Pemetrexed plus platinum as the first-line treatment option for advanced non-small cell lung cancer: a meta-analysis of randomized controlled trials


CRD summary
The review concluded that pemetrexed plus platinum chemotherapy in the first-line setting lead to a significant survival advantage for advanced non-small cell lung cancer patients and non-squamous patients compared with other platinum-based regimens. The authors' conclusions reflect the evidence available, but the limited study quality assessment makes it difficult to evaluate their reliability.

Authors' objectives
To compare the efficacy and toxicities of pemetrexed plus platinum chemotherapy with other platinum-based regimens in patients with previously untreated advanced non-small cell lung cancer.

Searching
PubMed, EMBASE and Cochrane Central Register of Controlled Trials (CENTRAL) databases were searched to December 2011 without language or date restrictions; search terms were reported. References of trials and reviews were searched. The American Society of Clinical Oncology and European Society for Medical Oncology annual meeting abstracts in the last 15 years were also searched.

Study selection
Eligible studies were randomised controlled trials (RCTs) that compared pemetrexed plus cisplatin or carboplatin chemotherapy with other platinum-based regimens (third-generation agents plus cisplatin or carboplatin regimens) in previously untreated non-small cell lung cancer patients (stage IIIIB or IV). The main outcomes of interest were overall survival, progression-free survival, overall response rate and toxicity.

Most patients were male, and most had stage IV non-squamous cell carcinoma. Median participant ages ranged from 59 to 66 years. Most studies used carboplatin. Comparator treatments included gemcitabine or docetaxel.

Two reviewers independently selected studies for inclusion, with disagreements resolved by all reviewers.

Assessment of study quality
Two reviewers independently assessed study quality using the Jadad scale with the following criteria: randomisation, blinding and withdrawals/drop-outs. The maximum possible score was 5 points. Disagreements were resolved by consensus.

Data extraction
Data were extracted to calculate hazard ratios or odds ratios with 95% confidence intervals. Authors were contacted for missing data when necessary. Two reviewers independently extracted data, with disagreements resolved by consensus.

Methods of synthesis
Meta-analyses were performed to calculate pooled odds ratios or hazard ratios with 95% confidence intervals. Heterogeneity was assessed using $I^2$ and $X^2$. A fixed-effect model was used, unless statistically significant heterogeneity was found, in which case a random-effects model was used. Evidence for publication bias was evaluated visually by inspecting funnel plots and statistically using Egger's test.

Results of the review
Four RCTs were included (2,518 participants, range 146 to 1,725). Three studies scored three points on the Jadad scale and one study scored two points. All trials reported withdrawals and drop-outs, but none reported use of double-blinding.

Pemetrexed plus platinum chemotherapy improved overall survival by 9% compared with other regimens (HR 0.91,
95% CI 0.83 to 1.00, 4 RCTs); the risk reduction was 13% in patients with non-squamous cell carcinoma (3 RCTs), although this result was largely driven by the one trial which used carboplatin. There were no statistically significant differences for progression-free survival (two RCTs) and overall response (3 RCTs).

Pemetrexed plus platinum chemotherapy resulted in less grade 3-4 neutropenia (OR 0.50, 95% CI 0.34 to 0.74; four RCTs) and leukopenia (OR 0.41, 95% CI 0.25 to 0.65; three RCTs), but more grade 3-4 nausea (OR 1.63, 95% CI 1.11 to 2.39; four RCTs). However, there were no significant differences for vomiting and diarrhoea. Further toxicity results were reported.

There was no evidence of statistically significant heterogeneity or publication bias, except for the grade 3-4 haematological toxicity outcomes, which were all subject to statistically significant heterogeneity.

**Authors’ conclusions**
Pemetrexed plus platinum chemotherapy in the first-line setting leads to a significant survival advantage for advanced non-small cell lung cancer patients and non-squamous patients compared with other platinum-based regimens.

**CRD commentary**
The review addressed a clear question and was supported by reproducible eligibility criteria. Attempts to identify all relevant studies in any language were undertaken by searching electronic databases and checking references and conference proceedings.

Suitable methods were employed to reduce the risks of reviewer error and bias throughout the review. Study quality was assessed using the Jadad scale. This produces limited evaluations since allocation concealment methods - an important potential source of bias - were not assessed, and only the reporting of withdrawals and drop-outs was assessed, rather than whether they may bias trial results.

Sufficient study details were provided and appropriate methods were used to pool data and to assess and investigate heterogeneity. The clinical value of the pooled results for grade 3-4 haematological toxicity was limited, due to the significant heterogeneity found. The authors' conclusions reflect the evidence available, but the limited study quality assessment makes it difficult to evaluate their reliability.

**Implications of the review for practice and research**
**Practice:** The authors stated that, taking into account less toxicity (such as neutropenia and leukopenia), pemetrexed plus platinum chemotherapy could be considered as the first-line treatment option for patients with advanced non-small cell lung cancer, especially those with non-squamous histology. They added that their conclusions should be applied to patients unsuitable for targeted therapy.

**Research:** The authors stated a need for an individual patient data analysis to confirm their findings and added that more trials that compared pemetrexed plus platinum with other platinum-based regimens were needed in chemotherapy-naïve advanced non-squamous non-small cell lung cancer patients.

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