate in one comparison (Table S3) of PfCT versus gefitinib (P=0.02) for discontinuation due to AEs. Furthermore, the global consistency was acceptable, as the DIC of the consistency model was close to that of the inconsistency model (Table S2). Heterogeneity in direct estimates of same comparison was found in gefitinib versus erlotinib, PfCT versus erlotinib, and PfCT versus gefitinib for grade ≥3 AEs (Figure S2).

Risk of bias

Risk of bias was evaluated using the Cochrane risk of bias tool. Seven trials were regarded as having a low risk of bias (4,11,14,16,19,21,22), 3 trials (5,24,28) an unclear risk of bias, and 13 trials (3,6-10,13,15,17,20,23,27,29) a high risk of bias. All 13 trials with a high bias risk were not blinded to patients or personnel, 3 of which exhibited other high-

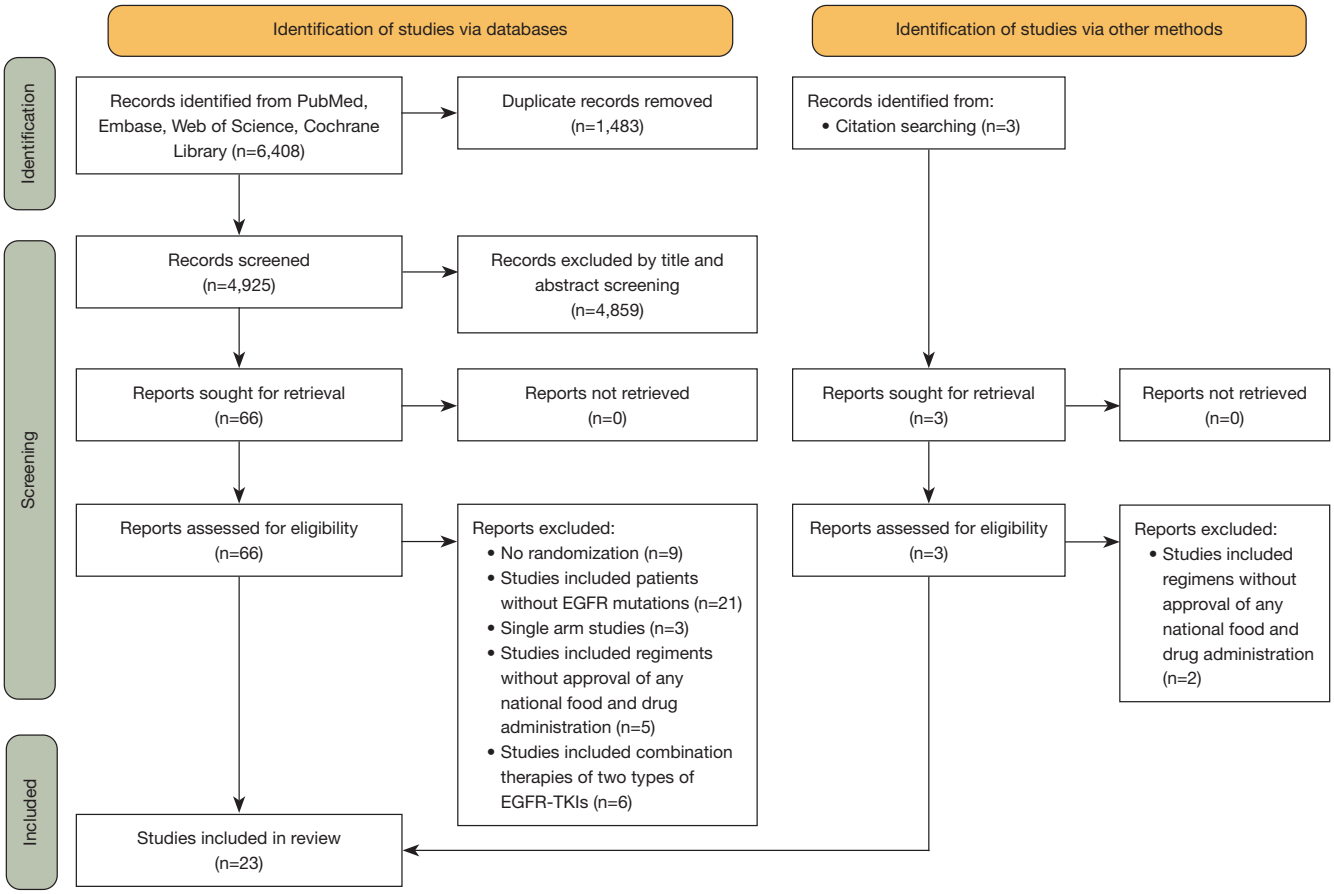


Figure 1 Study selection. EGFR-TKIs, epidermal growth factor receptor tyrosine kinase inhibitors.

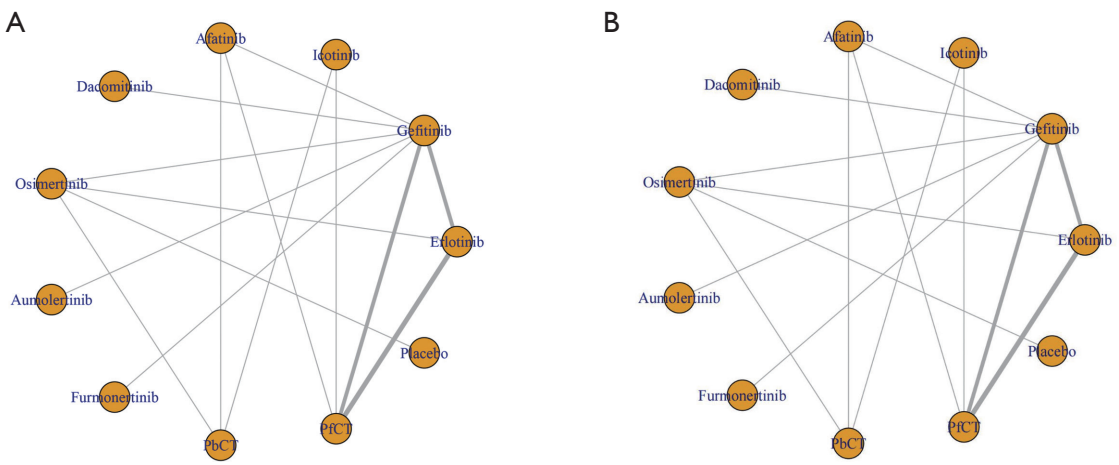


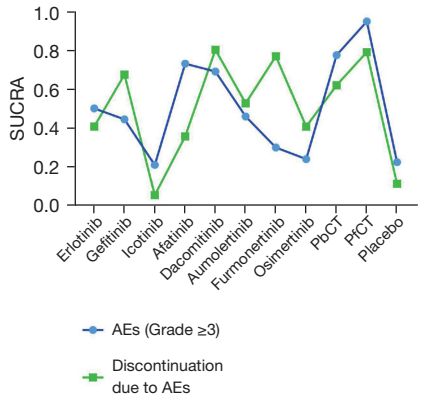
Figure 2 Network plot of eligible comparisons for overall grade ≥3 AEs and discontinuation due to AEs. (A) Network plot of eligible comparisons for overall grade ≥3 AEs; (B) network plot of eligible comparisons for discontinuation due to AEs. PbCT, pemetrexed-based chemotherapy; PfCT, pemetrexed-free chemotherapy; AEs, adverse events.

A

Erlotinib	0.87 (0.41, 2.27) Very low[1,2,4]	0.38 (0.07, 2.48) Moderate[1]	2.18 (0.55, 10.6) Low[1,2]	1.98 (0.26, 23.2) Low[1,2]	0.42 (0.1, 2.11) Moderate[1]	0.87 (0.11, 9.77) Moderate[1]	0.51 (0.06, 4.8) Moderate[1]	2.55 (0.52, 13.86) Low[1,2]	5.27 (2.54, 13.7) Low[2,4]	0.37 (0.03, 4.72) Moderate[1]
0.57 (0.24, 1.16) Low[1,2]	Gefitinib	0.44 (0.07, 2.41) Moderate[1]	2.51 (0.64, 9.14) Low[1,2]	2.26 (0.32, 19.18) Low[1,2]	0.49 (0.1, 2.42) Moderate[1]	1 (0.14, 7.79) Moderate[1]	0.6 (0.07, 4.54) Moderate[1]	2.97 (0.52, 14.38) Low[1,2]	6.07 (2.81, 13.91) Low[2,4]	0.42 (0.03, 5.35) Moderate[1]
6.74 (1.08, 52.05) High	11.51 (2.18, 100.15) High	Icotinib	5.78 (0.74, 42.43) Low[1,2]	5.55 (0.34, 81.91) Moderate[1]	1.15 (0.15, 8.17) Low[1,2]	2.3 (0.19, 40.08) Moderate[1]	1.33 (0.1, 19.14) Moderate[1]	6.65 (1.23, 36.24) Moderate[2]	14.04 (2.69, 81.89) High	0.98 (0.06, 15.23) Low[1,2]
1.19 (0.34, 4.19) Low[1,2]	2.09 (0.73, 6.35) Low[1,2]	0.17 (0.02, 1.03) Low[1,2]	Afatinib	0.92 (0.08, 11.81) Low[1,2]	0.2 (0.03, 1.19) Moderate[1]	0.4 (0.04, 5.28) Moderate[1]	0.23 (0.02, 3) Moderate[1]	1.17 (0.23, 5.85) Low[1,2]	2.44 (0.62, 10.52) Low[1,2]	0.17 (0.01, 2.45) Low[1,2]
0.35 (0.05, 1.99) Low[1,2]	0.63 (0.12, 3.23) Low[1,2]	0.05 (0, 0.58) High	0.3 (0.04, 2.22) Low[1,2]	Dacomitinib	0.21 (0.01, 2.7) Moderate[1]	0.44 (0.02, 8.28) Moderate[1]	0.26 (0.01, 4.39) Moderate[1]	1.27 (0.09, 16.08) Low[1,2]	2.61 (0.26, 23.5) Low[1,2]	0.18 (0.01, 4.87) Moderate[1]
1.06 (0.29, 3.64) Moderate[1]	1.9 (0.53, 6.38) Moderate[1]	0.16 (0.02, 0.99) Moderate[2]	0.88 (0.22, 3.84) Moderate[1]	3.03 (0.37, 26.03) Moderate[1]	Osimertinib	2.07 (0.17, 29.76) Moderate[1]	1.22 (0.09, 15.6) Moderate[1]	6 (1.16, 30.15) Moderate[2]	12.61 (2.59, 58.41) High	0.85 (0.12, 6.49) Moderate[1]
0.79 (0.11, 5.12) Moderate[1]	1.42 (0.24, 7.85) Moderate[1]	0.12 (0.01, 1.35) Moderate[1]	0.66 (0.09, 5.34) Moderate[1]	2.28 (0.22, 24.96) Moderate[1]	0.75 (0.09, 7.09) Moderate[1]	Aumolertinib	0.56 (0.03, 10.89) Moderate[1]	2.9 (0.21, 31.74) Moderate[1]	6.02 (0.61, 51.26) Moderate[1]	0.41 (0.02, 8.97) Moderate[1]
0.36 (0.04, 2.67) Moderate[1]	0.63 (0.09, 4.18) Moderate[1]	0.05 (0, 0.68) High	0.3 (0.03, 3.05) Moderate[1]	1.01 (0.08, 14.9) Moderate[1]	0.33 (0.03, 3.21) Moderate[1]	0.44 (0.03, 6.02) Moderate[1]	Furmonertinib	5.01 (0.38, 62.24) Moderate[1]	10.41 (1.12, 96.35) High	0.72 (0.03, 20.82) Moderate[1]
0.65 (0.13, 2.91) Low[1,2]	1.13 (0.27, 4.63) Low[1,2]	0.09 (0.02, 0.43) Moderate[2]	0.54 (0.14, 2.1) Low[1,2]	1.82 (0.21, 18.92) Low[1,2]	0.6 (0.16, 2.25) Low[1,2]	0.81 (0.08, 7.86) Moderate[1]	1.81 (0.16, 20.4) Moderate[1]	PbCT	2.05 (0.43, 10.24) Low[1,2]	0.14 (0.01, 1.61) Moderate[1]
0.44 (0.19, 0.98) Moderate[2]	0.76 (0.41, 1.66) Very low[1,2,3]	0.07 (0.01, 0.36) High	0.37 (0.13, 1.14) Low[1,2]	1.21 (0.21, 8.94) Low[1,2]	0.41 (0.12, 1.58) Moderate[1]	0.55 (0.09, 3.76) Moderate[1]	1.24 (0.16, 10.27) Moderate[1]	0.67 (0.18, 3) Low[1,2]	PfCT	0.07 (0.01, 0.91) Moderate[1]
4.56 (0.56, 37.26) Moderate[1]	7.96 (1.01, 65.72) High	0.67 (0.04, 6.84) Low[1,2]	3.8 (0.41, 40.86) Low[1,2]	12.29 (0.9, 224.19) Moderate[1]	4.2 (0.8, 22.07) Moderate[1]	5.77 (0.39, 90.51) Moderate[1]	12.76 (0.76, 190.45) Moderate[1]	6.93 (0.86, 61.69) Moderate[1]	10.56 (1.17, 82.4) High	Placebo

1. Rate down for imprecision
2. Rate down for risk of bias
3. Rate down for inconsistency (significant difference between direct and indirect estimates)
4. Rate down for inconsistency (heterogeneity of direct estimate effects across trials assessed same comparison)

B



C

SUCAR	Erl	Gef	Ico	Afa	Dac	Osi	Fur	Aum	PbCT	PfCT	Placebo
Grade ≥3 AEs	0.50	0.44	0.21	0.73	0.69	0.24	0.30	0.46	0.77	0.95	0.22
Discontinuation	0.41	0.67	0.05	0.35	0.80	0.41	0.77	0.53	0.62	0.79	0.11

Figure 3 Pooled estimates and SUCRA estimates for overall grade ≥3 AEs and discontinuation due to AEs of treatments. (A) Pooled estimates for overall toxicity profile of treatments. Each cell contains pooled odds ratio, 95% credibility interval and certainty of evidence which assesses comparison for column treatment versus row treatment. Upper triangle of table contains results for grade ≥3 AEs, and lower triangle contains results for discontinuation due to AEs; (B) curves depicting the SUCRA estimates for overall toxicity profile of treatments; (C) SUCRA estimates for overall toxicity profile of treatments. A larger SUCRA indicates a greater probability of AEs (grade ≥3), specific AEs, discontinuation due to AEs. PbCT, pemetrexed-based chemotherapy; PfCT, pemetrexed-free chemotherapy; SUCRA, surface under the cumulative ranking curve; AEs, adverse events; Erl, erlotinib; Gef, gefitinib; Ico, icotinib; Afa, afatinib; Dac, dacomitinib; Osi, osimertinib; Fur, furmonertinib; Aum, aumolertinib.

risk domains: 2 trials (3,17) had no blinding of outcome assessment, and 1 trial (27) had incomplete outcome data (Figures S3,S4).

Overall toxicity profile

The NMA for grade ≥3 AEs and discontinuation due to AEs included 23 RCTs, which yielded 11 individual nodes (*Figure 2A*).

Regarding grade ≥3 AEs (*Figure 3A*), chemotherapies were more associated with increased toxicity than were EGFR-TKIs, with significant differences for PfCT versus erlotinib (5.27; 95% credible interval: 2.54 to13.7, low certainty), gefitinib (6.07; 2.81–13.91, low certainty), icotinib (14.04; 2.69–81.89, high certainty), osimertinib (12.61; 2.59–58.41, high certainty), and furmonertinib (10.41; 1.12–96.35, high certainty), and for PbCT versus icotinib (6.65; 1.23–36.24, moderate certainty) and osimertinib (6; 1.16–30.15, moderate certainty). Among the first-generation EGFR-TKIs, icotinib might have fewer grade ≥3 AEs compared with erlotinib (0.38, 0.07–2.48, moderate certainty) and gefitinib (0.44; 0.07–2.41, moderate certainty), but this was based on evidence of moderate certainty. In terms of the second-generation EGFR-TKIs, dacomitinib showed little or no different risk of grade ≥3 AEs compared with afatinib (0.92; 0.08–11.81, low certainty). Among the third-generation EGFR-TKIs, furmonertinib (1.22; 0.09–15.6, moderate certainty) and aumolertinib (2.07; 0.17–29.76, moderate certainty) were associated with an increased incidence of grade ≥3 AEs compared with osimertinib.

As shown in *Figure 3B,3C*, PfCT (SUCRA =0.95) and PbCT (0.77) demonstrated higher probabilities of leading to grade ≥3 AEs than did EGFR-TKIs. Among EGFR-TKIs, icotinib (0.21) and osimertinib (0.24) showed the best and second-best safety in terms of the likelihood of causing grade ≥3 AEs. Afatinib (0.73) and dacomitinib (0.69) had a greater likelihood of causing grade ≥3 AEs than did the other EGFR-TKIs.

As for discontinuation due to AEs (*Figure 3A*), icotinib was less associated with discontinuation compared with the other EGFR-TKIs, but this was based on a low or moderate

certainty of evidence that did not exclude the possibility of more discontinuation. Use of afatinib (0.88; 95% credible interval: 0.22–3.84, moderate certainty) or icotinib (0.16; 0.02–0.99, moderate certainty) may result in a lower incidence of discontinuation compared with osimertinib, although the certainty of evidence was limited.

According to the SUCRA estimates, the top two therapies in terms of lowest likelihood of causing discontinuation were icotinib (0.05) and afatinib (0.35). Among EGFR-TKIs, dacomitinib (0.80) ranked first and furmonertinib (0.77) ranked second in terms of likelihood in causing discontinuation (*Figure 3B,3C*).

Specific toxicity and QoL improvement

Of the more than 100 types of AEs reported in the included RCTs, we chose 21 specific AEs as representative ones. The analysis of specific AEs included trials which only recruited early-stage NSCLC. Pooled odds ratios (*Table 2*) and SUCRAs (*Figure 4* and *Table 3*) for each specific AE were calculated.

Overall, the toxicity of chemotherapies was mainly hematologic or gastrointestinal in nature (appetite loss, nausea, vomiting, and constipation), while the toxicity of EGFR-TKIs was mainly dermatologic, pulmonary, and gastrointestinal in nature (diarrhea, liver enzyme elevation, and stomatitis).

The first-generation EGFR-TKIs had a relatively mild toxicity profile. Icotinib had the highest risk of dyspnea (SUCRA =0.93), gefitinib had the lowest risk of leukopenia (0.20) but the highest risk of liver enzymes elevation (0.99), and erlotinib had the highest risk of insomnia (0.70) but the lowest risk of anemia (0.19), cough (0.35), dyspnea (0.32), and infection or pneumonitis (0.33).

Compared with other EGFR-TKIs, second-generation TKIs were associated with a broader toxicity profile. Afatinib and dacomitinib had a high risk of dry skin (afatinib SUCRA =0.61, dacomitinib SUCRA =0.86), rash (0.88, 0.83), pruritus (0.85, 0.74), diarrhoea (0.93, 0.81), stomatitis (0.87, 0.76), and paronychia (0.90, 0.92).

Among the EGFR-TKIs, osimertinib had the lowest risk of dry skin (SUCRA =0.52), and rash (0.27) but the highest risk of leukopenia (0.67), prolongation of QTc (0.88), and fatigue (0.59). Aumolertinib had a toxicity profile mainly related to gastrointestinal effects, with the highest risk of anemia (0.57), nausea (0.55), vomiting (0.67) and cough (0.76).

The NMA for QoL improvement included five RCTs which yielded five individual nodes including erlotinib, gefitinib, afatinib, osimertinib, and chemotherapy (Figure S5A). According to the SUCRA and pooled odds ratios, the ranking of therapies by their probability to improve QoL was as follows: erlotinib > gefitinib > osimertinib > chemotherapy > afatinib (Figure S5B,S5C and Figure S6).

Sensitivity analysis

Sensitivity analysis was conducted for the primary outcomes (grade ≥3 AEs and discontinuation due to AEs). The first sensitivity analysis only involved 19 phase III RCTs (Figures S7,S8). The overall results were relatively robust, the rank ordering of EGFR-TKIs by causing grade ≥3 AEs and discontinuation remained the same. The second sensitivity analysis involved the RCTs that included patients with advanced NSCLC (Figures S9,S10). In this analysis, erlotinib demonstrated a lower probability for causing grade ≥3 AEs (ranking shift from 5 to 7), and osimertinib was the EGFR-TKI with the lowest probability of causing grade ≥3 AEs. The rank ordering of EGFR-TKIs by causing discontinuation remained the same.

Discussion

Compared with a previous study (25), this NMA exclusively included patients with NSCLC and *EGFR* mutations, providing a more accurate and rational reflection of the patient population who currently receive EGFR-TKIs in clinical practice. For the first time, our study compared overall and specific toxicity among third-generation of EGFR-TKIs. Furthermore, this study yielded a more comprehensive hierarchy of EGFR-TKI toxicity, as evidenced across various parameters, including grade ≥3 AEs, discontinuation due to AEs, multiple specific AEs, and QoL improvement, which can provide a toxicity-based rationale for treatment decisions.

Our results indicated that EGFR-TKIs exhibited milder toxicity compared to chemotherapy. Specifically, we observed that icotinib and osimertinib demonstrated superior safety while second-generation EGFR-TKIs were associated with greater toxicity. These results can be attributed to the inconsistent structural characteristics of TKIs. Second-generation EGFR-TKIs, with their high-potency *EGFR* wild-type inhibition and irreversible binding activity, may lead to more AEs. Conversely, the reversible binding activity of first-generation EGFR-TKIs may explain their modest toxicity, and mutant-selective

Table 2 Pooled estimates of specific toxicity

Treatment	Anemia	Leukopenia	Diarrhoea	Elevated liver enzymes	Stomatitis	Appetite loss	Nausea	Vomiting	Constipation	Dry skin	Rash	Pruritus	Paronychia	Alopecia	Prolongation of QTc	Headache	Fatigue	Insomnia	Cough	Dyspnea	Infection or pneumonitis
Versus Afa																					
Aum	1.30	1.11	0.03	0.68	1.11	NA	1.18	2.81	1.84	NA	0.22	0.21	0.16	NA	NA	0.84	0.62	0.59	1.61	NA	0.52
Dac	0.79	1.56	0.47	0.80	1.56	1.73	0.84	0.64	1.23	2.00	0.92	0.68	1.10	1.73	NA	0.23	1.02	0.46	1.29	0.60	0.38
Erl	0.54	0.73	0.06*	1.33	0.73	1.77	1.06	0.71	0.80	0.88	0.71	0.16	0.14*	1.77	NA	0.27	1.21	1.66	0.91	0.57	0.28
Osi	1.04	6.1	0.07	0.25*	6.10	0.62	0.92	1.16	1.67	0.82	0.05*	0.25	0.17*	0.62	NA	0.43	1.39	0.46	1.27	1.06	0.53
Fur	0.59	1.42	0.05	0.53	1.42	NA	0.66	1.51	2.48	NA	0.16	NA	0.02*	NA	NA	0.46	NA	NA	1.26	1.14	0.36
Gef	0.56	0.56	0.08*	2.14*	0.56	0.76	1.01	1.05	1.32	1.06	0.51	0.40	0.17*	0.76	NA	0.32	0.92	0.70	1.09	0.63	0.41
Ico	1.36	1.56	0.02	0.13*	1.56	NA	0.17	0.06	NA	1.08	0.10	0.11	NA	NA	NA	NA	0.61	NA	1.26	4.62	NA
PbCT	7.63*	15	0.01*	0.29*	15.00	1.33	5.98*	2.73	4.72	0.07*	0.01*	0.05*	0.01*	1.33	NA	1.33	3.3*	0.49	0.92	1.51	0.26
PfCT	7.03*	30.27*	0.03*	0.73	30.27*	8.84	48.13*	16.05*	7.97*	0.06*	0.02*	0.03*	0.01*	8.84	NA	0.49	4.43*	2.94	0.37*	0.25	0.12*
Versus Aum																					
Dac	0.56	1.37	17.68	1.18	1.37	NA	0.70	0.24	0.69	NA	4.34	3.19	6.61	NA	NA	0.26	1.59	0.80	0.8	NA	0.81
Erl	0.40	0.67	2.02	1.98	0.67	NA	0.90	0.25	0.46	NA	3.27	0.79	0.83	NA	0.85	0.31	1.88	2.88	0.57	NA	0.57
Osi	0.79	5.86	2.28	0.37	5.86	NA	0.80	0.43	0.93	NA	0.24	1.24	1.00	NA	2.40	0.52	2.22	0.82	0.79	NA	1.08
Fur	0.45	1.24	1.75	0.78	1.24	NA	0.55	0.55	1.40	NA	0.70	NA	0.15	NA	1.07	0.54	NA	NA	0.8	NA	0.73
Gef	0.42	0.51	2.91	3.13*	0.51	NA	0.85	0.40	0.75	NA	2.28	2.02	1.07	NA	0.81	0.37	1.46	1.17	0.68	NA	0.80
Ico	1.02	1.36	0.65	0.18	1.36	NA	0.14	0.03	NA	NA	0.46	0.56	NA	NA	NA	NA	0.99	NA	0.78	NA	NA
PbCT	5.76	14.06	0.39	0.43	14.06	NA	5.06	0.95	2.72	NA	0.03*	0.26	0.04	NA	0.46	1.67	5.33*	0.81	0.58	NA	0.5
PfCT	5.30	27.45	1.08	1.09	27.45	NA	40.81*	5.88	4.46	NA	0.11*	0.15	0.05	NA	NA	0.59	7.10*	5.01	0.23*	NA	0.24
Versus Dac																					
Erl	0.68	0.45	0.11	1.64	0.45	1.08	1.27	1.09	0.66	0.45	0.77	0.26	0.13*	1.08	NA	1.19	1.21	3.66	0.69	0.95	0.72
Osi	1.32	4.12	0.14	0.32	4.12	0.35	1.12	1.53	1.36	0.43	0.06*	0.4	0.15*	0.35	NA	1.90	1.39	0.99	0.97	1.78	1.37
Fur	0.76	0.9	0.1	0.66	0.90	NA	0.79	NA	2.13	NA	0.16	NA	0.02*	NA	NA	2.06	NA	NA	0.97	1.77	0.89
Gef	0.71	0.36	0.17	2.68*	0.36	0.44	1.21	1.48	1.08	0.53	0.55	0.63	0.15*	0.44	NA	1.41	0.92	1.47	0.83	1.03	0.99
Ico	1.73	0.91	0.04	0.16*	0.91	NA	0.21	0.10	NA	0.54	0.11	0.20	NA	NA	NA	NA	0.62	NA	0.95	8.10	NA
PbCT	9.99*	9.54	0.02	0.37	9.54	0.77	7.15*	3.61	3.76	0.04*	0.01*	0.08	0.01*	0.77	NA	6.28	3.31	1.02	0.70	2.59	0.66
PfCT	8.84*	19.86	0.06	0.93	19.86	5.15	57.14*	22.63	6.46	0.03*	0.03*	0.05	0.01*	5.15	NA	2.30	4.49*	6.40	0.28	0.42	0.31
Versus Erl																					
Osi	1.96	8.21	1.25	0.19*	8.21	0.34	0.87	1.57	2.05	0.92	0.07*	1.55	1.21	0.34	2.84	1.61	1.17	0.27	1.40	1.82	1.94
Fur	1.08	1.9	0.94	0.40	1.90	NA	0.61	NA	3.19	NA	0.22	NA	0.19	NA	1.26	1.74	NA	NA	1.40	1.86	1.28
Gef	1.04	0.78	1.49	1.60	0.78	0.42	0.96	1.54	1.64	1.18	0.71	2.58	1.24	0.42	0.97	1.18	0.77	0.40	1.20	1.09	1.41
Ico	2.55	2.03	0.32	0.09*	2.03	NA	0.16	0.10	NA	1.22	0.14	0.75	NA	NA	NA	NA	0.52	NA	1.34	8.02	NA
PbCT	14.34*	21.56	0.18	0.21*	21.56	0.76	5.71*	3.77	5.78	0.08*	0.01*	0.32	0.05*	0.76	0.56	5.15	2.75	0.29	0.99	2.67	0.91
PfCT	13.04*	41.35*	0.56	0.55*	41.35*	5.04*	46.27*	23.51*	9.89*	0.07*	0.03*	0.19	0.07*	5.04	NA	1.81	3.73*	1.73	0.40*	0.45	0.43

Table 2 (*continued*)

Table 2 (*continued*)

Treatment	Anemia	Leukopenia	Diarrhoea	Elevated liver enzymes	Stomatitis	Appetite loss	Nausea	Vomiting	Constipation	Dry skin	Rash	Pruritus	Paronychia	Alopecia	Prolongation of QTc	Headache	Fatigue	Insomnia	Cough	Dyspnea	Infection or pneumonitis
Versus Osi																					
Fur	0.57	0.22	0.8	2.1	0.22	NA	0.70	NA	1.52	NA	2.84	NA	0.15	NA	0.43	1.08	NA	NA	1.01	1.01	0.65
Gef	0.53	0.09	1.25	8.48*	0.09	1.25	1.08	0.95	0.79	1.25	9.48	1.64	1.01	1.25	0.33	0.74	0.66	1.48	0.86	0.59	0.72
Ico	1.32	0.23	0.28	0.5	0.23	NA	0.19	0.06	NA	1.38	1.85	0.49	NA	NA	NA	NA	0.45	NA	0.97	4.53	NA
PbCT	7.33*	2.39	0.15	1.14	2.39	2.13	6.41*	2.36	2.80	0.09*	0.13*	0.21	0.04*	2.13	0.2	3.28	2.39	1.04	0.73	1.44	0.47
PfCT	6.64*	4.93	0.46	2.89*	4.93	13.96	51.61*	13.80	4.76	0.07*	0.45	0.13	0.06*	13.96	NA	1.15	3.20*	6.43	0.29*	0.24	0.22
Versus Fur																					
Gef	0.93	0.42	1.56	4.01*	0.42	NA	1.55	NA	0.52	NA	3.29	NA	6.69*	NA	0.77	0.68	NA	NA	0.86	0.57	1.08
Ico	2.31	1.04	0.34	0.24	1.04	NA	0.27	NA	NA	NA	0.64	NA	NA	NA	NA	NA	NA	NA	0.97	4.39	NA
PbCT	13.35*	10.72	0.21	0.56	10.72	NA	8.94	NA	1.91	NA	0.04*	NA	0.26	NA	0.46	3.02	NA	NA	0.72	1.36	0.73
PfCT	12.08*	22.57	0.6	1.41	22.57	NA	74.25	NA	3.06	NA	0.16	NA	0.38	NA	NA	1.08	NA	NA	0.29*	0.23	0.35
Versus Gef																					
Ico	2.47	2.74	0.21	0.06*	2.74	NA	0.17	0.07	NA	1.00	0.2	0.28	NA	NA	NA	NA	0.67	NA	1.13	7.53	NA
PbCT	13.74*	26.09	0.13	0.13*	26.09	1.78	5.98*	2.49	3.60	0.07*	0.01*	0.13	0.04*	1.78	0.6	4.50	3.62*	0.69	0.83	2.45	0.63
PfCT	12.51*	53.45*	0.36	0.34*	53.45*	11.41*	47.33*	14.86*	6.05*	0.06*	0.05*	0.07*	0.05*	11.41	NA	1.59	4.90*	4.37	0.34*	0.41	0.31
Versus Ico																					
PbCT	5.56	10.23	0.58	2.28	10.23	NA	34.92*	38.14*	NA	0.07*	0.07*	0.45	NA	NA	NA	NA	5.35*	NA	0.74	0.32	NA
PfCT	5.11	20.73	1.72	5.89*	20.73	NA	276.8*	215.4*	NA	0.06	0.24	0.26	NA	NA	NA	NA	7.27*	NA	0.30	0.05	NA
Versus PbCT																					
PfCT	0.91	2.07	2.99	2.54	2.07	6.84	8.15*	5.90	1.66	0.82	3.66	0.59	1.47	6.84	NA	0.36	1.35	6.13	0.39	0.16*	0.48

Value in each cell are pooled odds ratios. *, statistically significant results. QTc, corrected QT interval; Afa, afatinib; Aum, aumolertinib; Dac, dacomitinib; Erl, erlotinib; Osi, osimertinib; Fur, furmonertinib; Gef, gefitinib; Ico, icotinib; PbCT, pemetrexed-based chemotherapy; PfCT, pemetrexed-free chemotherapy; NA, not available.

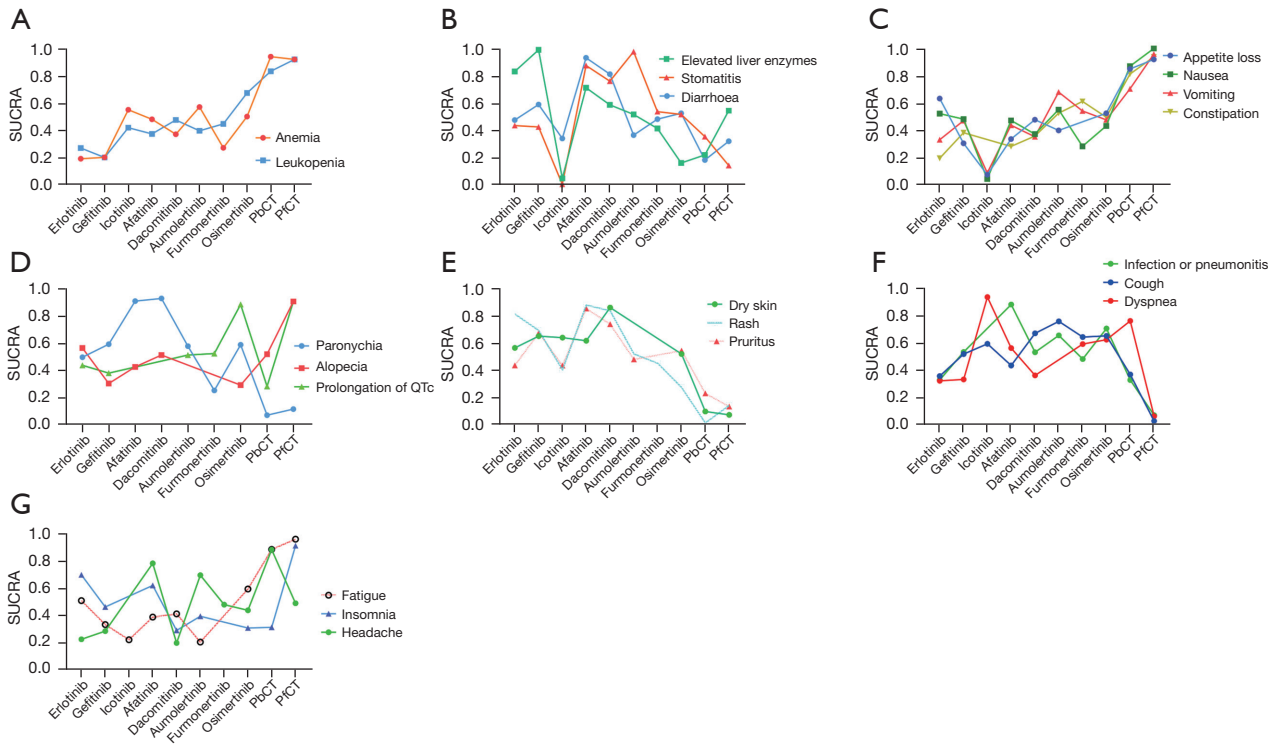


Figure 4 Curves depicting the SUCRA estimates for specific toxicity of treatments. Curves depicting the SUCRA estimates of treatments. A larger SUCRA indicates a greater probability of specific AEs. (A) SUCRA estimates for anemia and leukopenia; (B) SUCRA estimates for elevated liver enzyme, stomatitis, and diarrhoea; (C) SUCRA estimates for appetite loss, nausea, vomiting, and constipation; (D) SUCRA estimates for paronychia, alopecia, and prolongation of QTc; (E) SUCRA estimates for dry skin, rash, and pruritus; (F) SUCRA estimates for infection (or pneumonitis), cough, and dyspnea; (G) SUCRA estimates for fatigue, insomnia, and headache. SUCRA, surface under the cumulative ranking curve; PbCT, pemetrexed-based chemotherapy; PfCT, pemetrexed-free chemotherapy; AEs, adverse events; QTc, corrected QT interval.

inhibition may be the source of the superior safety of third-generation EGFR-TKIs (2).

Among EGFR-TKIs, icotinib and dacomitinib showed the best and worst safety profiles, respectively. Previous study has noted that icotinib was well tolerated, possibly because of its highly selective inhibition and wide therapeutic window (40). Our results showed that toxicity of icotinib ranked behind placebo. This might be attributed to the following reasons: the ADAURA trial is the only placebo-controlled RCT included in this NMA which used osimertinib and placebo as adjuvant therapy. Most patients in ADAURA (19) received adjuvant therapy within 10 weeks after surgery. Therefore, surgery and anesthesia might magnify the toxicity of placebo. In addition, lack of blinding to participants and relative short duration of treatment in the CONVINCE trial (10) might underestimate the toxicity of icotinib (41). Our results indicated that afatinib exhibited a favorable rate of discontinuation but a high risk of grade ≥3 AEs. This may be attributable to the early and proactive implementation of dose reduction and management strategies in the LUX-Lung 3 (9), LUX-Lung 6 (3), and LUX-Lung 7 (23) trials. Among the commonly reported AEs associated with afatinib, such as rash, diarrhea, and paronychia, discontinuation was observed. A *post hoc* analysis of the LUX-Lung 3 and LUX-Lung 6 trials revealed that dose reduction led a decrease in the incidence of rash (from 86.2% to 35.5% for all grades and from 30.6% to 7% for grade ≥3), diarrhea (from 95.3% to 38.1% for all grades and from 17.5% to 2% for grade ≥3), and paronychia (10.6% to 3.2% for grade ≥3) (12). Furmonertinib demonstrated low probability of leading grade ≥3 AEs but high probability of leading discontinuation. In the FURLONG trial (22), although furmonertinib only resulted in 6 (3%) discontinuations among 178 patients, it exhibited a

Table 3 SUCRA estimates of specific toxicity

Toxicity	Erlotinib	Gefitinib	Icotinib	Afatinib	Dacomitinib	Aumolertinib	Furmonertinib	Osimertinib	PbCT	PfCT
Anemia	0.19	0.20	0.55	0.48	0.37	0.57	0.27	0.50	0.94	0.92
Leukopenia	0.27	0.20	0.42	0.37	0.47	0.40	0.45	0.67	0.83	0.92
Diarrhoea	0.47	0.59	0.34	0.93	0.81	0.36	0.48	0.52	0.18	0.32
Elevated liver enzymes	0.83	0.99	0.04	0.71	0.58	0.51	0.41	0.16	0.22	0.54
Stomatitis	0.43	0.42	0.00	0.87	0.76	0.97	0.53	0.51	0.35	0.14
Appetite loss	0.63	0.30	0.07	0.33	0.48	0.40	NA	0.52	0.85	0.92
Nausea	0.52	0.48	0.04	0.47	0.37	0.55	0.28	0.43	0.88	0.99
Vomiting	0.33	0.46	0.08	0.44	0.35	0.67	0.54	0.48	0.70	0.96
Constipation	0.18	0.38	NA	0.26	0.36	0.50	0.61	0.48	0.81	0.92
Dry skin	0.56	0.65	0.64	0.61	0.86	NA	NA	0.52	0.10	0.07
Rash	0.81	0.69	0.40	0.88	0.83	0.52	0.45	0.27	0.01	0.14
Pruritus	0.43	0.67	0.43	0.85	0.74	0.48	NA	0.54	0.23	0.13
Paronychia	0.50	0.59	NA	0.90	0.92	0.56	0.25	0.58	0.07	0.12
Alopecia	0.56	0.30	NA	0.42	0.51	NA	NA	0.29	0.52	0.90
Prolongation of QTc	0.43	0.38	NA	NA	NA	0.51	0.52	0.88	0.28	0.90
Headache	0.24	0.29	NA	0.78	0.20	0.71	0.48	0.43	0.88	0.50
Fatigue	0.51	0.33	0.22	0.39	0.41	0.20	NA	0.59	0.89	0.96
Insomnia	0.70	0.46	NA	0.62	0.29	0.39	NA	0.31	0.31	0.91
Cough	0.35	0.52	0.59	0.43	0.67	0.76	0.64	0.65	0.37	0.02
Dyspnea	0.32	0.33	0.93	0.56	0.36	NA	0.59	0.60	0.74	0.06
Infection or pneumonitis	0.33	0.53	NA	0.88	0.53	0.66	0.48	0.70	0.32	0.07

SUCRA, surface under the cumulative ranking curve; PbCT, pemetrexed-based chemotherapy; PfCT, pemetrexed-free chemotherapy; QTc, corrected QT interval; NA, not available.

relatively higher discontinuation rate than gefitinib (2%). In other comparisons, gefitinib demonstrated relative high probability of leading discontinuation. Therefore, furmonertinib demonstrated high probability of leading discontinuation in NMA. However, this conclusion is mainly based on indirect comparisons and further studies are warranted to assess this conclusion.

This NMA revealed a diverse toxicity spectrum of EGFR-TKIs. Erlotinib demonstrated highest pulmonary safety with the lowest risk of cough, dyspnea, and pneumonitis. Gefitinib showed a generally modest toxicity profile, but a notable increased risk of liver enzyme elevation was observed. Both gefitinib and erlotinib had favorable hematologic safety. Icotinib had a mild and relatively narrow toxicity profile, particularly in terms of gastrointestinal system safety. Dermatologic toxicity and nail effects commonly occurred during EGFR-TKI therapy, especially with afatinib and dacomitinib. However, a post hoc analysis indicated immediate dose modification could decrease the incidence of dermatologic AEs significantly. Afatinib and dacomitinib were also associated with a high risk of gastrointestinal toxicity, frequently manifesting as diarrhea and stomatitis. In comparison with most EGFR-TKIs, osimertinib exhibited a generally milder toxicity profile, especially in terms of dermatologic, nail, and hair safety. In contrast to a previous study (25), we found osimertinib

had a notable risk of gastrointestinal toxicity, commonly manifesting as appetite loss, vomiting, and constipation. Results demonstrated osimertinib had a high hematologic toxicity with an elevated incidence rate of anemia and leukopenia. Three case reports for aplastic anemia indicated that osimertinib may suppress stromal cells in bone marrow directly or indirectly (42-44). However, presently, no evidence suggests there to be a difference in aplastic anemia between osimertinib and other EGFR-TKIs. Although osimertinib was most associated with QT prolongation among the EGFR-TKIs examined in this study, a previous post hoc analysis indicated that this cardiotoxicity was not associated with any cardiac failure or adverse clinical outcomes (45). In terms of other third-generation EGFR-TKIs, we found furmonertinib had a generally mild toxicity profile especially for causing less paronychia and nausea. Aumolertinib had a moderate toxicity profile with notable risk of gastrointestinal toxicity. We evaluated the QoL of different EGFR-TKIs by comparing the proportion of patients who reached clinical improvement of QoL. Five trials reported the results about QoL improvement while they assessed QoL results through different questionnaires. Two trials (erlotinib and gefitinib involved) evaluated the QoL outcomes by using Functional Assessment of Cancer Therapy-Lung (FACT-L) questionnaire and three trials (osimertinib and afatinib) used European Organization for Research and Treatment of Cancer (EORTC) QoL core questionnaire QLQ-C30. Therefore, the results of QoL should be generalized with caution.

As safety and efficacy are of equal importance, this study can assist physicians in selecting the most suitable treatment regimens for their patients. First, before the initiation of treatment, physicians could select the appropriate EGFR-TKI for an individual patient considering their comorbidities and physical performance. For instance, patients with gastrointestinal diseases should avoid using aumolertinib. During the treatment, physicians could early identify potential AEs and implement proactive dose reduction or management strategies to avoid higher-grade AEs and continue treatment as far as possible. Based on the experience of LUX-Lung 3 (9), LUX-Lung 6 (3), and LUX-Lung 7 (23) trials, immediate dose reduction and management strategy might be useful approaches to continue treatment even after AEs occur. When severe AEs lead to inevitable discontinuation, alternative EGFR-TKIs could be chosen appropriately. Moreover, understanding the toxicity profile could optimize combination therapy designs and help researchers explore more combinations of regiments.

Limitations

There are several limitations in this study. First, the majority of comparisons among treatments were indirect, and most direct comparisons were based on data from a single clinical trial. Therefore, the results should be interpreted with caution. Second, we were unable to assess the potential different toxicity spectra across specific populations, as this was a literature-based meta-analysis rather than a study of individual patient data. Future studies could investigate the difference of toxicity profiles across diverse populations, including smokers and nonsmokers, males and females, and different age cohorts. Third, although this NMA demonstrated acceptable transitivity and consistency, there was inevitable heterogeneity present between the included studies. Fourth, included trials assessed QoL results through different QoL questionnaires and biases induced by the difference in questionnaires are unavoidable. Therefore, the results of QoL improvement should be interpreted with caution. In addition, some EGFR-TKIs included in this NMA are only approved in certain countries or regions and the specific toxicity patterns of EGFR-TKIs could potentially vary by race. Consequently, our results should be generalized with caution.

Conclusions

This NMA demonstrated that EGFR-TKIs have clinically important differences in safety and limited included population to patients with *EGFR*-mutant NSCLC for the first-time. In general, osimertinib and icotinib were associated with better safety compared with other EGFR-TKIs. This study is also the first to compared toxicity comprehensively among the third-generation EGFR-TKIs. Furthermore, we elaborated the varied predominate toxicity spectra of EGFR-TKIs, which may serve as reference and inform the toxicity rationale for treatment decision-making.

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Footnote

Reporting Checklist: The authors have completed the PRISMA NMA reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-682/rc

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