Nimotuzumab combined with concurrent chemoradiotherapy benefits patients with advanced nasopharyngeal carcinoma

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Background: The potential benefits and possible risks associated with combined nimotuzumab and concurrent chemoradiotherapy in patients with advanced nasopharyngeal carcinoma (NPC) have yet to be determined.

Methods: The databases PubMed, Web of Science, China National Knowledge Infrastructure, and Wanfang were systematically searched through February 2017 for studies comparing combined nimotuzumab and chemoradiotherapy versus chemoradiotherapy alone in the treatment of NPC. Primary outcomes were complete and partial responses, and the secondary outcome was adverse reactions. The random-effect model was used to pool relative risks (RRs) and 95% confidence intervals (CIs).

Results: Nine randomized control trials and six cohort studies were included in the final analysis (n=1,015 patients). Compared with chemoradiotherapy alone, chemoradiotherapy combined with nimotuzumab was associated with an increased response rate (RR =1.11, 95% CI: 1.01–1.22). Combined treatment further reduced the occurrence rate of erythropenia (RR =0.11, 95% CI: 0.05–0.28) and neutropenia (RR =0.12, 95% CI: 0.05–0.27). The differences in the rates of other complications were not significant.

Conclusion: Nimotuzumab combined with concurrent chemoradiotherapy is more effective in patients with advanced NPC than chemoradiotherapy alone. Patients receiving combination therapy did not have a higher rate of adverse reactions. Nimotuzumab can thus be recommended as an adjunct therapy in patients with advanced NPC.

Keywords: randomized controlled trial, cohort studies, nasopharyngeal carcinoma, relative risk, radiotherapy, chemoradiotherapy

Introduction

Nasopharyngeal carcinoma (NPC) is a common malignant tumor of the head and neck, especially in China. The World Health Organization estimates that >80% of NPCs occur in China.1 In recent years, the use of intensity-modulated radiation therapy has increased the efficacy of treatment. The survival rate of patients with stage I or II NPC is 90%, and the rates of recurrence and metastasis are 8.2% and 15.4%, respectively.2,3 However, the primary lesion of NPC is often occult such that early detection, diagnosis, and treatment are challenging. Thus, at presentation, >70% of NPC patients have stage III or IV disease. The most common form of treatment for these patients with advanced disease is radiotherapy, but its efficacy is poor and severe adverse reactions occur at high rates.4 Moreover, the rates of local recurrence and distant metastasis are as high as 50%, and the 5-year survival rate for patients treated with radiotherapy alone is only 20%. Indeed, the main reasons for treatment failure are recurrence and...
metastasis. Therefore, patients with advanced NPC are currently treated with concurrent chemotherapy or neoadjuvant therapy. Emerging randomized controlled trials (RCTs) recommend cisplatin, paclitaxel, or both for use in concurrent chemoradiotherapy. However, despite the considerable therapeutic benefits, concurrent chemoradiotherapy considerably increases the occurrence of severe toxicities, including nausea and vomiting, gastrointestinal reactions, and skin injury. Thus, there is an urgent need to identify more effective and tolerable agents for the treatment of advanced NPC.

Many types of cancers overexpress growth factors on the tumor cell surface. In the non-keratinizing form of NPC, 90% of the tumor cells are positive for epidermal growth factor receptor (EGFR). Altered EGFR signaling has been widely implicated in processes such as apoptosis, proliferation, metastasis, and invasion. Thus, targeted therapy against EGFR has been proposed as an adjunct to radiotherapy to improve the curability of NPC. Nimotuzumab is a humanized anti-EGFR mouse monoclonal antibody that reduces immunoreactivity and promotes radiosensitivity. In clinical trials, nimotuzumab combined with concurrent radiotherapy seemed to facilitate radiosensitivity and thus increase treatment efficacy while maintaining low toxicity. These findings indicate a synergistic effect of nimotuzumab combined with radiotherapy. The efficiency of this combined approach versus chemoradiotherapy alone has been examined in several RCTs and cohort studies, but no conclusions were reached regarding the potential benefits and possible risks in patients with advanced NPC. We therefore conducted a meta-analysis of the recent literature to assess the efficacy and safety of combined nimotuzumab with traditional concurrent chemoradiotherapy.

Methods
Ethical approval was not needed for the present study since it was a meta-analysis of previously published studies. The analysis was conducted in accordance with Preferred Reporting Items for Systematic Reviews and Meta-analysis Statement (PRISMA; Figure S1) guidelines and the Cochrane Handbook for Systematic Reviews of Interventions. Ethical approval was also not needed for this secondary study.

Literature search
We performed systematic electronic and manual searches of the relevant literature in PubMed, Web of Science, China National Knowledge Infrastructure, and Wanfang databases from their inception to February 28, 2017. The searches were conducted using the following medical subject headings and key words: “Nimotuzumab OR h-R3” AND “nasopharyngeal carcinoma OR NPC”, “targeted therapy” AND “nasopharyngeal carcinoma OR NPC”, “nasopharyngeal carcinoma OR NPC” AND “radiotherapy OR chemotherapy”. Literature lists of reviews and relevant articles were also retrieved for potentially eligible studies. Only articles published in English and Chinese languages were included.

Inclusion and exclusion criteria
Two investigators independently performed the initial searches, excluding duplicates, and scanning the titles and abstracts of potentially eligible publications. The full text was then obtained for further screening. Any disagreement regarding the appropriateness of the study was solved by discussion and consensus. The criteria for study inclusion were as follows: (1) study design: RCT or cohort study; (2) population: patients with moderate or advanced NPC (stage ≥ III) as primarily confirmed by the pathological results (gold standard); (3) intervention: nimotuzumab combined with concurrent chemoradiotherapy in the experimental group and concurrent chemoradiotherapy alone in the control group; and (4) outcome: complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD), or adverse reactions.

Data extraction
The collected data were entered into a standardized Excel sheet, extracted by ZZL, and checked by LFS. The following information was extracted: first author, year of publication, mean ages of the two study groups, numbers of male and female patients, sample size, clinical setting (inclusion criteria for the study population), clinical stage, therapeutic schedules of the trial and control groups, and outcomes. The primary outcomes were CR, PR, SD, and PD, and the secondary outcome was adverse reactions. Any discrepancies were resolved by consensus with the other investigators involved in this study.

Assessment of quality
Our study included RCTs and prospective cohort studies. The Newcastle–Ottawa Scale was used to assess the quality of non-randomized studies based on a “star system” ranking selection, comparability, and outcome. Selection included the exposed cohort, nonexposed cohort, and ascertainment of the exposure and outcome of interest. The outcomes included assessment, length of follow-up, and adequacy of follow-up. Studies with ≥7 stars were considered to be of
priority quality, those with ≥5 stars of high quality, and those with ≤5 stars of low quality. The Cochrane Collaboration’s tool was used to assess the risk of bias in the RCTs. The risk was evaluated as high, low, or unclear according to the following items: random sequence generation, allocation concealment, blinding of participants and outcome assessment, incomplete outcome data, selective reporting, and other biases. Because blinding of the patients and clinicians in these trials was not possible, the studies were considered to have a high risk of bias when another risk item besides blinding was identified.

Statistical analysis
Relative risks (RRs) and 95% confidence intervals (CIs) were used to calculate estimates of dichotomous outcomes. A value of 1 was considered to indicate beneficial effects for patients because the primary outcome was either CR or PR. The heterogeneity of the studies was assessed using the Cochran Q and I² statistics. For the I² statistic, a value >50% was considered to indicate a high level of heterogeneity. The outcome data were pooled using the random-effect model for significant heterogeneity. The fixed-effect model was used for less significant heterogeneity. The risk of occurrence of 15 adverse reactions was also determined: nausea and vomiting, gastrointestinal reactions, skin injury, leucopenia, radiation dermatitis, mucosa reaction, declining hemoglobin, erythropeenia, thrombocytopenia, liver injury, renal injury, neutropenia, myelosuppression, hair loss, and fever. A sensitivity analysis was performed by sequentially excluding individual studies to assess the stability of the results. Publication bias was assessed by visually inspecting a funnel plot and using Egger’s linear regression test. All statistical analyses were performed using Stata 14.0 (Stata Corp., College Station, TX, USA) and Review Manager 5.3 (Cochrane Center). P-value <0.05 was considered to indicate statistical significance.

Results

Study selection
A flow chart of the study selection process is presented in Figure 1. Our initial search returned 386 results. No record
was obtained from additional sources. After the removal of 92 duplicate records, 294 articles were screened for their titles and abstracts. After the full text of 69 articles eligible for inclusion was reviewed, nine RCTs and six cohort studies were finally included in the meta-analysis.42–34

General characteristics of the included studies

The general characteristics of the included studies are summarized in Table 1. The studies were published from 2012 to 2016, and the sample sizes ranged from 31 to 183, with a total of 1,015 patients. In three of the 15 studies, nimotuzumab was combined with cisplatin and paclitaxel, in six studies with cisplatin and radiotherapy, in three studies with nedaplatin and radiotherapy, in two studies with paclitaxel and radiotherapy, and in one study with carboplatin and radiotherapy. All studies were conducted in adult patients. All outcomes were assessed within 1 year. Consistent with the finding of the World Health Organization that 80% of NPCs occur in China, all of the included studies were from this location.35

Quality assessment

Quality was assessed based on an assessment of the risk of bias (Figures S2 and S3). Among the nine RCTs, three were considered to have a low risk of bias, five an unclear risk, and one a high risk. The main sources of bias were related to allocation concealment, the blinding of participants and personnel, and outcome assessment. Each of the six cohort studies received >5 stars. The overall quality of the cohort studies was high (Table 2).

Nimotuzumab and chemoradiotherapy versus chemoradiotherapy alone

Fourteen studies with 877 NPC patients provided data on CRs and PRs. Compared with chemoradiotherapy alone, patients treated with nimotuzumab combined with chemoradiotherapy had a significantly improved response rate (RR =1.11, 95% CI: 1.01–1.22). The heterogeneity of the studies was 75% (Figure 2).

Figures 3–5 present the pooled results for adverse reactions. Compared with chemoradiotherapy alone, the combination of nimotuzumab and chemoradiotherapy did not lower the occurrence rate of nausea and vomiting (RR =0.74, 95% CI: 0.39–1.42), gastrointestinal reactions (RR =1.04, 95% CI: 0.42–2.36), skin injury (RR =0.82, 95% CI: 0.39–1.70),
| Last Name | Year | 1/9 | 2/9 | 3/9 | 4/9 | 5/9 | 6/9 | 7/9 | 8/9 | 9/9 | 10/10 |
|-----------|------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-------|
| Lu et al  | 2014 | 39.2/39.3 | 28/26 | 27/27 | KPS ≥ 80, no metastasis | III–IVa | IMRT: 60–70 Gy (lesion); cisplatin: 40 mg/m²; nimotuzumab: 100 mg/250 mL saline, once a week for 8 weeks | CR, PR, SD, PD, adverse reactions |
| Cheng et al  | 2016 | 49.8/50.6 | 50/30 | 40/40 | Expected lifetime > 6 months; KPS ≥ 70; no severe infection or hemorrhagic, endocrine, heart, brain, liver, or renal diseases; no metastasis | III–IV | 3D-CRT: 70–75 Gy (lesion); cisplatin: 20 mg/m²; paclitaxel: 175 mg/m²; nimotuzumab: 100 mg/250 mL saline for 7 weeks | CR, PR, SD, PD, adverse reactions |
| Tu et al  | 2013 | –/- | 19/12 | 14/17 | Expected lifetime > 6 months; no severe infection, or hemorrhagic, endocrine, heart, brain, liver, or renal diseases; no metastasis; PS: 0–1 | III–IV | IMRT: 68–72 Gy (lesion); cisplatin: 20 mg/m²; nimotuzumab: 100 mg/250 mL saline for 6 weeks | CR, PR, SD, PD, adverse reactions |
| Yu et al  | 2014 | –/- | 29/15 | 20/24 | Expected lifetime > 6 months; PS: 0–1; no liver, renal, or heart diseases; no metastasis | III–IV | IMRT: 66–70 Gy; cisplatin: 20 mg/m²; nimotuzumab: 100 mg/250 mL saline for 6 weeks | CR, PR, SD, PD, adverse reactions |
| Tang et al  | 2012 | 54.2/55.2 | 79/44 | 63/60 | Expected lifetime > 6 months; KPS ≥ 60; no metastasis; no serious organic disease | III–IVa | IMRT: 70–76 Gy; cisplatin: 60 mg/m²; paclitaxel: 175 mg/m²; nimotuzumab: 100 mg/250 mL saline | CR, PR, SD, PD, adverse reaction |
| Zhou and Liao  | 2013 | –/- | –/- | 16/16 | No metastasis; no serious organic disease | III–IVa | IMRT: 60–70 Gy; cisplatin: 60 mg/m²; nimotuzumab: 100 mg/250 mL | CR, PR, SD, PD, adverse reactions |
| Shao et al  | 2014 | 47/50 | 35/13 | 24/24 | Expected lifetime > 6 months; KPS ≥ 70; no serious organic disease | III–IVa | IMRT: 72–76 Gy; nedaplatin; nimotuzumab: 100 mg/250 mL | CR, PR, SD, PD, adverse reactions |
| Li et al  | 2015 | 57.3/54.6 | 38/22 | 30/30 | Expected lifetime > 6 months; KPS ≥ 70; no liver, renal, or heart diseases | III–IVb | IMRT: 60–70 Gy; nedaplatin: 40 mg/500 mL saline; nimotuzumab: 100 mg/250 mL | CR, PR, SD, PD, adverse reactions |
| Lou et al  | 2016 | –/- | –/- | 161/22 | Expected lifetime > 6 months; KPS ≥ 60; no liver, renal, or heart diseases | III–IV | IMRT: 60–70 Gy; nedaplatin: 40 mg/500 mL saline; nimotuzumab: 100 mg/250 mL | CR, PR, SD, PD, adverse reactions |
| Zhuang et al  | 2016 | 65.8 | 37/5 | 18/15 | Expected lifetime > 6 months; KPS ≥ 60 | III–IVa | IMRT: 72–80 Gy; cisplatin: 10 mg/m²; 5-fluorouracil: 500 mg/m²; nimotuzumab: 100 mg/250 mL | CR, PR, SD, PD, adverse reactions |
| Li et al  | 2016 | –/- | 78/26 | 52/52 | Expected lifetime > 6 months; KPS ≥ 60 | III–IVa | IMRT: 70–74 Gy; cisplatin: 25 mg/m²; nimotuzumab: 200 mg/250 mL; 5-fluorouracil: 600 mg/m² | CR, PR, SD, PD, adverse reactions |

**Abbreviations:** KPS, Karnofsky Performance Scale; IMRT, intensity-modulated radiation therapy; CR, complete response; PR, partial disease; SD, stable disease; PD, progressive disease; 3D-CRT, three-dimensional conformal radiotherapy; PS, performance status.
leucopenia (RR =1.43, 95% CI: 0.79–2.57), radiation dermatitis (RR =1.08, 95% CI: 0.15–7.74), mucosal reactions (RR =0.79, 95% CI: 0.31–2.02), declining hemoglobin (RR =0.99, 95% CI: 0.62–1.59), thrombocytopenia (RR =0.72, 95% CI: 0.36–1.45), liver injury (RR =1.12, 95% CI: 0.54–2.30), renal injury (RR =0.97, 95% CI: 0.39–2.41), myelosuppression (RR =1.14, 95% CI: 0.30–4.24), hair loss (RR =0.39, 95% CI: 0.02–9.73), or fever (RR =0.80, 95% CI: 0.21–3.12). The results of the overall effect test were not significant (P>0.05). However, the occurrence rates of erythropenia and neutropenia were significantly lower in the combined nimotuzumab group than in the chemoradiotherapy-alone group (RR =0.11, 95% CI: 0.05–0.28; RR =0.12, 95% CI: 0.05–0.27).

Sensitivity analyses were conducted by sequentially excluding one study at a time. Figure 5 shows that the pooled estimation was not altered; therefore, the results were statistically robust.

Begg’s and Egger’s tests were used to test for publication bias. Begg’s test did not detect publication bias (Z=1.480, P=0.155), but Egger’s test was based on an inspection of the funnel plot and formal statistical tests (t=2.17, P=0.050). A trim-and-fill analysis showed that four studies were required to balance the asymmetry of the funnel plot (Figure 6).

**Discussion**

A comprehensive and systematic literature retrieval and meta-analysis of the eligible articles suggested that nimotuzumab combined with concurrent chemoradiotherapy benefits patients with advanced NPC and is better than chemoradiotherapy alone. The two treatment methods did not differ significantly in the occurrence rates of most of the adverse reactions. However, combined therapy lowered the occurrence rates of erythropenia and neutropenia compared with chemoradiotherapy alone.

**Table 2 Methodological quality assessment (risk of bias) of included studies by Newcastle–Ottawa Scale**

| Study | Selection | Comparability | Outcome |
|-------|-----------|---------------|---------|
|       | Exposed cohort | Nonexposed cohort | Ascertainment of exposure | Outcome of interest | Assessment of outcome | Length of follow-up | Adequacy of follow-up | Total score |
| Li et al | * | * | * | * | * | * | * | 7 |
| Chen et al | * | * | * | * | * | * | * | 6 |
| Lu et al | * | * | * | * | * | * | * | 7 |
| Li et al | * | * | * | * | * | * | * | 7 |
| Lou et al | * | * | * | * | * | * | * | 8 |
| Li | * | * | * | * | * | * | * | 6 |

*Note: *1 point; **2 points.*

**Table 2** Methodological quality assessment (risk of bias) of included studies by Newcastle–Ottawa Scale

**Figure 2** Forest plot of nimotuzumab combined with concurrent chemoradiotherapy versus chemoradiotherapy alone in advanced NPC.

**Abbreviations**: NPC, nasopharyngeal carcinoma; IV, inverse variance; CI, confidence interval.
### Gastrointestinal reactions

| Study or subgroup | Experimental Events | Control Events | Weight (%) | Odds ratio IV, random, 95% CI | Odds ratio IV, random, 95% CI |
|-------------------|---------------------|----------------|------------|-------------------------------|-------------------------------|
| Subtotal (95% CI) | 120                 | 120            | 100        | 1.00 (0.98, 1.01)             | 1.00 (0.98, 1.01)             |
| Total events      | 97                  | 99             |            |                               |                               |

### Skin injury

| Study or subgroup | Experimental Events | Control Events | Weight (%) | Odds ratio IV, random, 95% CI | Odds ratio IV, random, 95% CI |
|-------------------|---------------------|----------------|------------|-------------------------------|-------------------------------|
| Subtotal (95% CI) | 142                 | 140            | 100        | 1.00 (0.98, 1.01)             | 1.00 (0.98, 1.01)             |
| Total events      | 144                 | 149            |            |                               |                               |

### Leucopenia

| Study or subgroup | Experimental Events | Control Events | Weight (%) | Odds ratio IV, random, 95% CI | Odds ratio IV, random, 95% CI |
|-------------------|---------------------|----------------|------------|-------------------------------|-------------------------------|
| Subtotal (95% CI) | 240                 | 230            | 100        | 1.04 (0.97, 1.11)             | 1.04 (0.97, 1.11)             |
| Total events      | 166                 | 156            |            |                               |                               |

### Radiation dermatitis

| Study or subgroup | Experimental Events | Control Events | Weight (%) | Odds ratio IV, random, 95% CI | Odds ratio IV, random, 95% CI |
|-------------------|---------------------|----------------|------------|-------------------------------|-------------------------------|
| Subtotal (95% CI) | 50                  | 50             | 100        | 1.00 (0.98, 1.02)             | 1.00 (0.98, 1.02)             |
| Total events      | 54                  | 50             |            |                               |                               |

### Mucosa reaction

| Study or subgroup | Experimental Events | Control Events | Weight (%) | Odds ratio IV, random, 95% CI | Odds ratio IV, random, 95% CI |
|-------------------|---------------------|----------------|------------|-------------------------------|-------------------------------|
| Subtotal (95% CI) | 207                 | 204            | 100        | 1.00 (0.98, 1.02)             | 1.00 (0.98, 1.02)             |
| Total events      | 108                 | 119            |            |                               |                               |

### Hemoglobin descended

| Study or subgroup | Experimental Events | Control Events | Weight (%) | Odds ratio IV, random, 95% CI | Odds ratio IV, random, 95% CI |
|-------------------|---------------------|----------------|------------|-------------------------------|-------------------------------|
| Subtotal (95% CI) | 211                 | 204            | 100        | 1.00 (0.98, 1.02)             | 1.00 (0.98, 1.02)             |
| Total events      | 115                 | 110            |            |                               |                               |

**Figure 3** Forest plot of adverse reactions between nimotuzumab group and chemoradiotherapy alone.

**Abbreviations:** IV, inverse variance; CI, confidence interval.
Several studies have examined the efficacy of combined nimotuzumab therapy, but ours is the first to comprehensively evaluate the efficacy of nimotuzumab combined with chemoradiotherapy. In previous studies of head and neck carcinomas and NPC, concurrent chemoradiotherapy was shown to be more effective than radiotherapy or chemotherapy alone. However, these cases are rare, as most patients with these cancers do not need concurrent chemoradiotherapy. The 5-year overall survival rate of patients with stage II NPC treated with concurrent chemoradiotherapy is 94.5%, and the treatment plan is effective and feasible. The addition of nimotuzumab to the standard treatment protocol increases the CR rate without increasing the occurrence of adverse reactions. Our results support these findings.

Platinum has always been the main chemotherapeutic agent used to treat NPC, serving as a sensitizer during chemotherapy, radiotherapy, or both. Although patients with NPC greatly benefit from concurrent chemoradiotherapy, relapses and metastases are frequent, especially for patients with advanced NPC. Thus, there is an urgent need for adjunct therapies for advanced disease. Nimotuzumab is a human monoclonal antibody that specifically recognizes EGFR-binding sites and blocks other factors from binding to them. The Chinese government approved clinical trials of nimotuzumab in 2002. By binding to extracellular segments of EGFR, nimotuzumab blocks its activation pathways, including those linked to tumor angiogenesis factors, and potently inhibits tumor proliferation and metastasis. Our results suggest that nimotuzumab synergizes with chemoradiotherapy, as reported in clinical populations. In the study of Nabid et al, the CR of patients treated with nimotuzumab for locally advanced squamous cell cancer of the head and neck after radiotherapy was 70%. Crombet et al reported a 3-year survival rate for nimotuzumab combined with radiotherapy of 66.7%, which is significantly higher than that for radiotherapy alone, and fewer adverse reactions. The Chinese Academy of Medical Sciences conducted a multicenter Phase II RCT to assess the efficacy and adverse reactions of nimotuzumab combined with radiotherapy in patients with advanced NPC. In that study, the 3-year survival rate was significantly higher in the treated than in the control group (84.3% versus 77.6%), a result attributed to the binding ability of nimotuzumab. The affinity of nimotuzumab for EGFR is several times higher than that for the endogenous ligand. Moreover, the occurrence of erythropenia and neutropenia was lower. However, these results were specifically reported in only two studies and remain to be confirmed.

A major strength of our meta-analysis is that it was conducted in accordance with PRISMA guidelines and the recommendations outlined in the Cochrane Center handbook. Another strength is the study population, which consisted of first-visit patients with advanced NPC. Our sensitivity analyses confirmed the findings of the included studies. However, there are several limitations that still need to be addressed. First, the studies included in our meta-analysis were performed in different clinical settings, and the standard treatment plans were different (nimotuzumab was combined with cisplatin, paclitaxel, or nedaplatin). This potential heterogeneity must be taken into account in interpreting the results of our analysis. Second, most of the included RCTs were not blinded, which may have caused performance and detection biases. Third, some adverse reactions were examined in only two or three studies; thus, the results may be unstable. Finally, the included studies used experimental arms, including cisplatin and paclitaxel, as the control arms. While their findings address these patients, for others the results remain to be determined.

In conclusion, the use of nimotuzumab combined with concurrent chemoradiotherapy was shown to benefit patients with advanced NPC and was better than chemoradiotherapy alone. Moreover, combined therapy did not increase the rates of adverse reactions. Nimotuzumab can therefore be recommended as adjunct therapy in patients with advanced NPC.
| Study or subgroup | Experimental Events | Control Events | Weight (%) | Odds ratio IV, random, 95% CI | Odds ratio IV, random, 95% CI |
|------------------|---------------------|----------------|------------|-------------------------------|-------------------------------|
| **Erythrocytopenia** |                     |                |            |                               |                               |
| Hu et al<sup>1</sup> | 3                   | 16             | 27         | 40.6                          | 0.08 (0.02, 0.32)             |
| Li<sup>2</sup>     | 5                   | 18             | 33         | 59.4                          | 0.15 (0.05, 0.48)             |
| **Subtotal (95% CI)** | 63                  | 60             | 100        | 0.11 (0.05, 0.28)             |                               |
| **Total events**   | 8                   | 34             |            |                               |                               |
| Heterogeneity: z=0.00; χ²=0.50, df=1 (P=0.48); I²=0% | Test for overall effect: Z=4.72 (P=0.00001) |

| **Thrombocytopenia** |                     |                |            |                               |                               |
| Chen et al<sup>1</sup> | 3                   | 11             | 33         | 13.4                          | 0.20 (0.05, 0.80)             |
| Li<sup>2</sup>     | 6                   | 4              | 20         | 12.7                          | 1.71 (0.40, 7.34)             |
| Li et al<sup>3</sup> | 2                   | 1              | 30         | 6.3                           | 2.07 (0.18, 24.15)            |
| Li et al<sup>4</sup> | 20                  | 52             | 52         | 20.9                          | 1.00 (0.45, 2.20)             |
| Lu et al<sup>5</sup> | 2                   | 10             | 26         | 11.1                          | 0.13 (0.02, 0.66)             |
| Shao et al<sup>6</sup> | 9                   | 12             | 24         | 16.1                          | 0.60 (0.19, 1.90)             |
| Tang et al<sup>7</sup> | 15                  | 10             | 60         | 19.5                          | 1.56 (0.64, 3.82)             |
| **Subtotal (95% CI)** | 249                 | 245            | 100        | 0.72 (0.36, 1.45)             |                               |
| **Total events**   | 57                  | 68             |            |                               |                               |
| Heterogeneity: z=0.44; χ²=12.93, df=6 (P=0.04); I²=54% | Test for overall effect: Z=0.91 (P=0.36) |

| **Liver injury** |                     |                |            |                               |                               |
| Li<sup>2</sup>     | 6                   | 4              | 20         | 24.8                          | 1.71 (0.40, 7.34)             |
| Li et al<sup>3</sup> | 1                   | 2              | 30         | 8.7                           | 0.48 (0.04, 5.63)             |
| Shao et al<sup>6</sup> | 2                   | 3              | 24         | 14.7                          | 0.64 (0.10, 4.20)             |
| Tang et al<sup>7</sup> | 10                  | 6              | 60         | 51.8                          | 1.23 (0.45, 3.35)             |
| **Subtotal (95% CI)** | 137                 | 134            | 100        | 1.12 (0.54, 2.30)             |                               |
| **Total events**   | 19                  | 17             |            |                               |                               |
| Heterogeneity: z=0.00; χ²=1.18, df=3 (P=0.76); I²=0% | Test for overall effect: Z=0.30 (P=0.77) |

| **Renal injury** |                     |                |            |                               |                               |
| Li<sup>2</sup>     | 4                   | 5              | 20         | 37.4                          | 0.75 (0.17, 3.33)             |
| Tang et al<sup>7</sup> | 7                   | 6              | 60         | 62.6                          | 1.13 (0.36, 3.56)             |
| **Subtotal (95% CI)** | 83                  | 80             | 100        | 0.97 (0.39, 2.41)             |                               |
| **Total events**   | 11                  | 11             |            |                               |                               |
| Heterogeneity: z=0.00; χ²=0.18, df=1 (P=0.67); I²=0% | Test for overall effect: Z=0.07 (P=0.94) |

| **Neutropenia** |                     |                |            |                               |                               |
| Chen et al<sup>1</sup> | 7                   | 22             | 33         | 56.2                          | 0.13 (0.04, 0.41)             |
| Lu et al<sup>5</sup> | 7                   | 27             | 27         | 43.8                          | 0.10 (0.03, 0.35)             |
| **Subtotal (95% CI)** | 60                  | 60             | 100        | 0.12 (0.05, 0.27)             |                               |
| **Total events**   | 14                  | 13             |            |                               |                               |
| Heterogeneity: z=0.00; χ²=0.12, df=1 (P=0.73); I²=0% | Test for overall effect: Z=5.06 (P=0.00001) |

| **Myelosuppression** |                     |                |            |                               |                               |
| Chen et al<sup>1</sup> | 5                   | 18             | 33         | 22.6                          | 0.15 (0.05, 0.48)             |
| Cheng et al<sup>2</sup> | 2                   | 3              | 40         | 17.8                          | 0.88 (0.14, 5.63)             |
| Tu<sup>6</sup>     | 5                   | 4              | 17         | 19.8                          | 1.81 (0.38, 8.64)             |
| Yu et al<sup>7</sup> | 7                   | 5              | 24         | 21.4                          | 2.05 (0.53, 7.87)             |
| Zhou and Liao<sup>8</sup> | 7                   | 2              | 16         | 18.3                          | 5.44 (0.92, 32.31)            |
| **Subtotal (95% CI)** | 113                 | 130            | 100        | 1.14 (0.30, 4.24)             |                               |
| **Total events**   | 26                  | 32             |            |                               |                               |
| Heterogeneity: z=1.64; χ²=15.16, df=4 (P=0.004); I²=74% | Test for overall effect: Z=0.19 (P=0.85) |

| **Hair loss** |                     |                |            |                               |                               |
| Chen et al<sup>1</sup> | 6                   | 21             | 27         | 51.8                          | 0.08 (0.02, 0.29)             |
| Lou et al<sup>5</sup> | 4                   | 2              | 30         | 48.2                          | 2.15 (0.36, 12.76)            |
| **Subtotal (95% CI)** | 57                  | 57             | 100        | 0.39 (0.02, 9.73)             |                               |
| **Total events**   | 10                  | 23             |            |                               |                               |
| Heterogeneity: z=4.73; χ²=8.55, df=1 (P=0.003); I²=88% | Test for overall effect: Z=0.57 (P=0.57) |

| **Fever** |                     |                |            |                               |                               |
| Lu et al<sup>5</sup> | 0                   | 2              | 27         | 13.7                          | 0.19 (0.01, 4.05)             |
| Tu<sup>6</sup>     | 6                   | 14             | 17         | 25.5                          | 0.63 (0.92, 34.57)             |
| Zhou and Liao<sup>8</sup> | 3                   | 16             | 16         | 27.2                          | 0.69 (0.13, 3.75)             |
| Zhuang et al<sup>7</sup> | 7                   | 13             | 22         | 33.5                          | 0.37 (0.11, 1.10)             |
| **Subtotal (95% CI)** | 77                  | 82             | 100        | 0.80 (0.21, 3.12)             |                               |
| **Total events**   | 16                  | 21             |            |                               |                               |
| Heterogeneity: z=1.03; χ²=6.73, df=3 (P=0.08); I²=55% | Test for overall effect: Z=0.32 (P=0.75) |

Figure 5: Sensitivity analysis of the pooled estimation.

Abbreviations: IV, inverse variance; CI, confidence interval.
Acknowledgments
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Disclosure
The authors report no conflicts of interest in this work.

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# Supplementary materials

**PRISMA 2009 checklist**

| Section/topic | # | Checklist item                                                                                                                                                                                                 | Reported on page # |
|---------------|---|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------|
| Title         |   | Identify the report as a systematic review, meta-analysis, or both.                                                                                                                                               | 1                  |
| Abstract      | 2 | Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number. | 2–3                |
| Introduction  | 3 | Describe the rationale for the review in the context of what is already known.                                                                                                                                    | 4                  |
| Objectives    | 4 | Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).                                                   | 5                  |
| Methods       |   |                                                                                                                                                                                                             |                    |
| Protocol and registration | 5 | Indicate if a review protocol exists, if and where it can be accessed (eg, Web address), and, if available, provide registration information including registration number.                                               | 5–6                |
| Eligibility criteria | 6 | Specify study characteristics (eg, PICOS, length of follow-up) and report characteristics (eg, years considered, language, publication status) used as criteria for eligibility, giving rationale.                                     | 6–7                |
| Information sources | 7 | Describe all information sources (eg, databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.                                        | 6–7                |
| Search        | 8 | Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.                                                                               | 6                  |
| Study selection | 9 | State the process for selecting studies (ie, screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).                                                           | 6                  |
| Data collection process | 10 | Describe method of data extraction from reports (eg, piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.                                           | 7                  |
| Data items    | 11 | List and define all variables for which data were sought (eg, PICOS, funding sources) and any assumptions and simplifications made.                                                                             | 7                  |
| Risk of bias in individual studies | 12 | Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis. | 6–7                |
| Summary measures | 13 | State the principal summary measures (eg, risk ratio, difference in means).                                                                                                                                     | 7–8                |
| Synthesis of results | 14 | Describe the methods of handling data and combining results of studies, if done, including measures of consistency (eg, I^2) for each meta-analysis.                                                                 | 7–8                |
| Risk of bias across studies | 15 | Specify any assessment of risk of bias that may affect the cumulative evidence (eg, publication bias, selective reporting within studies).                                                                     | 8                  |
| Additional analyses | 16 | Describe methods of additional analyses (eg, sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.                                                                 | 8                  |
| Results       |   |                                                                                                                                                                                                             |                    |
| Study selection | 17 | Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.                                                  | 9                  |
| Study characteristics | 18 | For each study, present characteristics for which data were extracted (eg, study size, PICOS, follow-up period) and provide the citations.                                                                     | 9–14               |
| Risk of bias within studies | 19 | Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).                                                                                                | 15                 |

*Figure S1 (Continued)*
**PRISMA 2009 checklist**

| Section/topic                         | #   | Checklist item                                                                 | Reported on page # |
|---------------------------------------|-----|--------------------------------------------------------------------------------|--------------------|
| Results of individual studies         | 20  | For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot. | 15                 |
| Synthesis of results                  | 21  | Present results of each meta-analysis done, including confidence intervals and measures of consistency. | 16                 |
| Risk of bias across studies           | 22  | Present results of any assessment of risk of bias across studies (see item 15). | 16–17              |
| Additional analysis                   | 23  | Give results of additional analyses, if done (eg, sensitivity or subgroup analyses, meta-regression [see item 16]). | 17                 |

**Discussion**

| Section/topic                         | #   | Checklist item                                                                 | Reported on page # |
|---------------------------------------|-----|--------------------------------------------------------------------------------|--------------------|
| Summary of evidence                   | 24  | Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (eg, healthcare providers, users, and policy makers). | 17–19              |
| Limitations                           | 25  | Discuss limitations at study and outcome level (eg, risk of bias), and at review-level (eg, incomplete retrieval of identified research, reporting bias). | 19                 |
| Conclusions                           | 26  | Provide a general interpretation of the results in the context of other evidence, and implications for future research. | 20                 |

**Funding**

| Section/topic                         | #   | Checklist item                                                                 | Reported on page # |
|---------------------------------------|-----|--------------------------------------------------------------------------------|--------------------|
| Funding                               | 27  | Describe sources of funding for the systematic review and other support (eg, supply of data); role of funders for the systematic review. | Declared on online PLoS submission system |

**Figure S1** PRISMA checklist.

Notes: Reproduced from Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med. 2009;6(6):e1000097. For more information, visit: [www.prisma-statement.org](http://www.prisma-statement.org).

**Figure S2** Risk of bias and applicability concerns graph: review authors’ judgments about each domain presented as percentages across included studies.
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