The best platinum doublet for chemo-naive extensive-disease small cell lung cancer: network meta-analysis.

[PROTOCOL]

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Lung cancer, which is currently the most common malignant neoplasm in the world\(^1\). Small-cell lung cancer (SCLC) is distinguished clinically from non-small cell lung cancer by its rapid doubling time, high growth fraction, and the early development of metastases. Actually, most cases with the SCLC are detected after the disease has already progressed to non-radically-treatable extensive stage. For such patients, chemotherapy is usually the preferred therapeutic choice because accumulated evidence from trials has revealed that current standard chemotherapy treatments have substantial benefit for extensive-disease (ED) SCLC, though SCLC usually regrows months later. Currently, some platinum doublets are regarded as the standard regimens for SCLC\(^2-5\). Among platinum doublet regimens, Cisplatin (CDDP) + Etoposide (ETP) is the most commonly used as the first-line combination chemotherapy for ED SCLC, especially in Western countries, since CDDP+ETP replaced alkylator/anthracycline-based regimens\(^2,4,5\). Another promising regimen is CDDP + Irinotecan (CPT-11). In 2002, an interim analysis of phase III trial in Japan, JCOG9511, showed that, compared to CDDP+ETP, CDDP+CPT-11 had superior overall survival (OS), better progression-free survival (PFS), less hematological toxicity, and frequent but acceptable gastrointestinal toxicity\(^6\). However, this result could not be replicated in two larger trials in USA in 2006 and 2009\(^7,8\). Since then, some thought CDDP-CPT-11 is effective only for Asian population because of pharmacogenomic differences between the Japanese and American patient populations\(^7,8\). However, another multi-national European trial successfully showed non-inferiority of CDDP+CPT-11 to CDDP+ETP\(^9\). Besides, OS in CDDP+CPT-11 arm had marginally better OS compared to CDDP+ETP\(^9\). To overcome the discrepancy among trials, few meta-analyses have been done\(^10-13\). Although these meta-analyses were not conclusive, they generally admitted the possible advantage of CDDP+CPT-11 over CDDP+ETP. In addition to CDDP+ETP and CDDP+CPT-11 regimens, some trials suggested that other regimens including CBDCA+CPT-11, CBDCA+ETP, and CDDP+TOP have reasonable therapeutic effect.

When we have three or more acceptable treatment options, network meta-analysis, rather than conventional head-to-head pairwise meta-analysis, has an advantage in the collective comparison among multiple treatment arms\(^14-16\). The goal of the current network meta-analysis is to identify the best platina doublet regimens as the first-line chemotherapies for ED SCLC by comparing the OS, PFS, and adverse effects profile.
METHODS

Protocol registration
This protocol of the systematic review and network meta-analysis has been uploaded on the website of International Prospective Register of Systematic Reviews\(^\text{17}\). We have composed this protocol following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement\(^\text{18}\). Institutional review board approval and informed consent of patients were waived because of review nature of this study.

Study search
Search formulas for electrical databases have been created with the support of Cochrane Japanese. Search formulas for Pubmed, Web of Science Core Collection, Cochrane Central Register of Controlled Trials, and EMBASE are presented at the end of this protocol. The search will be done during December 30\(^{\text{th}}\)-31st, 2016.

An additional manual search will be conducted by two investigators (NH and YS) independently.

Candidate articles will be first screened and then scrutinized independently by two investigators. If discrepancies exist during the study selection process, they will be resolved by discussion between the two investigators.

Inclusion criteria

Publication type and trial design
We will include individually randomized trials comparing two or more of platinum doublet regimes for ED SCLC, which have been reported and published in full papers. Cross-over of doublets will not be accepted. Language restriction will not be set. We will allow a trial with three or more arms. We will allow superiority, non-inferiority, phase II, phase III, non-blinded, single-blinded, and double-blinded trials. A trial evaluating only the co-secondary outcomes of our analysis will be allowed. Duplicate use of the same study will be carefully checked and avoided.

Treatments
Our concern is the first-line platinum doublet regimens. Platinum agents should be either Cisplatin (CDDP), Carboplatin (CBDCA), Oxaliplatin (OXA), or Nedaplatin (CDGP). Any counterpart anti-cancer medication, including CPT-11, ETP, TOP, and AMR, can be combined with platinum agent.
However, we will not include the following regimens: single agent chemotherapies, non-platinum doublets, platinum-triplets, and alternating administration of two regimens. Perioperative chemotherapy, adjuvant chemotherapy, neo-adjuvant chemotherapy, and radio-chemotherapy will also be excluded. We will not include studies that planned to stop the first-line regimen before administration of the third course.

Regimens that used the same medication will be evaluated collectively regardless of administration route, speed, dosage, and schedule.

**Patients**

Chemo-naive patients with ED SCLC will be included. Disease stage should be ED defined by the Veterans' Administration system. Our inclusion criteria will not directly question the TNM classification. Patients with history of any adjuvant chemotherapy, neoadjuvant chemotherapy, or radio-chemotherapy will be excluded. The age, sex, performance status, co-morbidities, and organ functions of patients will not be questioned. If a study is focused on patients with a large cell neuroendocrine carcinoma, it will be excluded though this carcinoma is usually treated by SCLC regimens.

**Quality assessment**

We will assess the quality of original studies using six domains of the Cochrane Risk of Bias: selection, performance, detection, attrition, reporting, and other biases\(^\text{19}\).

**Outcomes**

The primary outcome is hazard ratio (HR) for Overall survival (HR\text{OS})\(^\text{20}\).

The co-secondary outcomes are HR for progression-free survival (HR\text{PFS}) \(^\text{20}\), odds ratio (OR) for response rate (RR, OR\text{RR}) \(^\text{21}\), and OR for severe adverse events (SAE) including neutropenia, anemia, thrombopenia, febrile neutropenia, nausea, and diarrhea. Severity of adverse events will be defined as adverse event with Common Terminology Criteria for Adverse Events grade three or higher\(^\text{22}\). The number of SAE will be counted by patient-based, not by per-cycle based.

Evaluation of disease progression to assess the PFS and evaluation of response to assess RR should not greatly deviate from the Response Evaluation Criteria In Solid Tumors 2000 guidelines and the 2009 revised guidelines\(^\text{21}\). Time to progression and time to treatment failure will not be regarded as PFS.

**Data extraction**

Data for included studies, including author name, publication year, country of origin,
numbers of patients randomized, chemotherapy regimen, and data related to the study outcomes such as OS, PFS, RR, and SAE will be extracted by the two investigators (NH and YS) independently. The data extracted by the two investigators will be cross-checked and any discrepancies will be discussed between them. We will extract data from inferiority studies using the same method as for superiority trials. For three- or more-arm studies, data of every pair-wise comparison will be extracted. For example, a four-arm trial provides six comparisons. If only two arms of a three-arm study are of interest to us, we will only use data of the two arms. For example, if a three-arm study evaluates CDDP+ETP, CDDP+CPT-11, and ETP monotherapy, we only use the data comparing CDDP+ETP and CDDP+CPT-11. If updated data for survival is available, the most updated data will be preferred. If necessary, we will adopt Parmar’s method. Intention-to-treat analysis will be preferred over full-analysis-set analysis and per-protocol analysis if two or more of them are available.

**Statistical analyses**

We will pool the logarithm of OR, HR, and their SE using the frequentist weighted least squares approach random-model network meta-analysis. All the binary outcomes will be transformed to OR preceding the network meta-analysis. When one or more cells in a two-by-two contingency are zero, 0.5 will be added to all the cells. If a diagram shows two or more independent loops, we will evaluate only the loop that contains major platinum doublet such as CDDP+IPT-11 and CDDP-ETP. A forest plot and a league table will be presented. For a forest plot, CDDP+ETP will be selected as the common reference comparator. This is because previously published guideline generally recommend CDDP+ETP as the most reliable first-choice medication for ED SCLC. This common reference comparator will be also used for the forest plot for secondary outcomes.

For the network meta-analysis, the "netmeta" command in the "netmeta" package of R will be used.

Sensitivity analyses using fixed-model network meta-analysis is planned.

**ACKNOWLEDGEMENT**

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REFERENCES


SEARCH FORMULAS

MEDLINE

#1 Carcinoma, Small-Cell Lung/
#2 SCLC
#3 small cell lung cancer OR small cell lung carcinoma OR small-cell lung cancer OR small-cell lung carcinoma
#4 #1 OR #2 OR #3
#6 #4 NOT #5
#7 extensive OR extended OR ED [title] OR ES [title] OR advance* OR meta* OR "stage 4" OR stage4 OR stage?IV OR "stage IV" OR stageIV OR incurable
#8 (naive OR untreated OR chemonaive OR chemo-naive OR non-treated OR untreated OR first-line OR front-line OR primary OR initial)
#9 (previously [title] "not"[title] treated [title]) OR (previous*[title] no[title] treat*[title])
#10 #8 OR #9
#11 platina OR platinum OR carboplatin OR CBDCA OR cisplatin OR CDDP OR oxaliplatin OR nedaplatin OR CDGP OR doublet
#12 controlled clinical trial OR randomi* OR placebo OR phase III OR phase 3 OR blind
#13 clinical trials as topic.sh.
#14 #12 OR #13
#15 exp animals/ NOT humans.sh.
#16 #6 AND #7 AND #10 AND #11 AND #14 NOT #15
Web of Science Core Collection
(All languages, All document types, Time span all, Science Citation Index Expanded)

#1 TS=(small cell lung cancer OR small cell lung carcinoma OR small-cell lung cancer OR small-cell lung carcinoma OR SCLC)
#2 TI=(non-small cell lung carcinoma OR non-small cell lung cancer OR adenocarcinoma OR non-squamous OR squamous OR NSCLC)
#3 #1 NOT #2
#4 TS=(extensive OR extended OR advanced OR metastasis OR stage 4 OR stage IV OR incurable)
#5 TI=(ED OR ES)
#6 #4 OR #5
#7 TS=(naive OR untreated OR chemo-naive OR chemo-naive OR non-treated OR untreated OR first-line OR front-line OR primary OR initial)
#8 TI=(previously "not" treated) OR TI=(previous* no treat*)
#9 #7 OR #8
#10 TS=(platina OR platinum OR carboplatin OR CBDCA OR cisplatin OR CDDP OR oxaliplatin OR nedaplatin OR CDGP OR doublet)
#11 TS=(controlled clinical trial OR randomi* OR placebo OR phase III OR phase 3 OR blind)
#12 #3 AND #6 AND #9 AND #10 AND #11
#1  (small cell lung cancer OR small cell lung carcinoma OR small-cell lung cancer OR small-cell lung carcinoma OR SCLC):ti,ab,kw
#2  (non-small cell lung carcinoma OR non-small cell lung cancer OR adenocarcinoma OR non-squamous OR squamous OR NSCLC):ti
#3  #1 NOT #2
#4  (extensive OR extended OR advanced OR metastasis OR stage 4 OR stage IV OR incurable):ti,ab,kw
#5  (ED OR ES):ti
#6  #4 OR #5
#7  (naive OR untreated OR chemo-naive OR chemo-naive OR non-treated OR untreated OR first-line OR front-line OR primary OR initial):ti,ab,kw
#8  (platina OR platinum OR carboplatin OR CBDCA OR cisplatin OR CDDP OR oxaliplatin OR nedaplatin OR CDGP OR doublet):ti,ab,kw
#9  (controlled clinical trial OR randomi* OR placebo OR phase III OR phase 3 OR blind):ti,ab,kw
#10  #3 AND #6 AND #7 AND #8 AND #9 in Trials
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sclc:ab,ti AND [embase]/lim NOT [medline]/lim
#1 OR #2 OR #3
#4 NOT #5
extensive:ab,ti OR extended:ab,ti OR ed:ab,ti OR advance*:ab,ti OR metastase*:ab,ti OR stage3:ab,ti OR 'stage iii':ab,ti OR stageiii:ab,ti OR stage4:ab,ti OR 'stage iv':ab,ti OR 'stage 4':ab,ti OR 'stage iv':ab,ti OR stageiv:ab,ti OR 'stage iii':ab,ti OR incurable:ab,ti AND [embase]/lim NOT [medline]/lim
naive:ab,ti OR untreated:ab,ti OR chemonaive:ab,ti OR 'chemo naive':ab,ti OR 'non treated':ab,ti OR nontreated:ab,ti OR 'first line':ab,ti OR 'front line':ab,ti OR primary:ab,ti OR initial:ab,ti AND [embase]/lim NOT [medline]/lim
'platinum complex'/de AND [embase]/lim NOT [medline]/lim
organoplatinum:ab,ti OR platin*:ab,ti AND [embase]/lim NOT [medline]/lim
'carboplatin'/de OR carboplatin*:ab,ti OR cbdca:ab,ti AND [embase]/lim NOT [medline]/lim
'cisplatin'/de AND cisplatin:ab,ti OR 'cis platinum':ab,ti OR cddp:ab,ti AND [embase]/lim NOT [medline]/lim
oxaliplatin:ab,ti AND [embase]/lim NOT [medline]/lim
'nedaplatin'/de OR nedaplatin:ab,ti OR cdgp:ab,ti AND [embase]/lim NOT [medline]/lim
doublet:ab,ti AND [embase]/lim NOT [medline]/lim
#9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15
#6 AND #7 AND #8 AND #16
'crossover procedure':de OR 'double-blind procedure':de OR 'randomized controlled trial':de OR 'single-blind procedure':de OR random*:de,ab,ti OR factorial*:de,ab,ti OR crossover*:de,ab,ti OR (cross NEXT/1 over*):de,ab,ti OR placebo*:de,ab,ti OR (double* NEAR/1 blind*):de,ab,ti OR (single* NEAR/1 blind*):de,ab,ti OR assign*:de,ab,ti OR allocat*:de,ab,ti OR volunteer*:de,ab,ti OR 'phase iii':de,ab,ti OR phaseiii:de,ab,ti OR 'phase 3':de,ab,ti OR phase3:de,ab,ti AND [embase]/lim NOT [medline]/lim
#18 NOT ([animals]/lim NOT [humans]/lim)
#17 AND #19