

Systematic review of first-line chemotherapy for chemo-naïve extensive-stage small-cell lung cancer: network meta-analysis

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Abstract

Background: Our goal was to organize the data from randomized controlled trials that evaluated first-line chemotherapy for chemo-naïve extensive disease small-cell lung cancer (ED-SCLC).

Methods: The protocol following PRISMA methodology was submitted as PROSPERO 154049. We included individually randomized trials comparing two or more chemotherapy regimens as the first-line treatment for chemo-naïve ED-SCLC regardless of the age, sex, performance status, comorbidities, and organ functions written in the English language since 2000. Molecular targeted agents and immune checkpoint inhibitors were considered chemotherapy along with cytotoxic medications. We pooled the logarithm of hazard ratio (HR) and its standard error using the frequentist weighted least squares approach random-model network meta-analysis.

Results: A total of 46 eligible trials that involved 11,987 patients were included. The primary endpoint, HR of overall survival (OS, HRos) of the selected comparisons was as follows: carboplatin+amrubicin (HRos 0.56, 95% confidence interval (CI) 0.33–0.96), carboplatin+etoposide+atezolizumab (HRos 0.70, 95% CI 0.53–0.92), and carboplatin+irinotecan (HRos 0.73, 95% CI 0.58–0.91) were compared with carboplatin+etoposide. The carboplatin+etoposide+atezolizumab regimen was compared with carboplatin+irinotecan (HRos 0.97, 95% CI 0.68–1.37) and cisplatin+irinotecan regimen (HRos 0.87, 95% CI 0.58–1.31). “Selective carboplatin or cisplatin (CBDCA/CDDP)”+etoposide+durvalumab was compared with CBDCA/CDDP+etoposide (HRos 0.73, 95% CI 0.59–0.91). Platinum+etoposide+durvalumab was compared with platinum+irinotecan (HRos 0.88, 95% CI 0.67–1.15). Cumulative meta-analysis suggested that platinum+irinotecan was associated with better OS than platinum+etoposide as of 2010 through 40 out of 46 trials in our review that used platinum+etoposide as a reference regimen.

Conclusion: Patients treated with carboplatin+amrubicin, carboplatin+etoposide+atezolizumab, CBDCA/CDDP+etoposide+durvalumab, and platinum+irinotecan showed better HRos than those treated with platinum+etoposide, one of the standard regimens.

Keywords: network meta-analysis, PD-L1 inhibitor, small cell lung carcinoma, survival

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Background

Small-cell lung cancer (SCLC) is a thoracic malignancy often caused by habitual smoking.¹ The majority of patients are diagnosed with SCLC after progression to extensive disease (ED) due to rapid growth and easy dissemination of the tumor

cells. Chemotherapy is usually considered in ED-SCLC patients with a good performance status because SCLC is highly sensitive to the treatment. A Japanese study by Noda *et al.* reported that the cisplatin (CDDP)+irinotecan (CPT11) regimen resulted in better overall survival (OS)

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than the CDDP+etoposide (ETP) regimen.² Since then, many physicians have believed that the CDDP+ CPT11 regimen was the best to treat patients with ED-SCLC, especially the non-elderly Asian population.³ However, the outcome was not confirmed as the primary endpoint in any of the subsequent phase III trials in the United States (US),^{4,5} Europe,⁶ and Korea,³ although CDDP+CPT11 showed a tendency of better OS in most of these trials. Therefore, others chose CDDP+ETP as the standard regimen.⁷ Both CDDP+CPT11 and CDDP+ETP have been considered the standard regimen for more than a decade.

Recently, oncologists were excited to learn that addition of atezolizumab (ATZ) or durvalumab (DUR) to platinum+ETP improved both OS and progression-free survival (PFS) in patients with ED-SCLC.^{8,9} Programmed death-ligand 1 (PD-L1) inhibiting regimens are an excellent therapeutic option for lung cancer as well as several other malignancies.¹⁰

Although the PD-L1 inhibiting agents including ATZ and DUR may be attractive options to treat patients with ED-SCLC, there could be other attractive regimens that are not currently featured in phase III trials.¹¹⁻¹³ Therefore, the goal of this systematic review was to organize data from randomized clinical trials (RCT) evaluating first-line chemotherapy regimens for ED-SCLC that were published in the last 20 years and apply network meta-analysis to assess the obtained data.

Methods

Protocol registration

The protocol was submitted to the International Prospective Register of Systematic Reviews (submission ID, 154049).¹⁴ The protocol was structured according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.¹⁵

Study search

Search strategies for PubMed, Web of Science Core Collection, Cochrane advanced search, and EMBASE are presented in Supplemental Text 1. The databases were searched on 10 October 2019. An additional manual search was also conducted independently by two investigators (NH and HC). Papers identified by hand search were

carefully evaluated before being added to the list of candidate articles.

Candidate articles were first screened and subsequently scrutinized independently by two investigators. Any discrepancies were resolved through discussions between the two investigators.

Publication type and trial design

We included individually randomized trials that compared two or more chemotherapy regimens as the first-line treatment for chemo-naïve ED-SCLC patients that were published as full papers in English since 2000. Conference abstracts in English reported after 2015 were also included to review prevailing regimens. We contacted author groups of abstracts to obtain relevant data.

All superiority, non-inferiority, phase II, phase III, non-blinded, single-blinded, and double-blinded trials were included. However, patients included in these trials had to be randomized before the initiation of chemotherapy. Therefore, trials that randomized relapsed or responsive cases were excluded.

Trials evaluating a specific population defined by age, race, or performance status were permitted. Further, we excluded trials that did not report survival data. Trials that included both limited disease and ED were included as long as the data of ED cases could be extracted.

Treatments

All regimens that included cytotoxic, molecular targeted agents, or an immune checkpoint inhibitor were considered chemotherapy. However, any regimen that included so-called “first-generation” cytotoxic agents developed around 1950 namely methotrexate, mitomycin, vincristine, cyclophosphamide, doxorubicin, and ifosfamide was excluded from our analysis because such regimens are outdated.⁷

Regimens that used the same medication were evaluated collectively regardless of the administration route, timing, frequency, dosage, and schedule. We equated placebo with “no treatment.” For example, CDDP + (placebo of ETP) arm was identical to the CDDP arm in our analysis. The best supportive care could not be a comparator of chemotherapy. Studies that reported

multimodality treatments including chemoradiotherapy, radiotherapy, or surgery were not included. Similarly, studies that reported irregular regimens, such as alternative regimens, were excluded.

Study that permitted the physician to select either carboplatin (CBDCA) or CDDP were regarded as “selective CBDCA or CDDP (CBDCA/CDDP) regimens” in order to discriminate from regular CDDP and CBDCA.

We used two models to assess the primary endpoint, OS. In the first model, CBDCA and CDDP were distinct from each other. In the second model, CBDCA, CDDP, and CBDCA/CDDP were collectively considered platinum.

Patients

Chemo-naïve ED-SCLC patients who underwent first-line chemotherapy were included. The age, sex, performance status, co-morbidities, and organ functions of patients were not considered as differentiating parameters.

Quality assessment

We assessed the quality of the original studies using six domains of the Cochrane Risk of Bias tool: random sequence generation, allocation concealment, performance, detection, attrition, and reporting.¹⁶

Outcomes

The primary outcome measure in our review was the hazard ratio (HR) for OS (HRos). The secondary outcomes were HR for PFS (HRpfs) and odds ratio (OR) of response rate (RR, ORrr).¹⁷ Evaluation of disease progression to assess the PFS and the objective response to assess RR was done by ensuring minimal deviation from the Response Evaluation Criteria In Solid Tumors 2000 guidelines and the 2009 revised guidelines.¹⁸ In studies where disease progression and objective response were evaluated both by physicians who treated patients and by the blinded Independent Central Review Board, we chose the data reviewed by the blinded evaluator. Time to progression was not regarded as PFS.

Additional cumulative meta-analysis comparing ETP and CPT11 regimens, head-to-head meta-analysis evaluating adding of PD-L1 inhibiting

agent on platinum+ETP, and head-to-head meta-analysis comparing CBDCA and CDDP doublet with the same counterpart were conducted. Although these analyses were not part of the protocol, in our opinion, these analysis could provide useful data to the readers.

Data extraction

Data, such as author name, publication year, country of origin, number of patients randomized, chemotherapy regimen, and outcomes were extracted from the included studies independently by two investigators (NH and HC). The data were cross-checked, and any discrepancies were discussed and resolved by the two investigators. Data from non-inferiority trials were extracted using the same method as applied for the superiority trials. For three-arm studies, data of each pair-wise comparison were extracted. We adopted Parmar’s method to extract data from Kaplan–Meier curves, where required.¹⁹ Intention-to-treat analysis was preferred over full analysis set analysis and per-protocol analysis when two or more of them were available.

Statistical analyses

We pooled the logarithm of OR, HR, and their standard errors using the frequentist weighted least squares approach random-model network meta-analysis.^{20,21} A league table of the HRos, HRpfs, ORrr, and their 95% confidence intervals (CI) was presented. For the network meta-analysis, the “netmeta” command in the “netmeta” package of R Project was used. The head-to-head meta-analysis and generation of a funnel plot were performed using Review Manager ver5.3 (Cochrane, London, UK). GraphPad Prism ver. 7.02 was used to draw figures as necessary (GraphPad Software, San Diego, CA, USA).

Results

Study selection and characteristics

We found 1431 and 5 articles through search engine and hand searching, respectively. Of the 1436 articles that met the preliminary criteria, 569, 669, and 152 were excluded due to duplication, title/abstract screening, and full-article scrutiny, respectively (Figure 1). We identified 46 eligible articles that provided data of HRos (45 studies), HRpfs (33 studies), and ORrr (43 studies), respectively (Supplemental Text 2, Table 1).

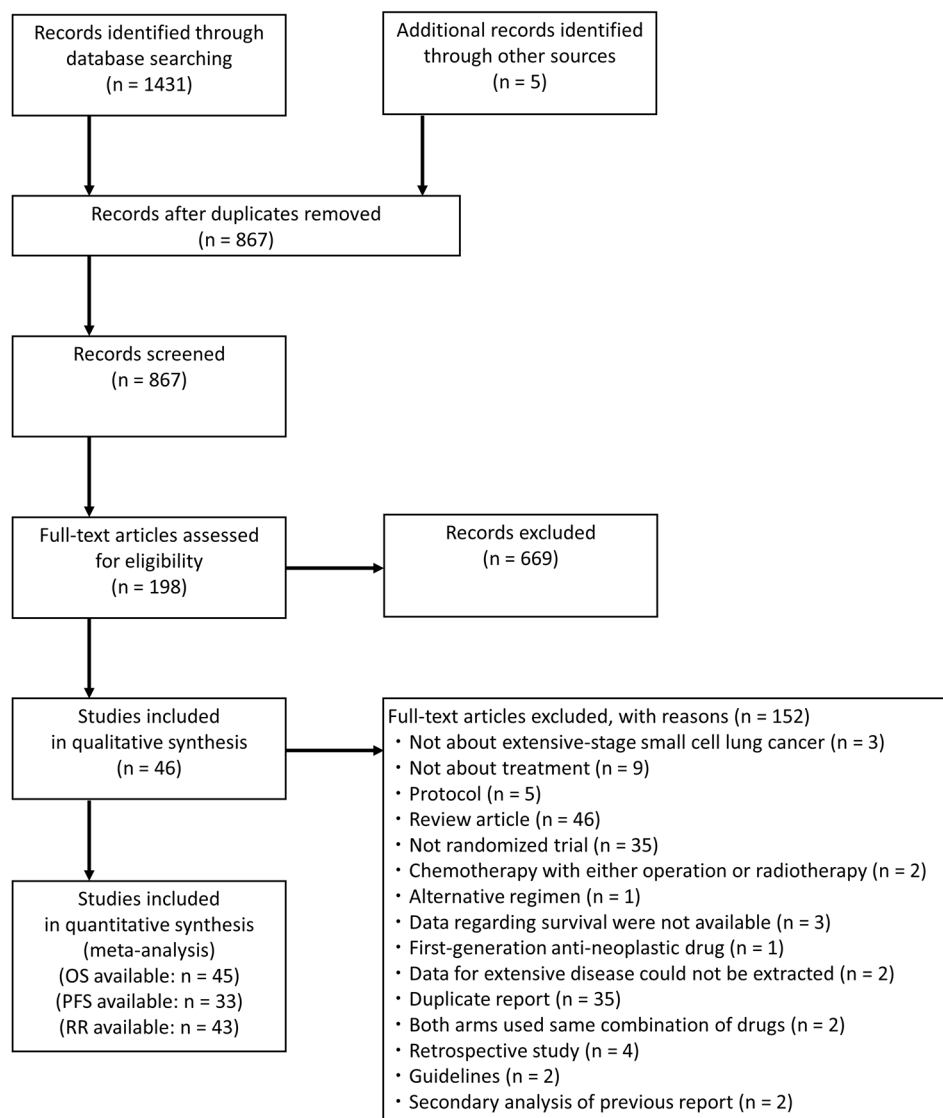


Figure 1. PRISMA flow diagram for the study search.

OS, overall survival; PFS, Progression-free survival; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RR, response rate.

Furthermore, we obtained data for the CASPIAN trial from the author group.⁹

Of the included studies, 18 were from the US, 15 were from the European Union (EU), 6 were from Japan, 4 were from China, 2 were from Korea, and 1 was from India; 24 studies were phase III and 20 were phase II trials. Two studies did not declare the study phase. Number of patients randomized in each trial ranged from 56 to 1132 with a median of 155, and the total number of cases was 11,987. A total of 26 trials included the ECOG performance status 0–2. Of the 46 trials, 3 were three-arm studies, and the

remaining 43 adopted a two-arm study design. The most common regimen was CDDP+ETP, which was used in 20 RCTs, followed by CBDCA+ETP, which was used in 13 trials; 7 trials considered ETP+selective CDDP/CBDCA as the reference arm. Therefore, 40 out of the 46 trials (87%) compared platinum+ETP with other regimens. The median years of publication of these three regimens were as follows: 2012 (IQR 2007.5–2016) for CDDP+ETP, 2014 (IQR 2008–2017) for CBDCA+ETP, and 2017 (IQR 2013.5–2018) for CBDCA/CDDP+ETP (Table 1). Therefore, we concluded that preferred reference regimen shifted from CDDP+ETP to

Table 1. Characteristics of included studies.

Study	Country	Phase n	Median age PS	Arm1 treatment	Arm2 treatment	Arm3 treatment	ROBH/U/L	Outcome missing
Cheng_2019	China	III 234	56* ECOG 0-1	lobaplatin 30 mg/m ² d1 + ETP 100 mg/m ² d1-3, q3w	CDDP 80 mg/m ² d1 + ETP 100 mg/m ² d1-3, q3w		2/0/4	
Weiss_2019	US	II 77	65* ECOG 0-2	Tx2 + trilaciclib 240 mg/m ² d1-3, q3w	CBDCA AUC5 d1 + ETP 100 mg/m ² d1-3, q3w		1/0/5	
Reck_2019	Germany	II 140	63 ECOG 0-1	Tx2 + roniciclib 3d/w, q3w	(CDDP 75 mg/m ² d1 or CBDCA ACU5) + ETP 100 mg/m ² d1-3, q3w		0/2/4	
Owonikoko_2019 ECOG-ACRIN2511	US	II 128	66 ECOG 0-1	Tx2 + veliparib 100 mg d1-7, q3w	CDDP 75 mg/m ² d1 + ETP 100 mg/m ² d1-3, q3w		0/2/4	
Paz-Ares_2019CASPIAN	Spain	III 557	63 ECOG 0-1	Tx2 + durvalumab 1500 mg, q3w	(CDDP 75-80 mg/m ² d1 or CBDCA ACU5-6) + ETP 80-100 mg/m ² d1-3, q3w		2/2/2	
Kim_2019	Korea	III 362	65 ECOG 0-2	CDDP 70 mg/m ² d1 + CPT11 65 mg/m ² d1,8, q3w	CDDP 70 mg/m ² d1 + ETP 100 mg/m ² d1-3, q3w		2/2/2	
Horn_2018IMpower133	US	III 403	64 ECOG 0-1	Tx2 + atezolizumab 1200 mg d1, q3w	CBDCA AUC5 d1 + ETP 100 mg/m ² d1-3, q3w		0/0/6	
Morikawa_2017NJLCOG0901	Japan	II 71	71 ECOG 0-2	CBDCA AUC4 d1 + AMR 35 mg/ m ² d1-3, q3w	CBDCA AUC5 d1 + CPT11 70 mg/m ² d1,8, q3w		1/2/3	
Jala_2017MATISSE	US	III 188	61 ECOG 0-2	Tx2 + palifosfamide 130 mg/m ² d1-3, q3w	CBDCA AUC4 d1 + ETP 100 mg/m ² d1-3, q3w		2/0/4	PFSRR
Seckl_2017LUNGSTAR	UK	III 482	63 ECOG 0-3	Tx2 + pravastatin 40 mg/d for 2 years	(CDDP 60 mg/m ² d1 or CBDCA ACU5-6) + ETP 120 mg/m ² d1, 100-120 mg/m ² d2,3, q3w		0/0/6	
Salgia_2017	US	II 94	65* ECOG 0-2	Tx2 + LY2510924 20 mg d1-7	CBDCA AUC5 d1 + ETP 100 mg/m ² d1-3, q3w		2/2/2	
Tiseo_2017GOIRC-AIFA FARM6PMFJM	Italy	III 205	63 ECOG 0-2	Tx2 + bevacizumab 7.5 mg/kg d1	CDDP 25 mg/m ² d1-3 + ETP 100 mg/m ² d1-3, q3w		2/0/4	
Sanborn_2017LUN06-113	Portland	II 67	64 ECOG 0-1	Tx2 + vandetanib 100 mg/d	(CDDP 60 mg/m ² d1 or CBDCA ACU5) + ETP 120 mg/m ² d1-3, q3w		1/2/3	PFS
Oh_2016	Korea	III 157	67 ECOG 0-2	CDDP 60 mg/m ² d1 + Belotecan 0.5 mg/m ² d1-4, q3w	CDDP 60 mg/m ² d1 + ETP 100 mg/m ² d1-3, q3w		1/2/3	
Reck_2016	Germany	III 1132	62 ECOG 0-2	Tx2 + ipilimumab 10 mg/kg	(CDDP 75 mg/m ² d1 or CBDCA ACU5) + ETP 100 mg/m ² d1-3, q3w		0/0/6	
Belani_2016E1508	US	II 155	63 ECOG 0-1	CDDP 75 mg/m ² d1 + ETP 100 mg/m ² d1-3, q3w	Tx1 + vismodegib 150 mg d1-3	Tx1 + Cixutumumab 6 mg/kg d1,8,15	2/2/2	
Sun_2016	China	III 300	59 ECOG 0-1	CDDP 80 mg/m ² d1 + AMR 40 mg d1-3, q3w	CDDP 80 mg/m ² d1 + ETP 100 mg/m ² d1-3, q3w		2/0/4	
Shi_2015	China	II 62	58 ECOG 0-2	CDDP 75 mg/m ² d1 + CPT11 65 mg/m ² d1,8, q3w	CDDP 75 mg/m ² d1 + ETP 100 mg/m ² d1-3, q3w		2/2/2	

(Continued)

Table 1. (Continued)

Study	Country	Phase n	Median age PS	Arm1 treatment	Arm2 treatment	Arm3 treatment	ROBH/U/L	Outcome missing
Lu_2015	China	II 140	58* ECOG 0-2	Tx2 + endostatin 7.5 mg/m ² d1-14	CBDCA AUC5 d1 + ETP 60 mg/m ² d1-5, q3w		1/2/3	
Beniwal_2015	India	120		CDDP 60 mg/m ² d1 + CPT11 65 mg/m ² d1,8, q3w	CDDP 40 mg/m ² d1-2 + ETP 120 mg/m ² d1-3, q3w		3/3/0	RR
Satouchi_2014JCO60509	Japan	III 284	63 ECOG 0-1	CDDP 60 mg/m ² d1 + AMR 40 mg d1-3, q3w	CDDP 60 mg/m ² d1 + CPT11 60 mg/m ² d1,8,15, q3w		1/2/3	
Sekine_2014	Japan	III 62	76 ECOG 0-2	AMR 40-45 mg/m ² d1-3, q3w	CBDCA AUC5 d1 + ETP 80 mg/m ² d1-3, q3w		2/2/2	PFS
Langer_2014	US	II 155	61 ECOG 0-2	Tx2 + obataclax 30 mg d1-3	CBDCA AUC5 d1 + ETP 100 mg/m ² d1-3, q3w		2/2/2	
Fink_2012	Germany	III 680	61* ECOG 0-3	CDDP 75 mg/m ² d5 + TOP 1 mg/ m ² d1-5, q3w	CDDP 75 mg/m ² d1 + ETP 100 mg/m ² d1-3, q3w		2/0/4	PFS
OBrien_2011EORTC08062	UK	II 99	60 ECOG 0-2	AMR 45 mg/m ² d1-3, q3w	CDDP 60 mg/m ² d1 + AMR 40 mg d1-3, q3w	CDDP 75 mg/m ² d1 + ETP 100 mg/m ² d1, 100-200 mg/m ² d2,3, q3w	1/2/3	
Spigel_2011SALUTE	US	II 102	62* ECOG 0-2	Tx2 + Bevacizumab 15 mg/kg d1	(CDDP 75 mg/m ² d1 or CBDCA ACU5) + ETP 100 mg/m ² d1-3, q3w		0/2/4	
Schmittel_2011	Germany	III 226	62 KPF ≥ 50	CBDCA AUC5 d1 + ETP 140 mg/ m ² d1-3, q3w	CBDCA AUC5 d1 + CPT11 50 mg/m ² d1,8,15, q3w		2/2/2	
Zatloukal_2010	Germany	III 405	60* WHO 0-2	CDDP 80 mg/m ² d1 + CPT11 65 mg/m ² d1,8, q3w	CDDP 80 mg/m ² d1 + ETP 100 mg/m ² d1-3, q3w		2/2/2	PFS
Socinski_2009	US	III 908	63 ECOG 0-2	CBDCA AUC5 d1 + PEM 500 mg/ m ² d1, q3w	CBDCA AUC5 d1 + ETP 100 mg/m ² d1-3, q3w		2/2/2	
Lara_2009SWOG0124	US	III 671	63 ECOG 0-1	CDDP 60 mg/m ² d1 + CPT11 60 mg/m ² d1,8,15, q3w	CDDP 80 mg/m ² d1 + ETP 100 mg/m ² d1-3, q3w		2/0/4	
Lee_2009	UK	240	62 ECOG 0-3	CBDCA AUC5 d1 + GEM 1200 mg/m ² d1,8	CDDP 60 mg/m ² d1 + ETP 120 mg/m ² d1, 100 mg d2-3, q3w		2/0/4	
Rudin_2008CALGB30103	US	II 56	68 ECOG 0-2	Tx2 + oblimersen 7 mg/kg d1-8	CBDCA AUC5 d6 + ETP 80 mg/m ² d6-8, q3w		2/0/4	
Dimitroulis_2008	Greece	III 108	63 ECOG 0-2	CDDP 80 mg/m ² d1 + PTX 175 mg/m ² d1-3, q3w	CDDP 80 mg/m ² d1 + ETP 120 mg/m ² d1-3, q3w		1/1/4	PFS
Hermes_2008	Germany	III 140	67 ECOG 0-4	CBDCA AUC5 d1 + ETP 120 mg/ m ² d1-5, q3w	CBDCA AUC5 d1 + CPT11 175 mg/m ² d1, q3w		2/0/4	PFSRR
Sekine_2008	Japan	II 109	62 ECOG 0-2	Tx2 + ETP 50 mg/m ² d1-3	CDDP 60 mg/m ² d1 + CPT11 60 mg/m ² d1,8, q3w		3/0/3	
Okamoto_2007JCO69702	Japan	III 220	74 ECOG 0-3	CBDCA AUC5 d1 + ETP 80 mg/m ² d1-3, q3w	CDDP 25 mg/m ² d1-3 + ETP 80 mg/m ² d1-3, q3w		2/2/2	

(Continued)

Table 1. (Continued)

Study	Country	Phase <i>n</i>	Median age PS	Arm 1 treatment	Arm 2 treatment	Arm 3 treatment	ROBH/U/L	Outcome missing
Glisson_2007	US	II 185	61 ECOG 0-2	(CDDP 75 mg/m ² or CBDCA ACU5 d1) + ETP 100 mg/m ² d1-3, q3w	Tx1 + rilotumumab 15 m/kg	Tx1 + Ganitumab 18 mg/kg	0/2/4	
Socinski_2006	US	II 78	64 ECOG 0-2	CDDP 75 mg/m ² d1 + PEM 500 mg/m ² d1, q3w	CBDCA AUC5 d1 + PEM 500 mg/m ² d1, q3w		2/2/2	PFS
Eckardt_2006	US	III 784	60* ECOG 0-3	CDDP 60 mg/m ² d5 + TOP 1.7 mg/m ² d1-5, q3w	CDDP 80 mg/m ² d1 + ETP 100 mg/m ² d1-3, q3w		2/2/2	
Hanna_2006	US	III 331	63 ECOG 0-2	CDDP 30 mg/m ² d1,8 + CPT11 65 mg/m ² d1,8 q3w	CDDP 60 mg/m ² d1 + ETP 120 mg/m ² d1-3, q3w		2/2/2	PFS
Schmitte_2006	Germany	II 70	61 KPS ≥ 60	CBDCA AUC5 d1 + CPT11 50 mg/m ² d1,8,15, q3w	CBDCA AUC5 d1 + ETP 140 mg/m ² d1-3, q3w		2/2/2	OS
Greco_2005	US	II 120	64 ECOG 0-2	CBDCA AUC6 d1 + ETP 50-100 mg/m ² d1-10 + PTX 200 mg/m ² d1, q3w	TOP 1.5 mg/m ² d1-3 + PTX 175 mg/m ² q3w		2/2/2	PFS
Quoix_2005	France	II 82	61 ECOG 0-2	CDDP 50 mg/m ² d5 + TOP 1.25 mg/m ² d1-5, q3w	ETP 60 mg/m ² d1-5 + TOP 0.75 mg/m ² d1-5, q3w		2/2/2	PFS
Niel_2005CALGB9732	US	III 587	61 ECOG 0-2	Tx2 + PTX 175 mg/m ² d1	CDDP 80 mg/m ² d1 + ETP 80 mg/m ² d1-3, q3w		1/2/3	PFS
Lyss_2002CALGB9430	US	II 57	61* ECOG 0-2	TOP 1 mg/m ² d1-5 + PTX 175-230 mg/m ² q3w	CDDP 75 mg/m ² d1 + TOP 1 mg/m ² d1-5, q3w		3/2/1	PFS
Noda_2002JCO69511	Japan	III 154	63 ECOG 0-2	CDDP 60 mg/m ² d1 + CPT11 60 mg/m ² d1,8,15, q3w	CDDP 80 mg/m ² d1 + ETP 100 mg/m ² d1-3, q3w		2/0/4	

n, number of patients randomized to concerned arms.
 Median age: *indicates mean age instead of median age.
 WHO PS 0-2 is roughly equivalent to ECOG PS 0-2; KPS, Karnofsky's index of PS.
 ROB H/U/L (High/Unclear/Low): Six domains of Cochrane risk of bias were assessed. 6/0/0, meaning 6 domains with high risk of bias, is the poorest score. 0/0/6, meaning 6 domains with low risk of bias, is the best score.
 Outcome missing: an indicated outcome was not reported in the article. Blank means all of OS, PFS, and RR were available.
 /m², per body surface area square meter; AUC, area under curve by Calvert formula; CBDCA, carboplatin; CDDP, cisplatin; d, day; ECOG, Eastern Cooperative Oncology Group; ETP, topotecan; CPT11, irinotecan; GEM, gemcitabine; OS, overall survival; PEM, pemetrexed; PFS, progression-free survival; PTX, paclitaxel; q3w, every 3 weeks; ROB, risk of bias; RR, response rate; TOP, topotecan; WHO, World Health Organization. In a two-arm trial, arm 1 and arm 2 may be switched from the original publication to place the reference arm to arm2.

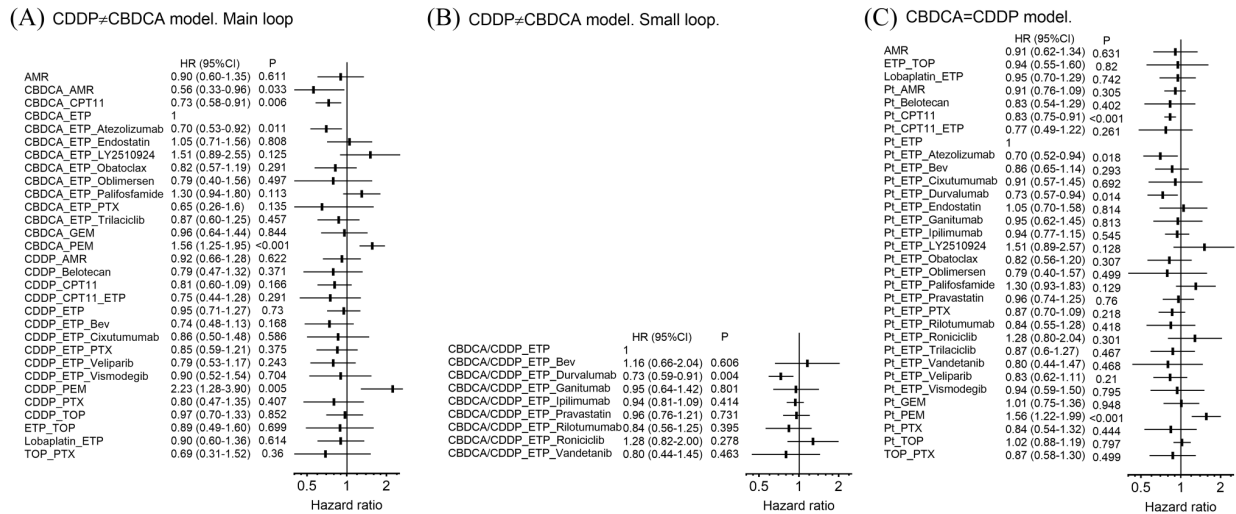


Figure 3. Network meta-analysis for HR of OS. (A) In the CDDP/CBDCA distinguished model, CDDP and CBDCA are recognized as different reagents. ($I^2=9.5\%$, P for heterogeneity 0.353). CBDCA+ETP is the common comparator. (B) In the CDDP/CBDCA distinguished model, some trials that allowed selective administration of CBDCA or CDDP (CBDCA/CDDP) made an independent loop. ($I^2=0\%$, P for heterogeneity not available). CBDCA/CDDP+ETP is the common comparator. (C) CBDCA=CDDP model. CDDP and CBDCA are recognized switchable Pt reagent ($I^2=22.3\%$, P for heterogeneity 0.200). Pt+ETP was the common comparator. A horizontal error bar indicates 95% CI. CBDCA, carboplatin; CDDP, cisplatin; CI, confidence interval; ETP, etoposide; HR, hazard ratio; OS, overall survival; Pt, platinum.

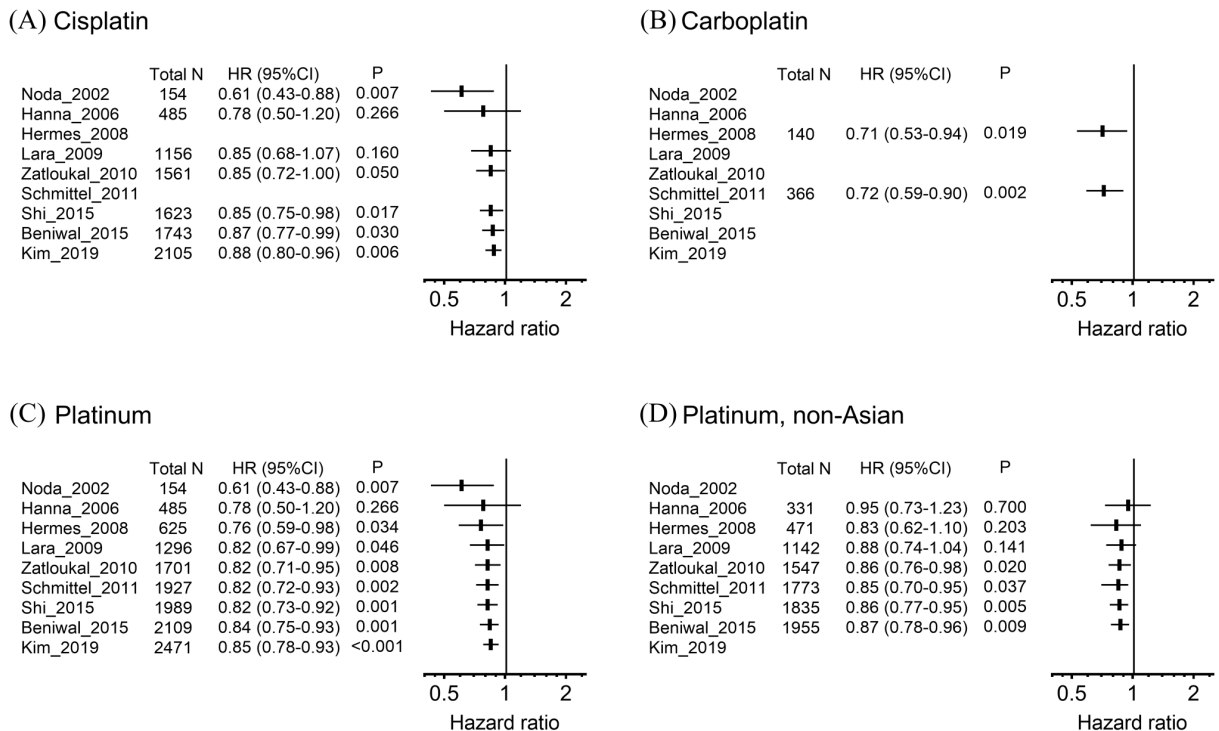
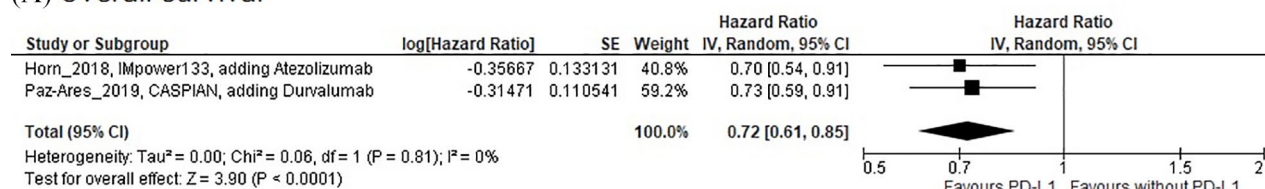
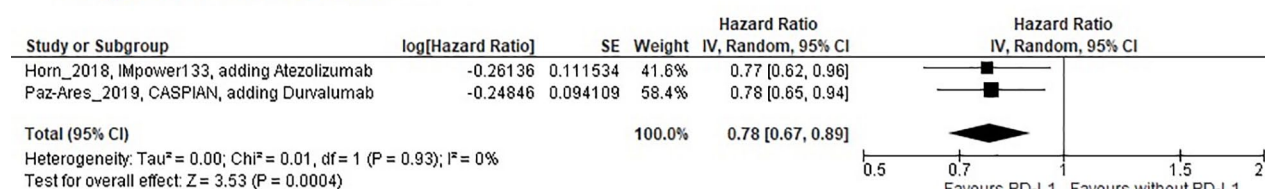


Figure 4. Cumulative meta-analysis for HR of OS comparing CPT11 regimen and ETP regimen. In a cumulative meta-analysis, each trial is merged into previous data. For example, in CDDP model, “Lara_2009” in the figure suggests pooled HR from Noda_2002, Hana_2006, and Lara_2009 is 0.85. (A) Seven trials compared cisplatin (CDDP)+CPT11 and CDDP+ETP were analyzed. (B) Two trials compared carboplatin (CBDCA)+CPT11 and CBDCA+ETP were analyzed. (C) Both CDDP and CBDCA were regarded Pt and all nine trials were analyzed. (D) Noda 2002 and Kim 2019, which were reports from Asia, were excluded. A horizontal error bar indicates 95% CI. CBDCA, carboplatin; CDDP, cisplatin; CI, confidence interval; CPT11, irinotecan; ETP, etoposide; HR, hazard ratio; OS, overall survival; Pt, platinum.

(A) Overall survival



(B) Progression-free survival



(C) Objective response rate

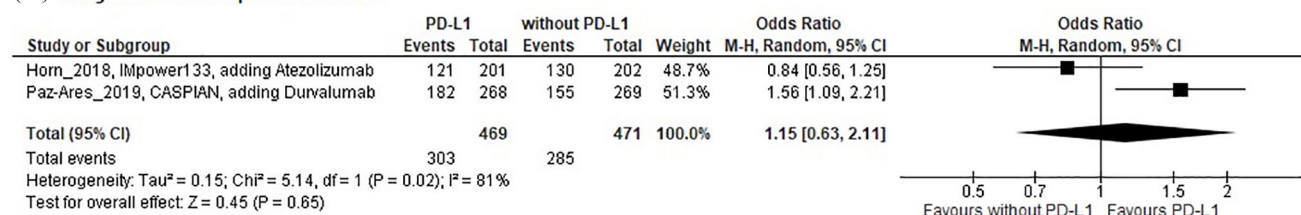


Figure 5. Key efficacy outcomes in trials adding PD-L1 inhibitor on Pt doublet. A horizontal error bar indicates 95% CI. CI, confidence interval; PD-L1, programmed death-ligand 1; Pt, platinum.

demonstrated better HRos, and the trend persists to date. The current cumulative HRos were 0.88 (95% CI 0.80–0.96), 0.72 (95% CI 0.59–0.90), 0.85 (95% CI 0.78–0.93), and 0.87 (95% CI 0.78–0.96), in the CDDP, CBDCA, platinum, and non-Asian platinum models, respectively.

Progression-free survival

Network graphs for HRpfs are similar to those of OS (Supplemental Figure S2).

The CBDCA+AMR (HR 0.43, 95% CI 0.24–0.78), CBDCA+ETP+ATZ (HR 0.77, 95% CI 0.60–0.99), and CBDCA+CPT11 (HR 0.73, 95% CI 0.56–0.96) regimens showed better PFS than the common comparator CBDCA+ETP (Supplemental Figure S3A, Supplemental Table S4).

In a small independent loop, addition of Bevacizumab (HR 0.53, 95% CI 0.32–0.87), DUR (HR 0.78, 95% CI 0.65–0.94), and ipilimumab (HR 0.85, 95% CI 0.75–0.97) to CBDCA/CDDP+ETP led to improved PFS (Supplemental Figure S3B, Supplemental Table S5).

Response rate

Network meta-analysis was performed for ORrr (Supplemental Figures S4 and S5, Supplemental Tables S6 and S7). In the main loop, the forest plot suggested that patients treated with the CDDP+ETP+PTX (OR 6.57, 95% CI 1.17–37.1) regimen demonstrated a more objective response compared with those treated with CBDCA+ETP.

In the independent small loop, addition of DUR (HR = 1.56, 95% CI 1.09–2.21) to CBDCA/CDDP resulted in a higher ORrr.

Efficacy outcome from PD-L1 inhibiting regimen

Two trials evaluated the effects of addition of PD-L1 inhibitor to platinum+ETP regimens. Adding PD-L1 inhibitor improved HRos (0.72, 95% CI 0.61–0.85, I² = 0, P for heterogeneity 0.81) and HRpfs (0.78, 95% CI 0.67–0.89, I² = 0, P for heterogeneity 0.93), while no increase was observed in the ORrr (1.15, 95% CI 0.63–2.11, I² = 81%, P for heterogeneity 0.020) (Figure 5).

OS comparison between CBDCA and CDDP doublet using the same counterpart

Only two trials directly compared CBDCA and CDDP with the same counterpart. Pooled HRos was 1.14 (95% CI 0.86–1.51, $I^2 = 11\%$, P for heterogeneity 0.29) using CBDCA as reference (Supplemental Figure S6).

Discussion

In this systematic review, we examined the efficacy data from 46 RCTs that were published since 2000 and included a total of 11,987 patients with ED-SCLC. The robustness of the data was supported by the use of the standard PRISMA methodology, sufficiently large number of trials and patients, low heterogeneity in the employed models, and the multifaceted meta-analysis approach. This review covered chemotherapy trials conducted in the last two decades in chemo-naïve ED-SCLC patients and raised several issues.

Based on results of the studies conducted in the last decade (Figure 4), it was evident that CPT11 regimen led to better OS than the ETP regimens (Figure 2). However, as many as 40 out of 46 trials in our review used the ETP doublet regimen as the reference. We had a long-lasting argument comparing platinum+ETP and platinum+CPT11. This discussion was in part “dogmatic.” Some insisted that CDDP+ETP was the standard regimens because CDDP+CPT11 did not show statistically significant superiority compared with CDDP+ETP in any study, with the exception of a Japanese trial.^{2–6} Other groups argued that relying on significance based on p value alone was not scientific,^{22,23} and preferred to accept “the trend” and the result from meta-analyses.^{11–13} Schmittel *et al.* claimed that the CBDCA+ETP regimen remained the standard treatment because the CBDCA+CPT11 regimen could not demonstrate statistically significant superiority in OS of patients with ED-SCLC (HR 1.29, 95% CI 0.96–1.73, $p = 0.095$; median OS 10.0 month *versus* 9.0 months, $p = 0.06$).²⁴ Although the pooled HRos calculated using data from Hermes and Schmittel was 0.72 (95% CI 0.59–0.90, $p = 0.002$) without heterogeneity (P for heterogeneity = 0.2, $I^2 = 0\%$) at the time of the publication of the study Schmittel (Figure 4B),^{11–13,24,25} several groups agreed with the results of the Schmittel and continued to use CBDCA+ETP as the standard reference treatment (Table 1, Figure 2). Two recent phase III trials reported addition of ATZ or DUR to the ETP regimen,

the results of which persisted to date.^{8,9} However, survival outcome of patients treated with the ETP regimen was clearly inferior to the CPT11 regimen (Figure 2, Supplemental Figure S3, Figure 4), as long as we can accept the data from meta-analysis. Consequently, although addition of ATZ or DUR to platinum+ETP provided better OS than platinum+ETP alone, the HRos of these PD-L1 inhibiting regimens was not greatly better compared with those of the platinum+CPT11 regimen (Figure 3).

Many trials permitted physicians to choose between CBDCA and CDDP (Table 1), which could mean that CBDCA and CDDP are interchangeable, especially when using ETP as the doublet counterpart. However, only two trials directly compared the CBDCA and CDDP regimens using the same doublet counterpart.^{26,27} In 2006, Socinski *et al.* randomized patients into CDDP+PEM and CBDCA+PEM arms and reported a median OS of 7.6 and 10.4 months, respectively.²⁷ However, the results of this study do not suggest that CDDP may be used as an alternative to CBDCA. Another trial (JCOG9702) that compared CDDP+ETP and CBDCA+ETP did not indicate a large difference in the efficacy endpoint between the two arms (HRos 1.04, HRpfs 0.92, and ORrr 1.0), using CDDP+ETP as reference.²⁶ However, this trial recruited only elderly Japanese patients; therefore, it remains unclear whether the results can be generalized to other patients with ED-SCLC (Supplemental Figure S6). Individual patient data meta-analysis of four trials by Rossi *et al.* in 2012 compared the CBDCA and CDDP regimens and revealed that HRos of 1.10 (95% CI 0.92–1.27) in the CBDCA arm compared with the reference CDDP arm.²⁸ However, this analysis included RCTs with different counterparts, for example CDDP+ETP *versus* CBDCA+GEM, and RCTs using chemoradiotherapy. Therefore, the results should be interpreted with caution. Although we should admit that CBDCA regimen that does not require prolonged hydration is a useful choice to treat outpatients in daily practice, available data do not support unthoughtful use of CBDCA as a substitute of CDDP.

The most desirable outcome for a trial evaluating chemotherapy for advanced lung cancer is OS,¹⁷ because it is easy to assess without bias and directly reflects the benefit to the patient. However, PFS and RR are often considered substitutes because assessment of OS requires a longer follow up. When

PFS and RR are considered surrogate outcomes, the surrogacy should be confirmed beforehand. Nonetheless, there is lack of clarity regarding the accuracy of PFS and RR as surrogates of OS at a trial level, especially in those evaluating molecular-targeted therapies. Compared with platinum+ETP alone, addition of bevacizumab (HRpfs 0.53, HRos 1.16), trilaciclib (HRpfs 0.70, HRos 0.87), and ipilimumab (HRpfs 0.85, HRos 0.94) improved PFS (Supplemental Figure S3); however, the OS outcomes were not satisfactory (Figure 3). We should not be excited about the positive PFS in cases of molecular targeted therapies. On the contrary, excellent PFS reported by trials on PD-L1 inhibitor were endorsed by promising OS (Figures 3 and 5; Supplemental Figures S3 and S5). As PD-L1 inhibiting regimens improve OS of patients with ED-SCLC, it is becoming difficult to obtain data on OS. According to our recent analysis of 29 phase III first-line trials that included 8573 patients with SCLC, HR of PFS excellently correlated with HRos with rank correlation coefficient of 0.87.²⁹ PFS might be a good surrogate endpoint for trials in cases where OS is prolonged.

In our network meta-analysis, the CBDCA+AMR regimen demonstrated the best HRos of 0.55 (95% CI 0.33–0.96) compared with the CBDCA+ETP regimen. This result was obtained from a single phase II trial by Morikawa *et al.*³⁰ Although this finding was significant, the trial did not validate CBDCA+AMR as the standard regimen because this phase II trial adopted RR as the primary endpoint. Nonetheless, this regimen appeared promising in some Japanese trials.^{30–33} However, efficacy of AMR is dependent on the race. Our previous analysis revealed that second-line AMR therapy was highly effective in the Japanese population compared with Euro-American populations.³⁴ In fact, the median OS of 10 months estimated in another single-arm phase II trial from the US was not promising.³⁵

Addition of PD-L1 inhibiting agents to the platinum doublet seems a reasonable strategy (Figure 5). Given the similar efficacy (Figure 3C) and the high drug price of DUR, some may suppose ATZ is a better option. Addition of ATZ to other platinum doublets such as CDDP+CPT11 may be an attractive option in the future.

There are some limitations of our study. First, the network between CBDCA and CDDP regimens is scarce. Therefore, comparison between these regimens was not solid. Second, most of RCTs

included only PS 0-1 or 0-2 cases though patients with higher PS should also be treated in the real world. Notably, ICI trials lack data of patients with PS score of two or higher.^{8,9} Third, we could not perform country-, PS-, age-based subgroup network meta-analyses due to the insufficient sample size and data format.

In conclusion, we organized the data of 46 RCTs evaluating the first-line chemotherapies for patients with ED-SCLC that were published in the last 20 years using network meta-analysis. Although platinum+ETP regimen appeared inferior to platinum+CPT11 regimen in terms of OS, a large majority of the published trials considered the former regimen as the standard. Patients treated with CBDCA+AMR, CBDCA+ETP+ATZ, platinum+ETP+DUR, and platinum+CPT11 showed better HRos than those treated with platinum+ETP doublet.

Author contributions

HC supported data acquisition and drafting. NH led conception, designing, acquisition, analysis, interpretation, and drafting. KI, HN, YH, NK, MY, MK, and TK supported interpretation and revision. All the authors provided final approval and agreement for accountability for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.


Conflict of interest statement

The authors have the following conflicts of interest to disclose: KI: lecture fee from AstraZeneca and Chugai Pharmaceutical co. ltd. YH: lecture fee from AstraZeneca. NK: lecture fee from AstraZeneca and Chugai Pharmaceutical co. ltd. MK: lecture fee from AstraZeneca. KT: lecture fee from AstraZeneca and Chugai Pharmaceutical co. ltd.

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Supplemental material

Supplemental material for this article is available online.

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