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# Assessing the relative effectiveness and tolerability of treatments in small cell lung cancer: A network meta-analysis

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ABSTRACT

*Background*: The combination of Cisplatin plus Etoposide (EP) is currently the standard treatment for small cell lung cancer (SCLC). However, a large number of alternative treatments (monotherapies and combinations) have been studied in randomized controlled trials (RCTs) to identify more effective treatments. Aim of the present study was to assess the relative effectiveness and tolerability of these treatments. *Methods*: PubMed, EMBASE and Cochrane Central Register of Controlled Trials were systematically searched to identify all RCTs that compared treatments for SCLC. Then, effectiveness of the treatments relative to the combination of Cisplatin plus Etoposide, reference treatment) was estimated by performing a network of treatments analysis. The analysis evaluated two efficacy outcomes (complete response – CR and objective response rate – ORR) and two tolerability outcomes (neutropenia and febrile neutropenia). All RCTs that provided data for calculating the odds ratios (OR) for the selected outcomes were considered. The network analysis involved direct and indirect analyses. *Results*: We identified 71 articles eligible for inclusion, involving 91 different treatments. In total, 16,026 patients were included in the analysis. In the direct analysis the combination of Cisplatin plus Cyclophosphamide plus Etoposide plus Epirubicin showed better response than EP for the ORR outcome, but with worse tolerability (presence of neutropenia). The indirect analysis revealed that the combination of Cisplatin plus Doxorubicin plus Etoposide (plus Vincrisitine) showed better response that EP for the ORR outcome. *Conclusions*: No therapy shows better response for the two efficacy outcomes (CR and ORR); though, Cisplatin plus Doxorubicin plus Etoposide plus Vincrisitine might be a promising therapy for SCLC. The results should be interpreted with caution because the network was dominated by indirect comparisons. Large scale head-to-head RCTs are needed to confirm the present findings.



## 1. Introduction

Small cell lung cancer (SCLC) accounts for about 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]. At the time of diagnosis, one third of patients diagnosed with SCLC have tumors confined to the hemithorax of origin, the mediastinum, or the supraclavicular lymph nodes (limited-stage disease, LD) and the remaining patients have tumors spread beyond the supraclavicular areas (extensive-stage disease, ED) [3].

Patients with SCLC typically develop distant metastases and thus, localized forms of treatment (e.g. surgical resection or radiation therapy) may not be effective [4]. Thus, chemotherapy remains the standard treatment of SCLC. The most used agents in SCLC are alkylating agents (cisplatin, carboplatin, ifosfamide and cyclophosphamide), antimitotic agents (vincristine and paclitaxel) and topoisomerase inhibitors (etoposide, irinotecan, topotecan and doxorubicin). In both ED and LD SCLC, the combination of cisplatin and etoposide remains the most widely used standard chemotherapeutic regimen [5]. However, the selection of the optimal chemotherapy agent or combination of chemotherapy agents is a difficult task since no studies have estimated the relative effectiveness and safety of all alternative treatments [6,7]. Thus, an integration of the current evidence and quantification of the relative effectiveness and safety of all these treatments based on published RCTs are needed.

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In order to evaluate the relative merits of the different treatments for SCLC based on the mode of action of each chemotherapy agent (or combination of individual chemotherapy agents), we systematically searched and cataloged all available published RCTs in SCLC. Then, we performed a network of multiple treatments analysis (network meta-analysis), involving direct analysis (synthesis of RCTs with the same treatment comparisons) and indirect analysis (comparison between treatments using an intermediate comparator) [8,9]. In the absence of direct comparison between treatments, the effect size can only be estimated only using an indirect comparison approach [8,9]. A network of treatments can be constructed by considering all investigated comparisons (direct and indirect) between treatments. The aim of the network meta-analysis is to synthesize all evidence originated from direct and indirect comparisons and to assess the effectiveness and tolerability of treatments using as reference treatment a standard first line treatment (such as the combination of cisplatin and etoposide). The present methodology has already been applied in ranking the relative effectiveness of treatments in acute myeloid leukemia [8] and multiple sclerosis [9].

## 2. Materials and methods

### 2.1. Search strategy-selection of RCTs

We searched PubMed, EMBASE, and the Central Registry of Controlled Trials of the Cochrane Library to identify all RCTs that investigated chemotherapy regimens in adult patients with histologically proven SCLC. The search was limited to English language, RCTs, adults, and concerned the time period from 1980 until end of May 2011. The articles were identified using as search criterion the terms: ''small cell lung cancer'' and ''chemotherapy''. The reference lists of the retrieved articles were also reviewed to identify additional publications. The search strategy for the selection of the eligible RCTs is shown in Fig. 1.

### 2.2. Eligibility criteria

RCTs that compared at least two arms of different chemotherapy regimens in chemotherapy naïve patients with histologically proven SCLC were included in the network analysis. Only studies that provided sufficient data to calculate odds ratios (ORs) for estimating the magnitude of difference between treatments, and the corresponding precision were considered.

The following studies were excluded: (i) studies comparing second line chemotherapy treatments; (ii) studies reporting radiotherapy interventions, i.e. radical radiotherapy in combination with chemotherapy or chemotherapy administration for sensitization to radiation; (iii) studies reporting surgical interventions; (iv) studies reporting adjuvant chemotherapy (i.e. chemotherapy following radical surgical intervention) or neo-adjuvant chemotherapy (i.e. chemotherapy prior to radical surgical interventions); (v) studies reporting supportive care interventions or comparison of chemotherapy with chemotherapy plus conventional supportive care and (iv) follow-up and extension studies. In addition, studies with a crossover design, meeting abstracts and conference proceedings were excluded.

In RCTs involving more than two treatment arms, each pairwise treatment comparison was considered as different study. Also, RCTs providing data for different SCLC stages were considered as separate studies in the analysis. In order to avoid the inclusion of duplicated data, the retrieved studies were appraised by geographic location, author names and period of study. Then, in studies with overlapping patients, the largest one was included in the analysis. Only studies conducted after approval from national ethical committees were considered.

### 2.3. Data extraction and outcomes definition

The following information was extracted from each eligible article: name of first author, year of publication, country of origin, reported stage of SCLC, sample size (randomized patients, totally and per arm), types and intensity (dose and duration) of chemotherapies, effect size of each outcome of interest and chemotherapy regimen. Data extraction was undertaken by 2 investigators (GB and CD), independently. The overall agreement rate was 89%. Any disagreement was resolved by a third independent investigator (EZ).

Two primary outcomes were considered for the network analysis: the CR and the ORR. Complete Response (CR) is achieved when all tumor lesions are disappeared after treatment initiation. Objective Response Rate (ORR) is the portion of patients with a predefined amount of tumor size reduction; ORR is defined as the sum of CR and partial response and it is a direct measure of drug antitumor activity. Among the many adverse events after treatment with chemotherapy, we chose to record the neutropenia (NP) and febrile neutropenia (FNP) because they are considered the most important ones.

### 2.4. Treatment definition

Chemotherapy regimens containing the same chemotherapy agents, irrespective of dosage scheme and maximum duration of each chemotherapy cycle, were defined as the same treatment since we are interested in the assessment of the relative effectiveness of the different agent-based therapies. In addition, the effect of different dosage schemes and chemotherapy cycle intensity remains unresolved [5]. Furthermore, the current grouping allows the definition of a less complicated and analyzable network. The combination of cisplatin and etoposide (EP) was set as the reference treatment in the subsequent treatment comparisons since it is the standard first line treatment and the most commonly investigated chemotherapy regimen.

### 2.5. Statistical methods

Treatments were compared using odds ratios (ORs) with their respective 95% confidence intervals (CI). When more than two studies compared the same treatments, a random effects (RE) pooled OR was calculated [10]. The RE model incorporates the between study variability and it is more conservative than the fixed effects model [11].

Indirect comparison was performed for treatments not compared directly [12]. Then, in comparing two treatments, A and B, where each treatment was compared directly with treatment C, the OR for comparing A and B was calculated using the following principle [8]: $\ln(OR_{AvsB}) = \ln(OR_{AvsC}) - \ln(OR_{BvsC})$, and the respective 95% CI was estimated assuming asymptotic normality and lack of covariance [12–16] (Fig. 2). The network of treatments was constructed based on all investigated comparisons between treatments and the indirect analysis was performed utilizing all the possible pathways provided by the network. The OR was considered significant when the 95% CI included the one (1).

The network graph was built using S-PLUS 8 (Seattle, WA, USA, http://www.insightful.com) [17] and the network analysis was carried out using NET-MS (http://netms.med.uth.gr) [8,9]. The algorithm was implemented using Compaq Visual Fortran90 with the IMSL library (Hewlett Packard, Avondale, PA) [18]. MetaAnalyst (Evidence-Based Practice Center, Tufts Medical Center, Boston, MA,