Comparing irinotecan/cisplatin with etoposide/cisplatin in patients with ED-SCLC: a meta-analysis of efficacy and toxicity

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CRD summary
The review concluded that irinotecan plus cisplatin did not lengthen overall survival or progression-free survival compared with etoposide plus cisplatin in patients with extensive-stage disease small cell lung cancer but the adverse events profile differs considerably. The uncertain quality of the evidence base and differences across studies limit the reliability of the authors’ conclusions.

Authors’ objectives
To quantify the magnitude of the benefit with irinotecan plus cisplatin compared with etoposide plus cisplatin in extensive-stage disease small cell lung cancer patients.

Searching
Cochrane Central Register of Controlled Trials (CENTRAL), EMBASE and PubMed were searched for articles in any language; search terms were reported. Abstracts published in the proceedings of the International Association for the Study of Lung Cancer, American Society of Clinical Oncology and European Society for Medical Oncology were searched.

Study selection
Randomised controlled trials (RCTs) of irinotecan plus cisplatin versus etoposide plus cisplatin in patients with extensive-stage disease small cell lung cancer (cytologically or histologically confirmed) were eligible for inclusion. Extensive-stage disease was defined as distant metastasis and/or contra lateral hilar-node metastasis. Patients had to have had no prior treatment with chemotherapy, radiotherapy or surgery. Patients with pleural effusion alone were excluded. Trials had to report on the primary endpoints of overall survival and progression-free survival. A range of secondary outcomes, including adverse events, were considered.

The included trials studied irinotecan (60 to 65mg/m²) plus cisplatin (30 to 80mg/m²) versus etoposide (100 to 120mg/m²) plus cisplatin (60 to 80mg/m²) in patients of primarily Caucasian ethnicity; one trial included East Asian patients. The median age of patients ranged from 60 to 63 years. Most patients had performance status 0 to 1.

The authors did note state how many reviewers undertook study selection.

Assessment of study quality
Quality assessment was undertaken using the Jadad scale of randomisation, blinding and withdrawals and drop-outs to give a maximum score out of five. Trials that scored 2 or less were deemed low quality.

Two reviewers independently undertook quality assessment and disagreements were resolved by discussion.

Data extraction
Data were extracted on continuous outcomes and used to calculate hazard ratios (HR) together with 95% confidence intervals (CI). Data on binary outcomes were extracted and used to calculate odds ratios (OR) and 95% CIs. Where survival data were not reported, survival curves were used to extract data.

Two reviewers independently extracted these data and disagreements were resolved by discussion.

Methods of synthesis
Fixed-effect meta-analysis was used to calculate pooled hazard ratios and odds ratios, together with 95% CIs. The I² statistic was used to assess statistical heterogeneity. Where there was evidence of moderate to high statistical heterogeneity (I²≥25%), a DerSimonian and Laird random-effects model was used. The number needed to treat was calculated for significant results. Publication bias was assessed using funnel plots. Sensitivity analysis excluded one
study at a time.

**Results of the review**

Four RCTs were included in the review (1,541 patients, range 154 to 651 patients). All of the trials scored 2 on the Jadad scale and were deemed poor quality. Median follow-up periods of 11.7 to 31.7 months were reported.

There was no significant difference in the rates of overall survival (HR 0.85, 95% CI 0.71 to 1.01; $I^2=61\%$; four RCTs) or progression-free survival (HR 0.91, 95% CI 0.74 to 1.12; $I^2=75\%$; four RCTs) between irinotecan or etoposide cisplatin regimens. There was also no significant difference for overall response rate ($I^2=65\%$; four RCTs), disease control rate ($I^2=0\%$; three RCTs), one-year survival ($I^2=40\%$; four RCTs) and two-year survival ($I^2=56\%$; three RCTs).

**Adverse events:** There were fewer haematological toxicities with irinotecan, compared with etoposide and notably statistically significantly lower rates of neutropenia (OR 0.20, 95% CI 0.11 to 0.38; $I^2=84\%$; four RCTs) and thrombocytopenia (OR 0.34, 95% CI 0.14 to 0.78; $I^2=74\%$; four RCTs). There were more non-haematological toxicities with irinotecan than with etoposide, notably statistically significantly higher rates of diarrhoea (OR 15.26, 95% CI 8.10 to 28.78; $I^2=40\%$; four RCTs) and vomiting (OR 1.74, 95% CI 1.18 to 2.58; $I^2=63\%$; three RCTs). Other results for toxicities were presented in the review.

Sensitivity analysis that excluded the study conducted in East Asian patients reduced the statistical heterogeneity in some analyses; full results were presented in the review.

**Authors’ conclusions**

Irinotecan plus cisplatin did not lengthen overall survival or progression-free survival compared with etoposide plus cisplatin in patients with extensive-stage disease small cell lung cancer but the adverse events profile differed considerably.

**CRD commentary**

Inclusion criteria for the review were clearly defined. Four relevant databases were searched. There were no language restrictions. Publication bias was assessed but the meaningfulness of an analysis with fewer than 10 trials was limited. Attempts were made to reduce reviewer error and bias during data extraction and quality assessment; it was unclear whether the same attempts were made for study selection. Quality assessment was undertaken using a standard checklist, which produced very little information about whether or not trial results were likely to be biased. The authors noted that there were differences in patient populations across the trials.

Data were combined using meta-analysis even though there was evidence of substantial statistical heterogeneity in many of the analyses. Much of the heterogeneity appeared to be due to inclusion of East Asian patients in a predominantly Caucasian patient sample. Given that most of the patients were Caucasians, the results of the review were limited to this patient group and this should be considered when interpreting results.

The uncertain quality of the evidence base and differences across studies limits the reliability of the authors’ conclusions. The authors’ call for further research appears warranted.

**Implications of the review for practice and research**

**Practice:** The authors stated that irinotecan in combination with cisplatin represented an equally effective regimen with a different toxicity profile that can be used when the toxicity of etoposide in combination with cisplatin is found to be severe in patients with extensive-stage small cell lung cancer.

**Research:** The authors stated that large prospective trials with long-term follow-up were needed. The differences in responses due to patient ethnicity needed better reporting and exploration using gene sequencing technology.

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