Published in final edited form as:
J Thorac Oncol. 2012 May ; 7(5): 866–872. doi:10.1097/JTO.0b013e31824c7f4b.

A systematic analysis of efficacy of second line chemotherapy in sensitive and refractory small cell lung cancer

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Abstract

Introduction—SCLC patients unresponsive or relapsing within 90 days following frontline chemotherapy have poor prognosis and are treated with regimens different than the first-line regimen. Potential differences in the efficacy of second line therapy for refractory and sensitive SCLC have not been well studied.

Methods—Studies that enrolled sensitive and refractory (relapse more than or less than 90 days) SCLC patients for second-line therapy were identified using electronic databases (MEDLINE, EMBASE, and Cochrane library) and meeting abstracts databases. A systematic analysis was conducted using Comprehensive Meta Analysis (Version 2.2.048) software to calculate the Odds ratio of response and 95% confidence limits. Median overall survival time for sensitive and resistant SCLC patients was compared by 2-sided Student's T-Test. We tested for significant heterogeneity by Cochran's chi-square test and I square index.

Results—Twenty one studies published between 1984 and 2011 were eligible for this analysis with a total of 1692 patients enrolled; 912 with sensitive and 780 with refractory SCLC. The overall RR was 17.9% with a higher RR of 27.7% (range: 0 – 77%) for sensitive SCLC versus 14.8% (range: 0 – 70%) for refractory patients; p=0.0001. Pooled overall Odds ratio of response was 2.235 (95% CI: 1.518 – 3.291; p=0.001) favoring patients with sensitive disease. Median overall survival time was 6.7 months with a weighted survival of 7.7 and 5.4 months for sensitive and refractory SCLC respectively (p=0.0035).

Conclusions—Refractory SCLC patients derive modest clinical benefit from second line chemotherapy. However, response and survival outcomes are superior with chemosensitive disease.

Keywords

small cell lung cancer; chemotherapy; sensitive; resistant; refractory

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This work was presented as a poster at the 2010 Chicago Multidisciplinary Symposium in Thoracic Oncology. Chicago December 9–11, 2010.

Introduction

Approximately 30,000 new patients are diagnosed with small cell lung cancer (SCLC) in the US on an annual basis.[1,2] Majority of these patients have extensive stage of the disease, which is incurable with currently available treatment options. The efficacy of platinum-based chemotherapy for frontline therapy has been established in randomized clinical trials[3–7] with objective responses in approximately 70% of patients with limited stage SCLC and in 50% of patients with extensive stage disease.[5,8–10] Despite this high initial response, majority of SCLC patients require salvage therapy for disease progression within several months following frontline therapy. Although various chemotherapeutic agents have been evaluated either singly or in combination for progressive SCLC following disease progression, topotecan is the only approved second line therapy for SCLC in the US population.[11,12]

The quality and duration of response to frontline therapy strongly predict the survival outcome in SCLC. Patients with durable response lasting more than 3 months are considered sensitive to the platinum-based frontline therapy. Refractory patients do not achieve any objective response while resistant disease is characterized by initial response followed by very early disease recurrence usually within 90 days of completing frontline therapy.[12–14] Patients with chemosensitive disease and durable response lasting more than 6 months are treated with the original frontline regimen at the time of progression whereas patients with resistant or refractory disease are considered for treatment options different from the frontline regimen. Whether this treatment paradigm results in better outcome for patients with resistant/refractory SCLC is an area that has not been well studied.[14,15] This systematic analysis is the first major attempt to bridge this knowledge gap by using data pooled from published results of clinical studies that enrolled sensitive and resistant/refractory SCLC patients to assess the clinical efficacy of systemic chemotherapy in the second line setting.

Materials and Methods

Study Eligibility

Prospective clinical trials that enrolled patients with both sensitive and resistant/refractory SCLC for the evaluation of second-line chemotherapy regimens were included in this analysis. In addition, qualifying studies must have enrolled minimum of 10 patients and reported on the clinical outcome (overall survival or response rate) for both subgroups of patients. Studies published in a language other than English were excluded.

Literature Search Strategy

We identified eligible clinical trials using the main computerized databases of published biomedical literature (MEDLINE, EMBASE, and Cochrane Library). We used the search terms “small cell lung cancer AND clinical trial” along with the following limit terms: humans, clinical trial, English, cancer, all adult: 19+ years for the MEDLINE search. Conference proceedings of the annual meetings of the American Society of Clinical Oncology (ASCO) and the International Association for the Study of Lung Cancer (IASLC) were also searched for relevant abstracts. The retrieved studies were reviewed independently by two of the authors (TKO, MB). Final determination of study eligibility was made by the concurrence of both investigators at a follow-up consensus meeting.

Data Extraction and Synthesis

Pertinent extracted data included patient demographics, number and distribution of enrolled patients, specific therapy and clinical outcome of response rate (RR) and overall survival (OS). The response rate data was pooled for the two patient subgroups to generate a

weighted overall RR for sensitive and resistant/refractory SCLC. We also calculated a weighted mean survival time for the sensitive and resistant/refractory patient groups as the product of the median survival time and number of patients.

Statistical Approach

Analysis of the extracted data was conducted using Comprehensive Meta Analysis (Version 2.2.048) software. Using a random-effect model, the likelihood of response to second line treatment based on patients' response to frontline chemotherapy (sensitive versus resistant/refractory) was calculated as Odds ratio along with 95% confidence interval. Statistical difference in the weighted mean RR and OS for sensitive and resistant/refractory SCLC patients was assessed by a 2-sided T-test.

Sensitivity testing

We conducted an initial analysis for the Odds ratio of response between sensitive and resistant/refractory population using the random effect model. A repeat analysis using a fixed effect model was performed to validate the initial results. Significant heterogeneity among the studies employed for this analysis was formally assessed by Cochran's chi-square test and the I^2 index where a p-value < 0.1 by chi-square test and I^2 value < 0.25 indicate a low degree of heterogeneity.[16] Finally, sensitivity analyses were conducted to exclude potential confounding of the results by an individual study or a group of studies by repeating the analysis after excluding each study in turn (leave-one-out model); by excluding studies of single agent and combination regimen; after excluding studies that evaluated topotecan and after excluding large studies that enrolled more than 50 patients.

Results

Study and patient demographics

Starting with 1141 studies, 53 studies published between 1984 and 2011 were identified as potentially eligible for this analysis. Based on the predefined eligibility criteria, we selected 21 studies that met the qualitative and quantitative requirements of the systematic analysis. A consort diagram of the stepwise identification of eligible studies is detailed in Figure 1. A total of 1692 patients were enrolled across the selected trials. Response data was available for 1055 patients across 20 studies; 570 (54.0%) with chemosensitive disease and 485 (45.9%) with resistant/refractory SCLC. Survival data from 1219 patients from 11 different studies was also analyzed; 678 (56%) and 541 (44%) with sensitive and resistant/refractory SCLC respectively. Details of patient demographics and study designs are included in Table 1.

Tumor Response

The overall response rate of relapsed SCLC patients to second line treatment was 17.9% with 27.7% in patients with sensitive disease (range: 0 – 77%) and 14.8% (range: 0 – 70%) for resistant/refractory patients; p<0.0001. The overall Odds ratio of response was 2.235 (95% CI: 1.518 – 3.291; p<0.0001) in favor of patients with sensitive disease (Figure 2).

Survival

The weighted average of the overall median survival time following second line therapy was 6.7 months with a weighted average of 7.73 months (range: 2.7 – 8.7) for sensitive SCLC and 5.45 months (range: 4.4 – 9.9) for resistant/refractory disease (p<0.0035).

Sensitivity testing

The test of heterogeneity using I^2 test was 9.029% (p= 0.347) indicating a low degree of heterogeneity. The overall trends from the initial results remained unchanged after repeat analyses using the fixed effect model (Odds ratio of 2.227; 1.550 – 3.198; Figure 3) and after excluding studies with large sample size (Odds ratio of 1.926; 1.093 – 3.393; Figure 4), studies of topotecan (2.170; 1.378 – 3.418; Figure 5), studies with combination regimens (2.480; 1.060 – 5.802, Figure 6) or studies of single agent treatment (2.040; 1.318 – 3.158, Figure 7) and following the leave-one-out analyses (Table 3).

Discussion

The result of this systematic analysis highlights the poor overall survival outcome for SCLC patients following progression on frontline therapy. More than 80% of patients enrolled in clinical trials employed for this systematic analysis did not achieve an objective response and a significant proportion of the patients died within 6 months. As previously observed with topotecan,[11–13,15] we observed in this pooled analysis that patients with disease refractory or resistant to frontline therapy were also less likely to respond to second line chemotherapy in general and consequently had a worse survival outcome. Nonetheless, our data indicates that patients with resistant/refractory SCLC derive clinical benefit with the receipt of second line therapy in contrast to historical experience with untreated refractory SCLC where the survival is measured in weeks.[6,38–40]

The studies included in our analysis evaluated different types of investigational agents. It is therefore not unexpected that heterogeneity in study design, patient population and therapeutic agents may confound the result of this analysis. We carefully excluded any such possibility with the extensive sensitivity testing looking at all potential confounders including sample size, the use of topotecan, which is the only approved agent in this setting, as well as a leave-one-out analysis to examine if any of the included studies had a disproportionate influence on the overall result. Irrespective of the sensitivity test employed, we observed a consistent result of a worse survival and lower likelihood of response in refractory SCLC. Our result is also consistent with the report by Treat et al. who employed individual patient data from five large randomized studies of topotecan as salvage treatment for SCLC. They reported an overall response rate ranging between 14 and 17% with higher responses in chemosensitive disease (range of 18 – 24%) than in chemorefractory patients (range of 3 – 4%).[15] Moreover, the reported outcome in this analysis is comparable to subset analysis of prospective studies of topotecan in the salvage setting.[12,15] Since the use of intensive multi-agent chemotherapy has been shown to achieve higher response rates in SCLC albeit with heightened toxicities,[41–43] we assessed whether this approach could result in higher likelihood of response in patients with resistant/refractory disease in the second line. However, we did not observe any reversal in the trend of higher odds of response in favor of patients with sensitive SCLC in studies evaluating both single agent and multi-agent chemotherapy regimens.

To our knowledge, this analysis using pooled data across 21 different prospective studies of second line chemotherapy is the largest such analysis in this patient population. Our data has now extended the results of previous small retrospective studies using local registry databases that reported superior survival with sensitive SCLC in the second line setting.[39,44,45] Overgeneralization of the result of this analysis requires some caution since the patient population enrolled in clinical trials represents a select subset with good performance status and preserved organ function that may not accurately represent the general patient population.[44] Indeed, majority of all patients in this analysis had an ECOG performance status of 0 or 1 but we were unable to ascertain whether this is balanced between the two subgroups of patients.

Based on our result and the observation in the frontline setting, we posit that the resistant/refractory SCLC patient population represents a biologically distinct subgroup of SCLC that requires a uniquely tailored therapeutic approach similar to the different approaches adopted for limited and extensive stage SCLC. In the absence of a highly effective salvage therapy regimen, we agree that patients with sensitive relapse should be retreated with a platinum/etoposide regimen in line with current management recommendations. In contrast, patient with resistant/refractory disease should be considered for innovative clinical trials, especially studies that are designed to exploit our evolving understanding of tumor biology and drug resistance. One such study is the ESCAPE study, a phase II study evaluating the efficacy of the combination of standard platinum/etoposide along with amuvatinib in patients with resistant/refractory SCLC [NCT01357395]. Amuvatinib is an oral multi-targeted tyrosine kinase inhibitor against mutant forms of c-Kit and PDGFR alpha and also suppresses DNA repair capacity by disrupting Rad51 protein activity and consequently homologous recombination, which is central to DNA damage repair capacity.

Pertinent limitations of our study include the retrospective nature of this analysis and the potential imbalances in important clinical characteristics that may also affect clinical outcome of SCLC patients such as gender, presence of brain metastasis, overall disease burden and dose intensity.[46–48] However, the large number of patients included in the analysis and the use of tumor biology as defined by response to initial therapy for patient categorization makes our result a very important benchmark that could inform prospective clinical and translational research for this greatly understudied patient population.

Acknowledgments

Supported by NIH P01 CA166999 grant awarded to FRK and P01 grant supplement award to TKO as well as unrestricted research funding to GS, WJC, FRK and SSR by the Georgia Cancer Coalition.

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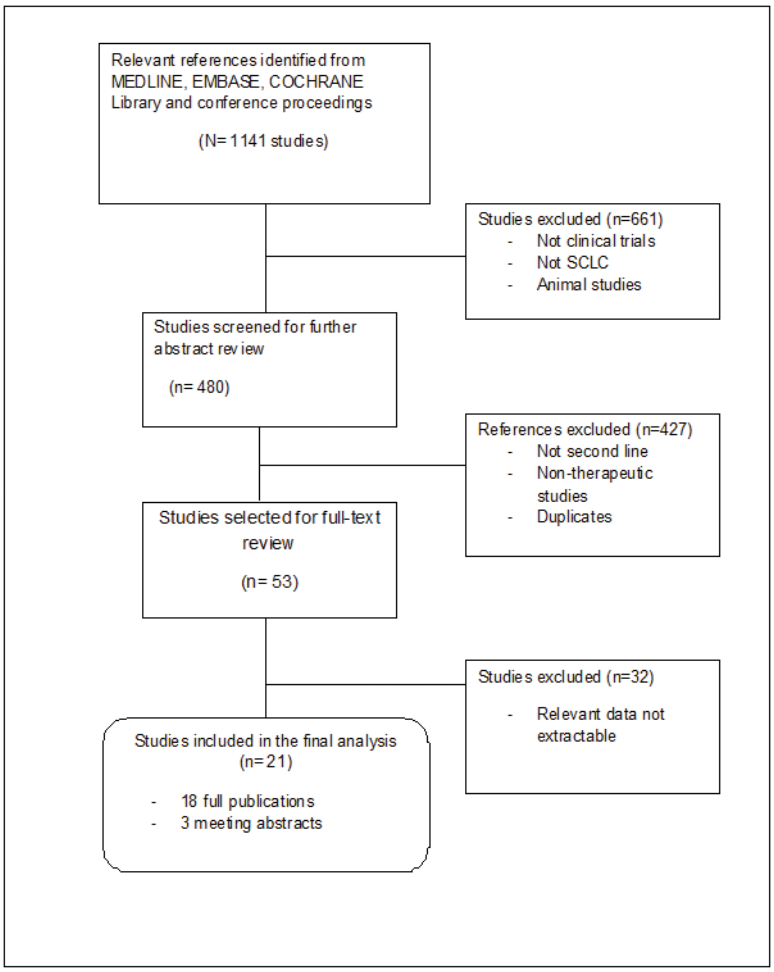

Figure 1.
Consort diagram detailing search strategy and study selection for this systematic analysis

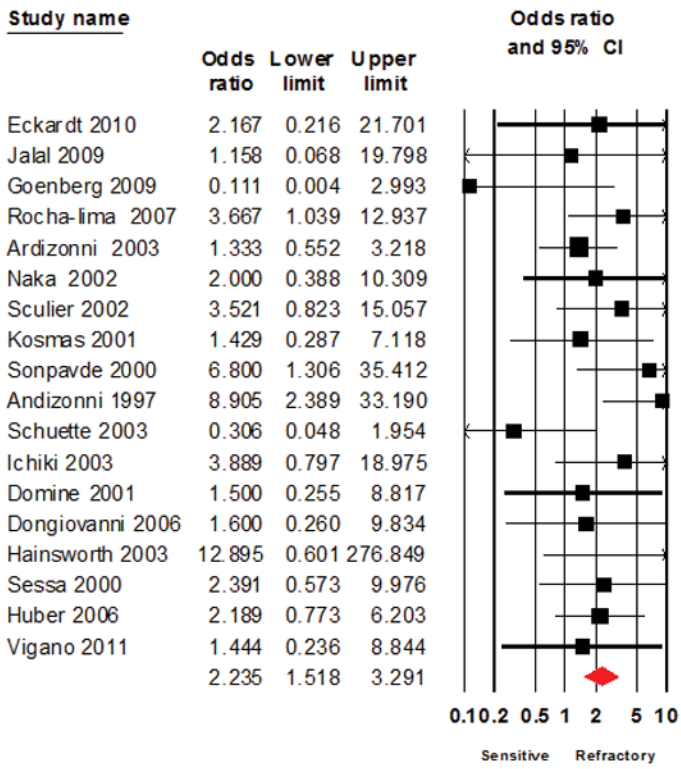

Figure 2.

Forest plot showing the primary analysis using a random effect model for Odds ratio of response to salvage chemotherapy between patients with sensitive disease or refractory SCLC as defined based on response to frontline chemotherapy

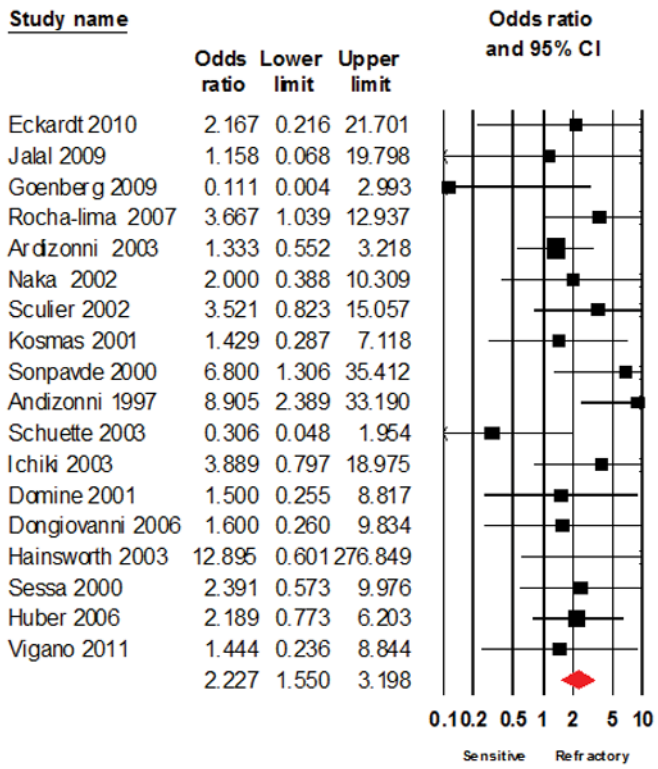

Figure 3.

Forest plot of analysis using a fixed effect model for Odds ratio of response to salvage chemotherapy between patients with sensitive disease or refractory SCLC as defined based on response to frontline chemotherapy.

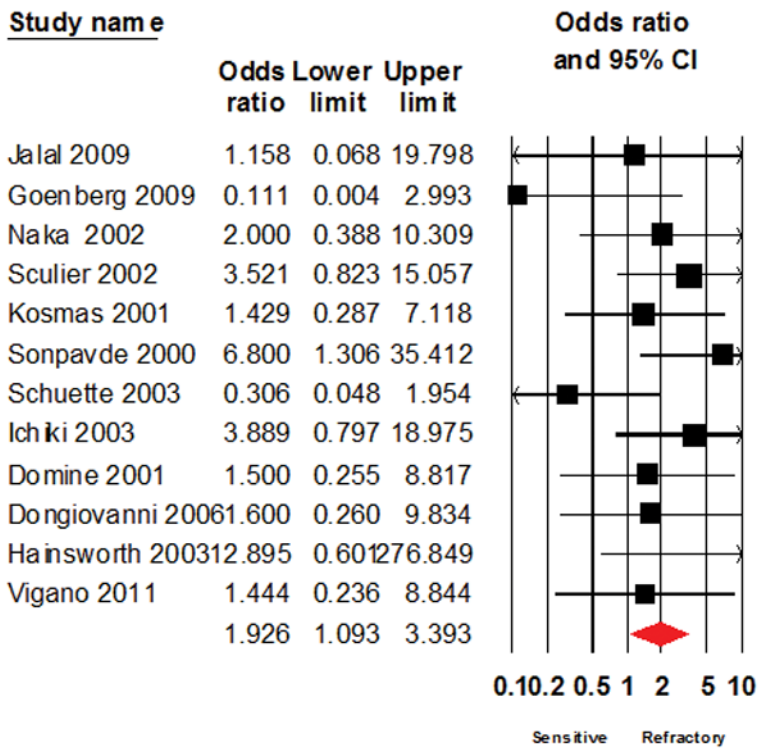

Figure 4.
Forest plot showing the result of Odds ratio analysis after excluding large studies that enrolled 50 or more patients

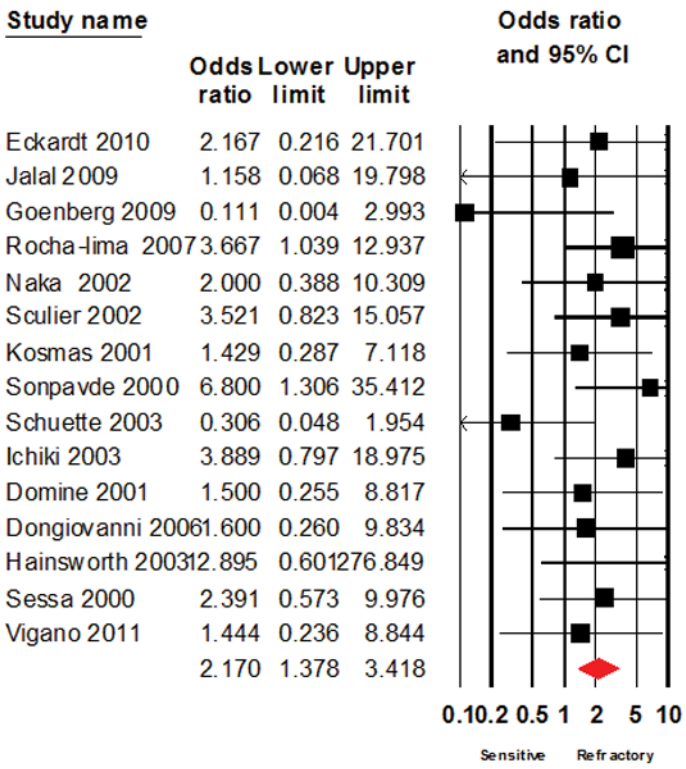

Figure 5.
Forest plot of the result of systematic analysis for Odds ratio of response to salvage chemotherapy after excluding studies that evaluated topotecan

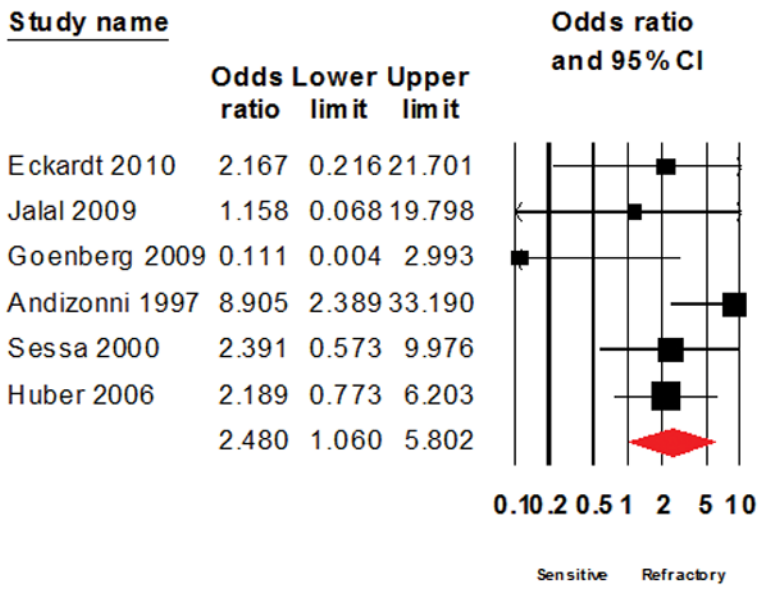

Figure 6.
Forest plot of the result of systematic analysis for Odds ratio of response to salvage chemotherapy after excluding studies that evaluated combination multi-agent therapy

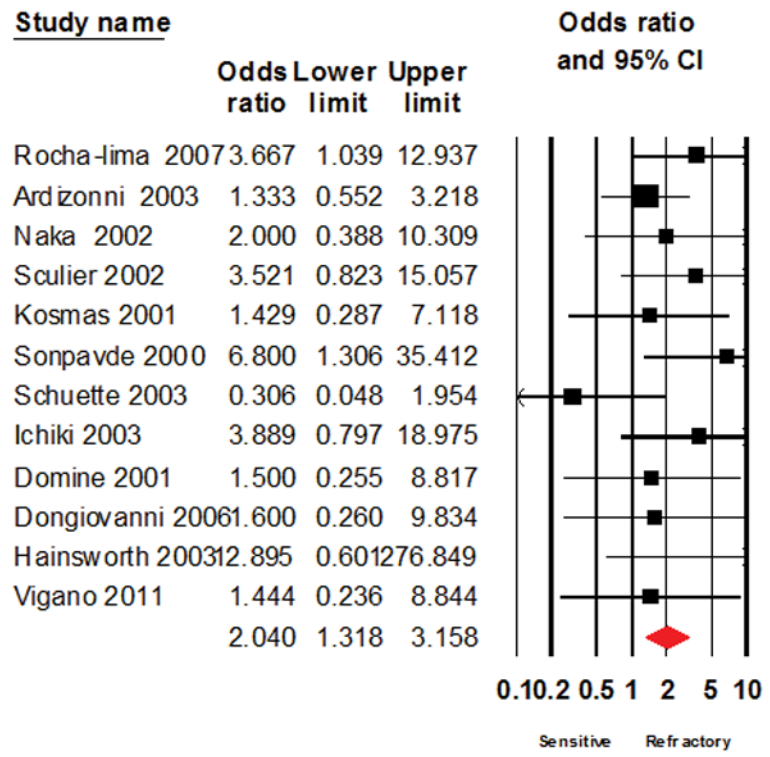

Figure 7.
Forest plot of the result of systematic analysis for Odds ratio of response to salvage chemotherapy after excluding studies that evaluated single agent treatment regimens

J Thorac Oncol. Author manuscript; available in PMC 2013 May 01.

Table 1

Study characteristics and clinical outcome of patients with sensitive or refractory SCLC following treatment with a second line chemotherapy. NR: Not reported. NA: Not adequate

Study	Total (Sensitive/Refractory)	PS (0/1/2)	Study Design	Therapy	RR (%)		OS (months)	
					Sensitive	Refractory	Sensitive	Refractory
Eckardt et al. 2009[17]	77 (6/71)	9/51/17	Phase II single arm	Picoplatin	17	8	NR	NR
Jalal et al. 2009[18]	43 (20/23)	14/18/11	Single arm phase II	Pemetrexed	5	4	4.4	2.7
Gronberg et al 2009[19]	34 (25/9)	5/18/11	Multicenter phase II	Pemetrexed	0	11	5.7	3.8
Rocha-Lima et al. 2007[20]	71 (35/36)	19/41/11	Phase II single arm	Irinotecan Gemcitabine	31	11	7.1	3.5
Ardizzoni et al. 2003[21]	110 (68/42)	17/75/18	Multicenter single arm phase II	Topotecan + Cisplatin	29	24	NR	NR
Naka et al. 2002[22]	29 (16/13)	0/16/13	Single arm phase II	Irinotecan + Carboplatin	38	23	6.1	5.7
Sculier et al. 2002[23]	45 (29/16)	NR	Randomized phase II	Cisplatin-etoposide/carboplatin	49	19	7.7	7.4
Kosmas et al. 2001[24]	33 (13/20)	NR	Single arm phase II	Paclitaxel, Ifosfamide and Cisplatin	77	70	NR	NR
Sonpavde et al. 2000[25]	46 (32/14)	NR	Single arm phase II	Doxorubicin + Paclitaxel	53	14	NR	NR
Ardizzoni et al. 1997[26]	92 (45/47)	NR	Single arm phase II	Topotecan	37.5	6.4	6.9	4.7
Schuette et al. 2005[27]	35 (20/15)	9/21/5	Single arm phase II	Gemcitabine + Irinotecan	10	26	4.5	4.5
Ichiki et al. 2003[28]	34 (24/10)	7/16/11	Single arm phase II	Irinotecan + Ifosfamide	62.5	30	NR	NR
Hensing et al. 2006[29]	37 (20/17)	NR	Single arm phase II	BBR 3464 (Triplatin)	NR	NR	6.8	2.5
Domine et al. 2001[30]	20 (10/10)	NR	Multicenter phase II	Gemcitabine + Paclitaxel	60	50	NR	NR
Dongiovanni et al. 2006[31]	31 (21/10)	3/20/8	Single institution phase	Gemcitabine + Paclitaxel	28.6	20	NR	NR
Hoang et al. 2003[32]	27 (15/12)	25/0/2	Single arm phase II	Gemcitabine	NR	NR	8.8	4.2

Study	Total (Sensitive/Refractory)	PS (0/1/2)	Study Design	Therapy	RR (%)		OS (months)	
					Sensitive	Refractory	Sensitive	Refractory
Hainsworth et al. 2003[33]	29 (12/17)	NR	Single arm phase II	Gemcitabine and Vinorelbine	25	0	NR	NR
Sessa et al. 2000[34]	66 (37/29)	15/39/12	Single arm phase II	GI147211 (Camptothecin)	21.6	10.3	NR	NR
Huber et al. 2006[35]	169 (111/58)	34/92/37	Multicenter single arm phase II	Topotecan	17.2	8.6	5.04	5.33
Von Pawel et al. 2011[36]	**Amrubicin (225/199)**	NR	Multicenter phase III trial	Amrubicin	NR	NR	9.2	6.2
	Topotecan (117/96)			Topotecan	NR	NR	9.9	5.7
Vigano et al. 2011[37]	27	NA	Single arm phase II	NGR-hTNF + Doxorubicin	27	19	NR	NR
Overall	1692 (901/764)	157/407/156			27.7	14.8	7.73	5.45

PS: Performance status using ECOG scale; NR: Not reported; NA: Not adequate

J Thorac Oncol. Author manuscript; available in PMC 2013 May 01.

Table 2

Resultant odds ratio and P-value by t-test when the indicated study was excluded in the leave-one-out analysis for response and survival. No individual study had a dominant effect on the overall result of this analysis. NR: data required for analysis not reported

Leave-One-Out Sensitivity testing for Odds Ratio and Survival Comparison			
Excluded Study	**Resultant Odds Ratio**	**95% CI for OR**	**P-value for median survival estimate comparison**
Eckardt et al. 2009[17]	2.24	1.49–3.36	NR
Jalal et al. et al. 2009[18]	2.26	1.51–3.38	P=<0.02
Gronberg et al. 2009[19]	2.31	1.60–3.32	P=<0.004
Rocha-lima et al. 2007[20]	2.14	1.41–3.22	P=<0.008
Ardizzoni et al. 2003[21]	2.45	1.61–3.70	NR
Naka et al. 2002[22]	2.25	1.48–3.4	P=<0.005
Sculier et al. 2002[23]	2.16	1.43–3.26	P=<0.005
Kosmas et al. 2001[24]	2.29	1.52–3.45	NR
Sonpavde et al. 2000[25]	2.10	1.43–3.09	NR
Ardizzoni et al. 1997[26]	1.98	1.36–2.89	P=<0.0017
Schuette et al. 2005[27]	2.40	1.66–3.48	P=<0.002
Ichiki et al. 2003[28]	2.16	1.44–3.25	NR
Domine et al. 2001[30]	2.27	1.51–3.42	NR
Dongiovanni et al. 2006[31]	2.27	1.50–3.41	NR
Hainsworth et al. 2003[33]	2.17	1.47–3.2	NR
Sessa et al. 2000[34]	2.22	1.46–3.37	NR
Huber et al. 2006[35]	2.24	1.46–3.44	0.0005
Vigano et al. 2011[37]	2.28	1.51–3.42	NR

Leave-One-Out Sensitivity testing for Odds Ratio and Survival Comparison			
Excluded Study	**Resultant Odds Ratio**	**95% CI for OR**	**P-value for median survival estimate comparison**
Hensing et al. 2006[29]	NR	NR	0.006
Hoang et al. 2003[32]	NR	NR	0.007
Von Pawel et al. 2011[36]			
Amrubicin	NR	NR	P=<0.019
Topotecan	NR	NR	P=<0.017