A meta-analysis of randomized controlled trials comparing irinotecan/platinum with etoposide/platinum in patients with previously untreated extensive-stage small cell lung cancer


CRD summary
The review found that irinotecan with platinum may be associated with higher overall response and survival rates than etoposide with platinum for previously untreated extensive-stage small cell lung cancer, with a differing side-effect profile. The authors suggested that their findings required cautious interpretation: this appears justified in view of the heterogeneity, small number and questionable quality of the primary studies.

Authors’ objectives
To compare the efficacy and safety of irinotecan with platinum versus etoposide with platinum for previously untreated extensive-stage small cell lung cancer.

Searching
PubMed and Cochrane Central Register of Controlled Trials (CENTRAL) were searched in April 2009. Search terms were reported. PDQ and Clinical Trials.gov databases, annual meeting abstracts for the previous 10 years of the American Society of Clinical Oncology and European Society for Medical Oncology and reference lists of primary studies and reviews were searched. The search was unlimited by language or publication status.

Study selection
Randomised controlled trials (RCTs) that compared IP (irinotecan with cisplatin or carboplatin) with EP (etoposide with cisplatin or carboplatin) in individuals with previously untreated pathologically confirmed small cell lung cancer with clinically diagnosed extensive-stage disease were eligible for inclusion.

Participants in the included studies were predominantly male (range 55% to 90%). Median age ranged from 51 to 68 years. The proportion of participants with a good performance status (such as World Health Organisation 0-1) ranged from 52% to 100%. The dose-intensity of interventions differed across studies.

Outcomes reported in the review were overall response to treatment, overall and progression-free survival, grade three or four toxicity and treatment-related death. Study settings included Japan and North America.

The authors did not state how many reviewers performed study selection.

Assessment of study quality
Study quality was evaluated using the Jadad scale of adequacy of reported randomisation, double-blinding and withdrawals or dropouts.

Two reviewers independently assessed study validity. Disagreements were resolved by discussion with a third reviewer.

Data extraction
Relative risks for response rates, hazard ratios (HRs) for survival and odds ratios (ORs) for toxicity were extracted or calculated for each study, all with 95% confidence intervals (CIs). Where the hazard ratio was not reported, it was estimated from Kaplan-Meier curves using published methods (Parmar 1998). Intention-to-treat analysis was used for efficacy outcomes and treatment-received analysis for toxicity outcomes.

Two reviewers independently extracted data. Disagreements were resolved by discussion with a third reviewer.
Methods of synthesis
Studies were combined by meta-analysis to obtain pooled effect estimates and 95% CIs. Fixed-effect models were used unless there was significant heterogeneity, in which case random-effects models were used. Heterogeneity was assessed using $\chi^2$. Publication bias was assessed using funnel plots and Begg’s and Egger’s tests. Subgroup analyses were conducted by type of platinum used (cisplatin or carboplatin).

Results of the review
Six RCTs were included in the review (n=1,476, range 30 to 327). Two RCTs (n=137) were Phase II (small preliminary studies). Quality scores were 2 (four RCTs), 3 (one RCT) and 4 (one RCT) from a possible maximum of 5. Only one RCT was double-blinded.

IP was associated with significantly higher rates of overall response to treatment (RR 1.10, 95% CI 1.00 to 1.21; five RCTs) and overall survival (HR 0.81, 95% CI 0.66 to 0.99; four RCTs) than EP. There was no significant difference between the groups in progression-free survival (four RCTs).

IP was associated with significantly lower rates of anaemia (OR 0.51, 95% CI 0.36 to 0.72; six RCTs), neutropenia (OR 0.26, 95% CI 0.12 to 0.54; six RCTs) and thrombocytopenia (OR 0.29, 95% CI 0.20 to 0.41; six RCTs). IP was associated with significantly higher rates of vomiting (OR 1.51, 95% CI 1.01 to 2.25; five RCTs) and diarrhoea (OR 10.52, 95% CI 5.94 to 18.65; six RCTs). There was no significant difference between the groups in treatment-related mortality (four RCTs).

There was significant heterogeneity in the analyses of overall survival ($I^2=67\%$), progression-free survival ($I^2=79\%$) and neutropaenia ($I^2=84\%$). No evidence of significant publication bias was found. Subgroup analyses restricted to studies that used cisplatin found no significant difference between the groups for efficacy outcomes.

Authors’ conclusions
IP may be associated with higher overall response and survival rates than EP in individuals with previously untreated extensive-stage small cell lung cancer, with a differing side-effect profile.

CRD commentary
The objectives and inclusion criteria of the review were clear. Relevant sources were searched for studies. There were no restrictions by language and publication status. Appropriate tests were used to assess for publication bias. Steps were taken to minimise risks of reviewer bias and error by having more than one reviewer undertake validity assessment and data extraction; it was unclear whether this also applied to study selection.

Overall study quality appeared to be poor, but no details were reported and study quality was hardly mentioned in the interpretation of results. Appropriate statistical techniques were used to combine the studies and assess for heterogeneity. There was significant heterogeneity for some outcomes, which the authors suggested might relate to differences in participant ethnicity and in the type and dose-intensity of the drugs used.

The authors suggested that their findings required cautious interpretation: this appears justified in view of the heterogeneity, small number and questionable quality of the primary studies.

Implications of the review for practice and research
Practice: The authors stated that IP may be an alternative to EP for first-line treatment of extensive-stage small cell lung cancer.

Research: The authors stated that the outcomes of ongoing studies were eagerly awaited and that an individual patient data meta-analysis was required.

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