

# Benefit from ifosfamide treatment in small-cell lung cancer: A meta-analysis

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**Abstract.** This study was conducted to compare the efficacy and safety of ifosfamide plus etoposide plus platinum (IEP) to that of etoposide plus platinum (EP) in patients with previously untreated small-cell lung cancer (SCLC). The Cochrane Library, Embase, MEDLINE and Chinese Biomedical Literature databases were searched to identify all randomized controlled trials comparing IEP to EP in patients with histologically proven SCLC. Two investigators independently assessed the quality of the relevant trials and extracted data. We analyzed the data using Review Manager software, version 4.2.8. A total of 4 trials with 447 previously untreated SCLC patients were included in this meta-analysis. The results of the meta-analysis indicated that there were no significant differences in the overall response [relative risk (RR) = 1.07, 95% confidence interval (CI): 0.97-1.19], 1-year survival rate (RR=1.22, 95% CI: 0.96-1.55) and 2-year survival rate (RR=1.52, 95% CI: 0.75-3.07) between the IEP and EP regimens. However, there were significant differences between the IEP and EP regimens regarding the incidence of grade 3/4 neutropenia (RR=1.52, 95% CI: 1.07-2.17) and grade 3/4 vomiting (RR=1.78, 95% CI: 1.02-3.11). In conclusion, our results suggested that IEP is not superior to EP regimen for the treatment of previously untreated SCLC, whereas the IEP regimen is associated with more severe hematological and gastrointestinal toxicities compared to EP. Therefore, the use of ifosfamide in multimodality treatment regimens requires further investigation.

## Introduction

Small-cell lung cancer (SCLC) accounts for ~15% of all lung cancers (1) and is characterized by a rapid tumor growth rate and early dissemination to regional lymph nodes and to distant sites (2). The emergence of chemotherapy has significantly improved quality of life and survival in SCLC patients. However, long-term survival in SCLC patients has not been satisfactory (3-5). Etoposide plus platinum (EP) is currently the standard first-line treatment used in SCLC to obtain longer overall survival (OS) and progression-free survival, although numerous chemotherapeutic regimens comprising various drugs have been investigated and tested in clinical trials (6,7).

Ifosfamide is considered to be effective for SCLC, even when administered alone (8). Previous studies demonstrated that regimens including ifosfamide may achieve comparable response rates, survival and safety with the standard chemotherapy regimens for SCLC (9-12). Loehrer *et al* (13) and Miyamoto *et al* (14) were the first to apply ifosfamide in combination with the EP regimen (IEP) for the treatment of SCLC. Particularly since the Hoosier Oncology Group initiated a pilot trial to evaluate the efficacy of IEP in extensive SCLC, reporting encouraging results in terms of complete response rate (CRR) and median survival time (15), several clinical trials were performed to further confirm the antitumor activity of ifosfamide in SCLC when used in combination with standard chemotherapeutic agents (16-20). Although discrepant conclusions have been reported by different trials, the IEP regimen is generally applied in SCLC patients according to the clinician's decision.

A meta-analysis reported that there was no strong clinical evidence indicating an advantage of other platinum-based regimens when compared to the EP regimen for patients with extensive SCLC requiring chemotherapy. Moreover, a clinical study comparing EP to the IEP regimen in SCLC was included in the meta-analysis, with the IEP group exhibiting no significant superiority to the EP group (6).

It has not been clearly determined whether the addition of ifosfamide to standard regimens is necessary. In order to evaluate the advantages and disadvantages of ifosfamide for SCLC, we systematically searched all available published randomized controlled trials (RCTs) comparing IEP and EP in SCLC. The aim of this meta-analysis was to synthesize all

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Table I. Characteristics of the 4 trials comparing ifosfamide + etoposide + platinum with etoposide + platinum in patients with previously untreated small-cell lung cancer.

Author	Sample size	Randomization	Allocation concealment	Blinding	Completeness of follow-up	Quality	(Refs.)
Miyamoto <i>et al</i>	92	Adequate	Unclear	Unclear	Adequate	C	(14)
Loehrer <i>et al</i>	171	Adequate	Adequate	Unclear	Adequate	B	(15)
Zhou <i>et al</i>	64	Adequate	Unclear	Unclear	Adequate	C	(19)
Wu <i>et al</i>	120	Adequate	Unclear	Unclear	Adequate	C	(20)

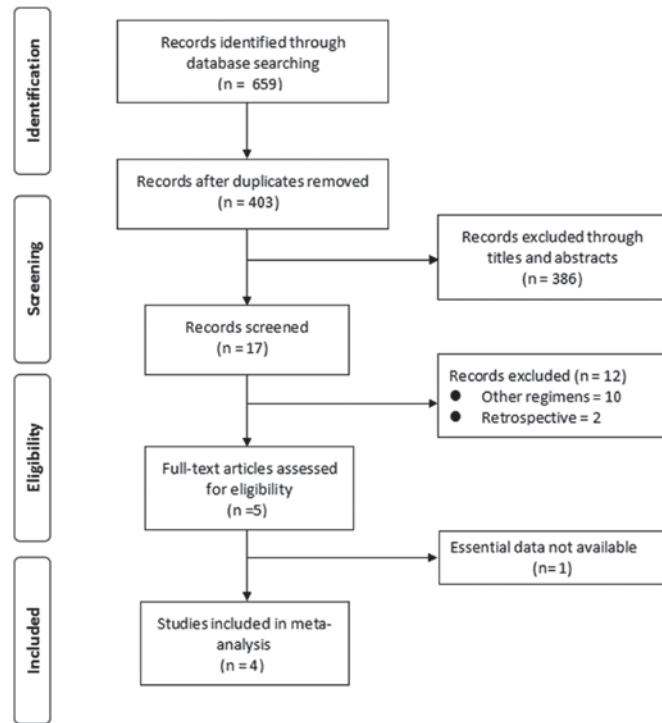


Figure 1. Flowchart of study selection process. The search identified trials comparing ifosfamide + etoposide + platinum to etoposide + platinum in the treatment of small-cell lung cancer.

evidence originating from direct comparisons and assess the efficacy and tolerability of the two regimens used as standard first-line treatment for previously untreated SCLC.

## Materials and methods

**Search strategy.** The Cochrane Library, Embase, MEDLINE and Chinese Biomedical Literature databases were searched to identify all RCTs comparing IEP to the EP regimen in patients with histologically proven SCLC. The following keywords were used: ‘small-cell lung cancer’ or ‘small-cell lung carcinoma’, ‘etoposide’ and ‘ifosfamide’. The search was limited to ‘randomized controlled trials’. No limits based on language were imposed.

**Selection of studies.** Two investigators (H.Z.Y. and Y.M.) independently assessed the retrieved articles. Any disagreements were resolved by consensus. The studies included in the meta-analysis were required to meet all the following criteria:

i) the IEP and EP regimens were compared in previously untreated SCLC patients; and ii) essential information for the meta-analysis was reported in the RCTs. The study selection process is summarized in Fig. 1.

**Data extraction.** The same investigators (H.Z.Y. and Y.M.) independently extracted relevant data on study characteristics and examination results by using a standardized form. To resolve any disagreements between the reviewers, a third reviewer (L.J.M.) assessed all discrepant items and the majority opinion was used for analysis.

The quality items assessed were randomization, allocation concealment, blinding (participants, investigators, outcome assessors and data analysis) and completeness of follow-up.

**Outcome measures.** The efficacy outcomes were CRR, objective response rate and survival rate. Adverse effects included grade 3/4 hematological toxicity and grade 3/4 gastrointestinal toxicity.

**Statistical analysis.** Review Manager software, version 4.2.8 (The Cochrane Collaboration) was used for statistical analyses. Relative risks (RRs) and their 95% confidence intervals (CIs) were calculated using the Mantel-Haenszel method for dichotomous outcomes. We estimated heterogeneity between trials by using the Cochran's Q statistic test and the  $I^2$  metric. The fixed-effects model was generally used for the calculations, unless there was significant heterogeneity, in which case the random-effects statistical model was applied. To assess the sources of possible variation in the study results, we performed a subgroup analysis. Descriptive techniques were employed to assess adverse effects.

## Results

**Search results.** Our search yielded 659 primary studies, of which 256 were duplicate trials, 10 trials referred to treatments other than IEP or EP and 2 retrospective trials were detected. Of the 5 trials considered eligible for assessment, 1 was excluded due to lack of essential data for the meta-analysis. Finally, 4 RCTs, totaling 447 patients, were included in this meta-analysis (Fig. 1). The quality and characteristics of the 4 included studies are summarized in Table I.

### Meta-analysis results

**Response.** Response rate was reported in the 4 trials (14,15,19,20) and the meta-analysis indicated that IEP was superior to the

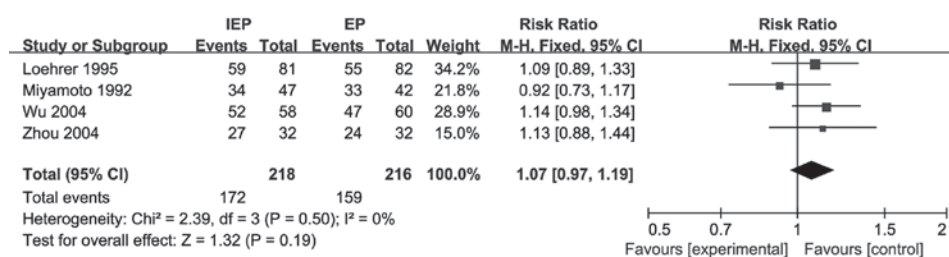


Figure 2. Meta-analysis of overall response of patients with small-cell lung cancer who were treated with ifosfamide + etoposide + platinum (IEP) vs. those treated with the etoposide + platinum (EP) regimen. CI, confidence interval.

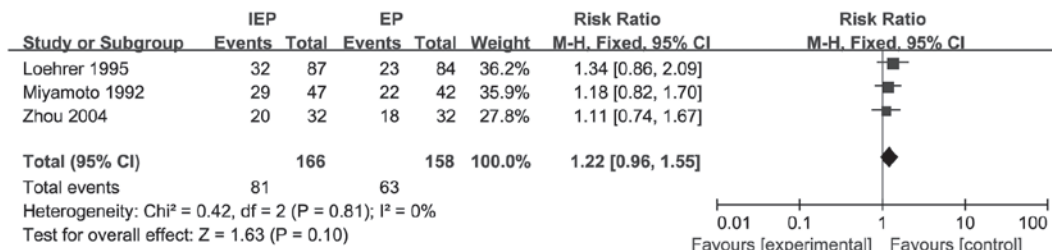


Figure 3. Meta-analysis of 1-year survival rate of patients with small-cell lung cancer who were treated with ifosfamide + etoposide + platinum (IEP) vs. those treated with the etoposide + platinum (EP) regimen. CI, confidence interval.

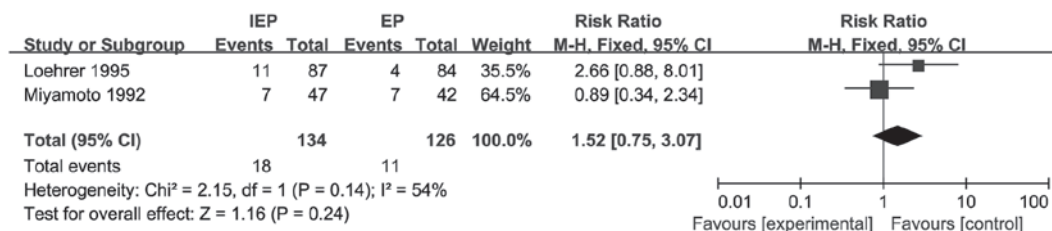


Figure 4. Meta-analysis of 2-year survival rate of patients with small-cell lung cancer who were treated with ifosfamide + etoposide + platinum (IEP) vs. those treated with the etoposide + platinum (EP) regimen. CI, confidence interval.

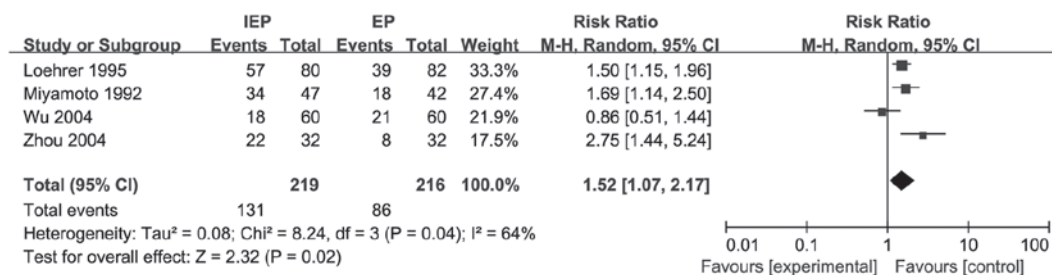


Figure 5. Meta-analysis of hematological toxicity in patients with small-cell lung cancer who were treated with ifosfamide + etoposide + platinum (IEP) vs. those treated with the etoposide + platinum (EP) regimen. CI, confidence interval.

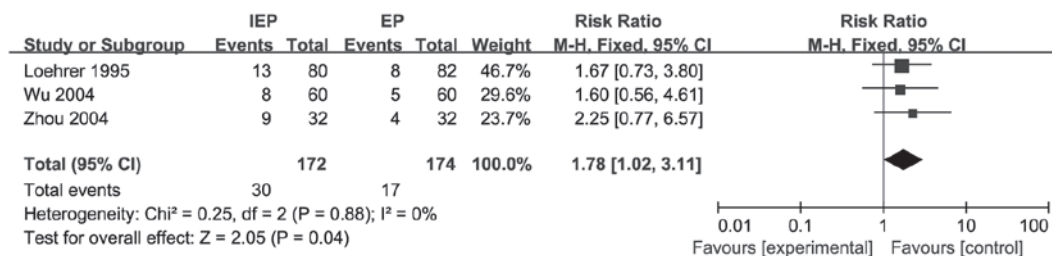


Figure 6. Meta-analysis of gastrointestinal toxicity in patients with small-cell lung cancer who were treated with ifosfamide + etoposide + platinum (IEP) vs. those treated with the etoposide + platinum (EP) regimen. CI, confidence interval.

EP regimen in terms of overall response; however, the difference was not significant (RR=1.07, 95% CI: 0.97-1.19). There was no heterogeneity ( $I^2=0\%$ ,  $P=0.50$ ) and the fixed-effects model was used to pool RR for overall response. The results are shown in Fig. 2.

**Survival rate.** RRs for 1-year survival rate data were available from 3 trials including 324 patients (14,15,19). The meta-analysis revealed no significant difference (RR=1.22, 95% CI: 0.96-1.55) between the IEP and EP regimens. There was no heterogeneity ( $I^2=0\%$ ,  $P=0.81$ ) and the fixed-effects model was used to obtain the pooled RR for 1-year survival rate. The results are shown in Fig. 3.

RRs for 2-year survival rate data were available from 2 trials including 260 patients (14,15). The pooled RR for the 2-year survival rate revealed that IEP may prolong OS in SCLC patients; however, the difference was not significant (RR=1.52, 95% CI: 0.75-3.07). There was significant heterogeneity ( $I^2=54\%$ ,  $P=0.14$ ) and the pooled RR for 2-year survival rate was calculated using the random-effects model. The results are shown in Fig. 4.

**Adverse effects.** All 4 trials reported grade 3/4 hematological toxicities and the IEP regimen was more frequently associated with grade 3/4 neutropenia compared to the EP regimen (RR=1.52, 95% CI: 1.07-2.17). There was significant heterogeneity ( $I^2=64\%$ ,  $P=0.04$ ) and the pooled RR for grade 3/4 neutropenia was calculated using the random-effects model. The results are shown in Fig. 5.

Non-hematological toxicities were reported in 3 trials (15,19,20). The pooled data demonstrated that grade 3/4 vomiting was more common with IEP compared to the EP regimen (RR=1.78, 95% CI: 1.02-3.11). There was no heterogeneity ( $I^2=0\%$ ,  $P=0.88$ ) and the fixed-effects model was used to obtain the pooled RR for grade 3/4 vomiting. The results are shown in Fig. 6.

## Discussion

Chemotherapy is an essential component of the treatment of all SCLC patients. Although the prognosis of SCLC has improved significantly, long-term survival remains <10%. According to the American National Comprehensive Cancer Network guidelines, the most common standard first-line therapy for SCLC is the EP regimen (1-5). To obtain an optimal response, more regimens were investigated by adding new drugs to the standard chemotherapy regimen and several clinical trials were conducted to confirm the efficacy and safety of those new regimens in SCLC (9-20).

The IEP regimen is considered as an alternative first-line treatment option for SCLC by an increasing number of physicians; however, it is our opinion that the superiority of IEP to EP requires further clinical confirmation, as different RCTs reported inconsistent results (14,15,19,20). Loehrer *et al* (15) first reported a group study comparing the IEP to the EP regimen in 163 patients with extensive SCLC and observed significant differences in terms of time-to-progression and OS in favor of the IEP arm. However, Miyamoto *et al* (14) reported that IEP was not superior to EP chemotherapy in SCLC. Subsequently, Zhou *et al* (19) and Wu *et al* (20) further confirmed the results of Loehrer *et al* in their clinical studies; in addition, Wu *et al* (20) proved that IEP may also be used as

salvage chemotherapy for patients with SCLC who failed to respond to EP chemotherapy.

The objective of this meta-analysis was to compare the efficacy and safety of IEP to that of EP in patients with previously untreated SCLC. A total of 4 RCTs involving 447 patients were included. Response rate and grade 3/4 neutropenia were reported in all 4 trials. One-year survival rate was reported by 3 studies and 2-year survival rate by 2 studies. Grade 3 vomiting/nausea were reported by 3 studies. The meta-analysis results demonstrated that IEP failed to achieve a higher response rate and longer survival time, but induced more severe grade 3/4 neutropenia and vomiting compared to the EP regimen.

In conclusion, IEP was not found to be superior to the EP regimen in the first-line treatment of SCLC; in addition, it induced more severe hematological and gastrointestinal toxicities. Therefore, SCLC patients did not obtain any benefit from the addition of ifosfamide to the EP regimen and the role of ifosfamide in multimodality treatment regimens requires further investigation.

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