Topotecan or other agents as second-line therapy for relapsed small-cell lung cancer: A meta-analysis of randomized studies

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Abstract. Small cell lung cancer (SCLC) is exceptionally responsive to chemotherapy and radiotherapy. In relapsed patients, particularly in resistant/refractory cases, the progression of disease occurs rapidly with second-line agents. Topotecan (TOPO), a camptothecin analog, is the only agent able to increase overall survival (OS) compared with the best supportive care alone. However, the efficacy of platinum-based chemotherapy rechallenge or other agents has not been systematically explored. In the present review, published articles, which evaluated outcome and toxicity associated with TOPO or non-TOPO-based chemotherapy in patients with SCLC from inception to September 2020 were systematically searched and identified by searching the PubMed, EMBASE and Cochrane Library databases. The primary outcome of interest was the risk of death (OS), and the secondary endpoints were risk of progression progression-free survival (PFS), overall response rate (ORR) and G3-4 hematological toxicities. A total of nine studies were included in quantitative synthesis for a total of 1,689 patients. They included platinum-based rechallenge, anthracycline-based combinations or camptothecin analogs. TOPO did not improve OS with respect to other therapies [hazard ratio (HR), 0.92; 95% confidence interval (95% CI), 0.78-1.09; P=0.33]. Similarly, PFS was similar in the two arms (HR, 1.1; 95% CI, 0.72-1.67; P=0.66). The ORR was not statistically higher with non-TOPO agents (relative risk, 1.53; 95% CI, 0.95-2.48). In subgroup analysis, combination chemotherapy was associated with an improved PFS but not OS or ORR compared with TOPO alone (HR, 1.85; 95% CI, 1.52-2.24; P<0.01). The rates of G3-4 anemia, febrile neutropenia and neutropenia were similar. In conclusion, in patients with relapsed SCLC, TOPO was associated with a similar survival, PFS and ORR as other agents. However, polychemotherapy was associated with improved PFS.

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Introduction

Small cell lung cancer (SCLC) is an aggressive lung cancer disease with a dismal prognosis in advanced stages. It is highly responsive to chemotherapy and radiotherapy but usually recurs within a few months in patients with extensive-stage SCLC. Recently, a first-line platinum plus etoposide-based chemotherapy with atezolizumab improved outcomes in first-line settings (1,2). In relapsed patients, in particular for resistant/refractory cases (during or within three months from the last day of upfront therapy), the progression of disease occurs rapidly with second-line agents (3). Topotecan, a camptothecin analog, has been demonstrated to increase overall survival (OS) compared with the best supportive care alone and results in greater symptom management relative to polychemotherapy regimens (3,4). The primary toxicities of TOPO are hematologic, with most patients experiencing grade [G]3 or 4 neutropenia, anemia, or thrombocytopenia. Recently, a phase III study compared TOPO alone with a combination of carboplatin/etoposide as a rechallenge schedule in patients with sensitive relapsed SCLC (5). Although a combination did not increase median OS, it provided a two-month benefit in progression-free survival (PFS) and showed similar rates of severe (G3-4) hematological toxicities. Despite platinum-based combinations may have a role in platinum-sensitive SCLC TOPO remain one of the referent treatment in relapsed disease. Recently it has been compared with platinum-etoposide-based doublets and triplets so it is reasonable to consider TOPO a pivotal comparator as second line agent.

To update the current state of the art, we performed a systematic review and meta-analysis of second-line studies comparing TOPO with other agents in patients with relapsed SCLC.

Materials and methods

Identification of trials and inclusion criteria. Trials were identified through a comprehensive systematic search of Pubmed,

EMBASE, and The Cochrane Library from inception, up to September 12th, 2020. All randomized clinical trials reporting on SCLC patients that examined the efficacy of TOPO compared with other agents or best supportive care as second-line therapy for relapsed (sensitive or refractory/resistant) disease and were published in the English language were identified. The search terms used to identify studies for the meta-analysis were: *('small-cell lung carcinoma'[MeSH Major Topic] OR 'small-cell lung cancer'[All Fields] OR 'small-cell lung carcinoma'[All Fields] OR 'sclc'[All Fields]) AND ('recurrence'[MeSH Terms] OR 'recurrence'[All Fields] OR 'relapse'[All Fields] OR 'relapses'[All Fields] OR 'relapsing'[All Fields] OR 'relapsed'[All Fields] OR 'relapser'[All Fields] OR 'relapsers'[All Fields] OR 'previously treated'[All Fields] OR ('recurrance'[All Fields] OR 'recurrence'[MeSH Terms] OR 'recurrence'[All Fields] OR 'recurrences'[All Fields] OR 'recurrencies'[All Fields] OR 'recurrency'[All Fields] OR 'recurrent'[All Fields] OR 'recurrently'[All Fields] OR 'recurrents'[All Fields]) OR 'second line'[All Fields] OR ('pretreat'[All Fields] OR 'pretreated'[All Fields] OR 'pretreating'[All Fields] OR 'pretreatment'[All Fields] OR 'pretreatments'[All Fields])) AND ('topotecan'[MeSH Terms] OR 'topotecan'[All Fields] OR ('topotecan'[MeSH Terms] OR 'topotecan'[All Fields]))*. Studies were excluded if they 1) were comparative observational series, 2) were phase 1 trials, and 3) compared different schedules or administration routes of TOPO.

Data extraction and risk of bias assessment. Two review authors (A.G. and F.P.) determined eligibility by reading the abstract of each study identified by the search. A third author (A.L.) independently read these studies and reached an agreement for trial inclusion. The primary outcome was OS defined as any death that occurred from the randomization date. The secondary outcomes were progression-free survival (PFS), overall response rate (ORR) and severe (grade [G] 3-4) adverse hematological events (anemia, thrombocytopenia, febrile neutropenia [FN] and neutropenia). Type of study, number of patients, median age, rate of PS 0-1 patients included, treatment setting, schedule of TOPO and the experimental arm, the HR for OS and PFS for TOPO vs. experimental arms, rate of overall response defined as the sum of partial and complete response, and rate of G3-4 hematological toxicities were extracted by two authors (F.P. and A.G.) independently from each study. For each trial, we assessed the risk of bias ('low risk,' 'some concerns,' or 'high risk') in the overall effect of TOPO on the outcome and serious adverse events using version 2 of the Cochrane Risk of Bias Assessment Tool (6). Risk of bias assessments were carried out independently by three of the investigators (A.G., F.P. and A.L.), with disagreements resolved through discussion. We used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to assess the certainty of the evidence that TOPO increased OS compared with other agents in patients with relapsed SCLC (7).

Statistical analysis. We classified the trials according to the setting of the intervention (refractory or sensitive disease). The convention-sensitive disease was considered, as progression occurred at least three months after the end of first-line, platinum-based chemotherapy. The primary analysis was an inverse variance-weighted fixed or random-effect meta-analysis of HRs for OS and PFS and an inverse variance-weighted fixed or random-effect analysis using risk ratios (RRs) for ORR and rates of toxicity. We used Parmar's method if HRs were not reported in the study (8). We quantified inconsistency in associations among the trials using the I^2 statistic and derived P-values for heterogeneity using the Cochran Q statistic. We report precise P-values. A P-value <0.05 denoted statistical significance. A meta-regression analysis was performed to examine the potential effect of the number of sensitive SCLC cases and death. All analyses were conducted using RevMan statistical software version 5.3 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014).

Results

Of 633 articles that met the preliminary criteria, we found nine eligible articles (4,5,9-14), which included five phase 3 and four phase 2 randomized trials that compared TOPO with other regimens (Fig. 1 and Table I). Overall, 1689 patients were included in these studies. In most of the studies, patients had a performance status of 0 or 1. The mean or median age was 64 years. Usually, the sensitive disease was considered when it recurs after 90 days. Intravenous, three-weekly TOPO was used in all studies except one where oral formulation was used. Combination chemotherapy was the experimental arm in n=3 trials, single agent in n=5, while best supportive care was the comparator arm in n=1 study. Sensitive disease ranged from 45 to 100% of included patients (median, 57.3%).

OS was not improved by TOPO with respect to other therapies (HR=0.92, 95% CI, 0.78-1.09; P=0.33; Fig. 2). Similarly, PFS was similar in the two arms (HR=1.1, 95% CI, 0.72-1.67; P=0.66; Fig. 3). The ORR was not statistically higher with non-TOPO agents (RR=1.53, 95% CI, 0.95-2.48; Fig. S1). In the meta-regression analysis, the rate of sensitive SCLC patients enrolled in each trial was significantly associated with OS (P=0.01). This means that agents different from TOPO are better in exquisite sensitive disease. In subgroup analysis, combination chemotherapy was associated with a better PFS but not OS or ORR than TOPO alone (HR=1.85, 95% CI, 1.52-2.24; P<0.01). The rates of G3-4 anemia, FN and neutropenia were similar. Instead, G3-4 thrombocytopenia was inferior in the experimental arms (RR=0.44, 95% CI, 0.26-0.74; P<0.01) (Figs. S2-S5). In the primary analysis, both Begg's and Egger's tests were not significant for publication bias. There is little evidence that TOPO has a similar outcome to other agents in a mixed population of SCLC patients. However, we can recommend that in platinum-sensitive disease, combination agents are probably better and similarly or even less toxic than TOPO.

Discussion

SCLC is a subtype of lung cancer burdened by high mortality. The treatment of advanced SCLC has not changed over the years due to the high aggressiveness and refractoriness of the disease. Recently, two studies in a first-line setting with chemotherapy plus anti-programmed cell death ligand-1 (PDL-1) therapy showed an improved OS vs. chemo alone (1,2).

Table I. Characteristics of included studies.

First author/s, year	Type of study	Patients, n	Setting (%)	PS 0-1, %	Median age, years	Topotecan schedule, mg/m^2	Exp arm	OS, months (Ctr vs. Exp)	PFS, months (Ctr vs. Exp)	ORR, % (Ctr vs. Exp)	G3-4 anemia, % (Ctr vs. Exp)	G3-4 thrombocytopenia, % (Ctr vs. Exp)	FN, % (Ctr vs. Exp)	G3-4 neutropenia, % (Ctr vs. Exp)	Risk of bias	(Refs.)
Baize, 2020	Phase 3	162	Sensitive (100)	92.5	64.5	Oral 2.3 d1-5 q21	Carboplatin + Etoposide	-	2.7 vs. 4.7	25 vs. 49	21 vs. 24	36 vs. 31	13 vs. 6	24 vs. 13	Low	(5)
Chiappori, 2016	Phase 2	44	Refractory (54.6); sensitive (45.4)	36	64	iv 1.5 d1-5 q21	Linsitinib	5.3 vs. 3.4	3 vs. 1.2	13.3 vs. 0	7.1 vs. 3.6	28.6 vs. 7.1	-	28.6 vs. NR	Uncertain	(14)
Evans, 2015	Phase 2	179	Refractory (49); sensitive (51)	99.4	61	iv 1.5 d1-5 q21	Cabazitaxel	6.8 vs. 5.2	3 vs. 1.4	10.1 vs. 0	26.1 vs. 3.4	45.5 vs. 4.5	22.7 vs. 18	78.4 vs. 56.8	Moderate	(13)
Goto, 2016	Phase 3	180	Sensitive (100)	97.2	64	iv 1 d1-5 q21	Cisplatin + Etoposide + Irinotecan	12.5 vs. 18.2	3.6 vs. 5.7	25.5 vs. 33.8	27 vs. 85	28 vs. 41	7 vs. 31	85 vs. 84	Low	(12)
Inoue, 2008	Phase 2	59	Refractory (39); sensitive (61)	85	69	iv 1 d1-5 q21	Amrubicina	8.4 vs. 8.4	2.2 vs. 3.5	13 vs. 38	30 vs. 21	40 vs. 28	3 vs. 14	87 vs. 93	Moderate	(11)
Jotte, 2011	Phase 2	76	Sensitive (100)	89.4	65.5	iv 1.5 d1-5 q21	Amrubicina	7.6 vs. 9.2	3.3 vs. 4.5	15.4 vs. 44	30 vs. 25	61 vs. 39	9 vs. 10	78 vs. 71	Moderate	(10)
O'Brien, 2006	Phase 3	141	Refractory (54); sensitive (46)	70.2	59.2	Oral 2.3 d1-5 q21	BSC	6.4 vs. 3.4	4 vs. NR (TTP)	7 vs. 0	25 vs. 0	38 vs. 0	3 vs. 0	61 vs. 0	Low	(3)
Von Pawel, 1999	Phase 3	211	Sensitive (100)	78.6	-	iv 1.5 d1-5 q21	Cyclophosphamide + Doxorubicin + Vincristine (CAV)	6.2 vs. 6.1	3.3 vs. 3 (TTP)	24.3 vs. 18.3	42.3 vs. 19.8	57.6 vs. 14.9	-	88.5 vs. 86.9	Low	(4)
Von Pawel, 2014	Phase 3	637	Refractory (46.4); sensitive (53.6)	97.9	61.5	iv 1.5 d1-5 q21	Amrubicina	7.8 vs. 7.5	3.5 vs. 4.1	16.9 vs. 31.1	31 vs. 16	54 vs. 21	3 vs. 10	54 vs. 41	Low	(9)

PS, performance status; OS, overall survival; PFS, progression-free survival; ORR, overall response rate; FN, febrile neutropenia; TTP, time to progression; NR, not reported.

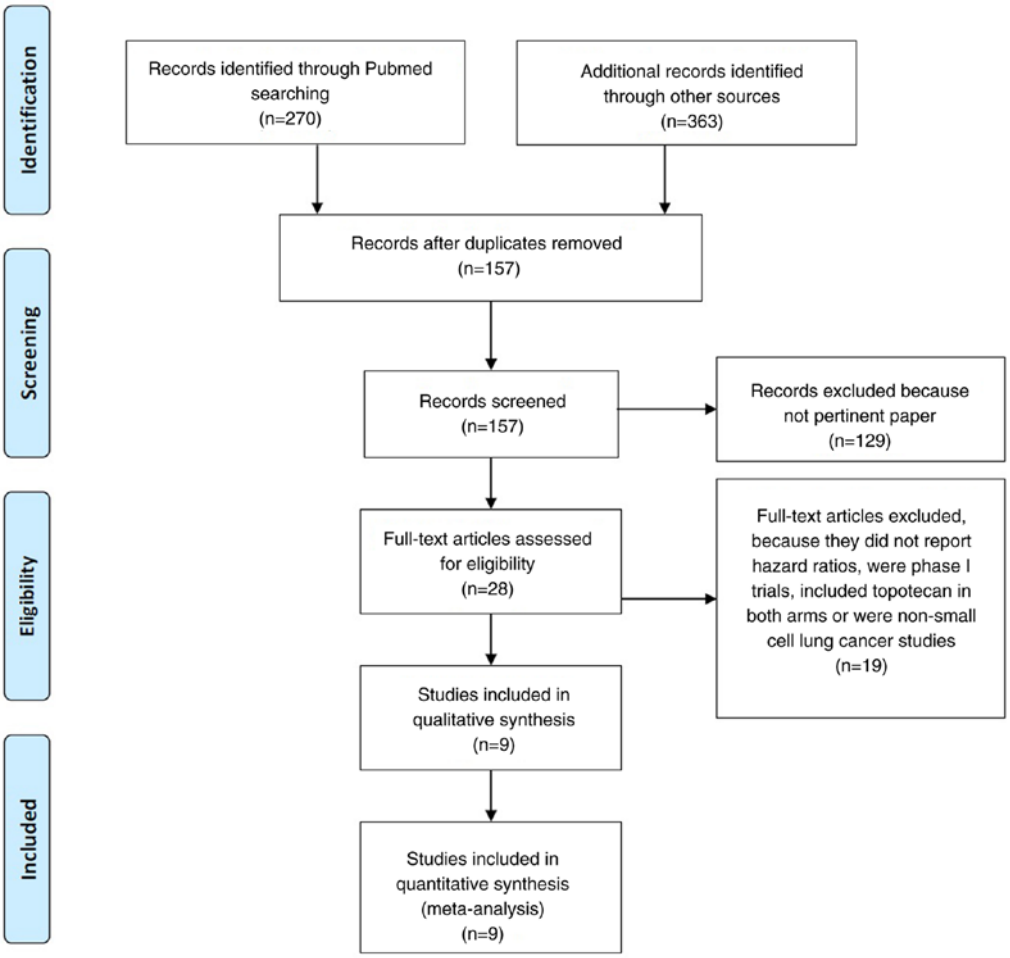

Figure 1. Flow diagram of included studies.

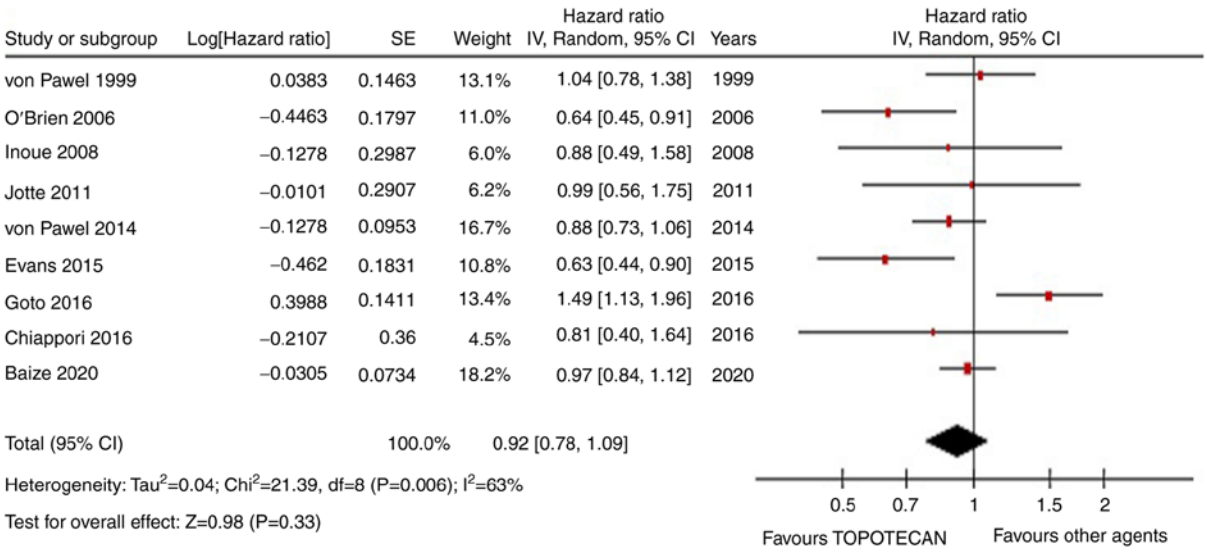

Figure 2. Forest plot for overall survival of topotecan vs. other agents. SE, standard error; IV, inverse variance; df, degree of freedom; 95% CI, 95% confidence interval.

Most patients progressed after first-line treatment, and the best second-line strategy remains to be elucidated. Topotecan is the only drug approved for second-line treatment due to the head-to-head comparison with cyclophosphamide-doxorubicin-vincristine triplet (CAV regimen) and a placebo-controlled trial with oral administration. However, there is still a debate about the magnitude of its clinical benefit, and this meta-analysis shows how

Table II. Irinotecan studies in pretreated small cell lung cancer.

First author/s, year	Type of study	Patients, n	Setting (%)	PS 0-1, %	Median age, years	Schedule, mg/m^2	OS, months	PFS, months	ORR, %	G3-4 anemia, %	G3-4 thrombocytopenia,%	FN,%	G3-4 neutropenia, %	(Refs.)
Kondo, 2018	Phase 2	30	Sensitive (40); resistant (60)	100	67	CPT-11 100d1, 8 q21	10.4	4.1	43	13.3	3.3	6.6	36.7	(15)
Trafalis, 2016	Phase 2	32	Resistant (100)	82	63.5	CPT-11 175 + bevacizumab 7.5 mg/kg q14	6	3	25	0	0	3.5	7.1	(16)
Xenidis, 2011	Phase 2	31	Refractory (100)	84	64	CPT-11 125 + PLD 15 d1,14 q 28	3.16	1.86	12.9	3.2	0	6.5	0	(17)
Ramalingam, 2010	Phase 2	55	Sensitive (51); refractory (49)	95	61	CPT-11 50 d1,8 + PAC 75 d1,8 q21	7.6 and 5.5[a]	3 and 2[a]	19.5	2	0	0	11	(18)
Chen, 2009	Phase 2	40	Sensitive (100)	85	65	CPT-11 150 + CBDCA AUC5 d1 q 21	10	-	50	15	23	3	55	(19)
Pallis, 2009	Randomized phase 2	69	Sensitive (52 vs. 35); refractory (47 vs. 64)	85 vs. 94	60 vs. 65	CPT-11 300 d8 + GEM 1000 d1, 8 q21 vs. CPT-11 300 d1 q21	8.6 and 5.7[a] (sensitive) vs. 8.6 and 3.8 (refractory)	4.3 and 2.5 vs. 1.7 and 1.1 (sensitive and refractory)	23.7 vs. 0	5.3 vs. 3.2	21 vs. 9.7	2.6 vs. 6.4	23 vs. 33	(20)
Ohyanagi, 2008	Phase 2	30	Sensitive (66); refractory (34)	65	90	CPT-11 150 q21 + GEM 1000 d1,14 q21	14.4	3	36.7	3.3	3.3	0	43	(21)
Rocha Lima, 2007	Phase 2	71	Sensitive (50); refractory (50)	85	62	CPT-11 100 d1,8 + GEM 1000 d1,8 q21	7.1 and 3.5[a]	3.1. and 1.6	21	7.5	31	4.5	38.5	(22)
Schuette, 2005	Phase 2	35	Sensitive (57); refractory (43)	86	63	CPT-11 100 d1,8 + GEM 1000 d1, 8 q 21	5.8	3.4	17	8.6	11.4	0	5.7	(23)
Ichiki, 2003	Phase 2	34	Sensitive (71); refractory (29)	68	69	CPT-11 80 d1,8,15 + IFO 1,5 g/m^2 d1-3 q 28	7.2	-	52.9	29.4	11.8	0	52.9	(24)

[a]Sensitive and refractory disease. CPT-11, irinotecan; GEM, gemcitabine; IFO, Ifosfamide; CBDCA, carboplatin; PAC, paclitaxel; PDL, pegylated lyposomal doxorubicin; PS, performance status; OS, overall survival; PFS, progression-free survival; ORR, overall response rate; FN, febrile neutropenia.

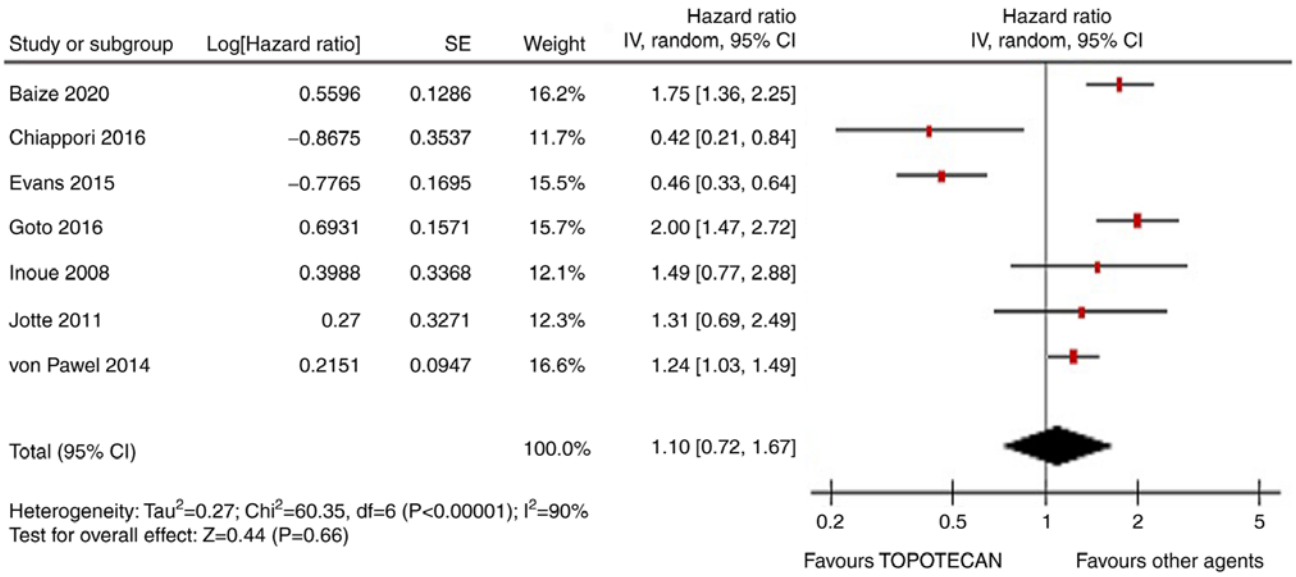

Figure 3. Forest plot for progression-free survival of topotecan vs. other agents. SE, standard error; IV, inverse variance; df, degree of freedom; 95% CI, 95% confidence interval.

the use of drugs other than TOPO could give comparable outcomes. Based on our analysis, TOPO performs worse than other drugs in sensitive diseases, and combination therapy gives better response rates compared with a single agent. TOPO, as a second-line strategy, remains controversial, with conflicting evidence regarding its superiority in terms of survival, toxicity and response rates. TOPO seems to give less thrombocytopenia, while other toxicities are similar to combination therapies across the studies.

As second-line treatments in relapsed small-cell lung cancer are usually considered 'palliative,' the question remains whether using a standard drug is still a choice to be considered in young and fit older patients. Based on the literature, discouraging results have come from all agents tested, and superiority data do not support the use of TOPO over the others in common clinical practice. Even if combination regimens have more toxicity, the benefits are small and not durable. The rechallenge strategy with etoposide + platinum-based chemotherapy, however, at least in sensitive diseases, is a reasonable choice to have better response rates and progression-free survival with manageable toxicities (5). In this setting, the combination chemotherapy has shown high response rates (40-55%). For patients with refractory/resistant disease and a good performance status, inclusion in clinical trials is the preferred choice. Other agents as camptothecin analogues (irinotecan) have been tested in progressive disease (Table II). Despite a relatively high number of tumor responses in particular for combinations (range 12-52.9%) and median OS up to 10 months, neutropenia was consistent and this agent is not currently approved for use in western countries (15-24).

In conclusion, TOPO is not better than other agents in relapsed SCLC, but there is weak evidence that it is inferior to platinum-based combinations in sensitive diseases.

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Availability of data and materials

All datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

FP, AG and AL contributed equally to manuscript writing. Data authentication is not applicable. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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