Relapsed small cell lung cancer: treatment options and latest developments

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Abstract: According to recent analyses, there was a modest yet significant improvement in median survival time and 5-year survival rate of limited stage small cell lung cancer (SCLC) in North America, Europe, Japan and other countries over the last 30 years. The median survival time of limited stage SCLC is 15–20 months and 5-year survival rate is 15% or less. In terms of extensive stage SCLC, a median survival time of 9.4–12.8 months and 2-year survival of 5.2–19.5% are still disappointing. Despite being highly sensitive to first-line chemotherapy and radiotherapy treatments, most patients with SCLC experience relapse within 2 years and die from systemic metastasis. While several clinical trials of cytotoxic chemotherapies and molecular targeting agents have been investigated in the treatment of relapsed SCLC, none showed a significant clinical activity to be able to exceed topotecan as second-line chemotherapy. There are problematic issues to address for relapsed SCLC, such as standardizing the treatment for third-line chemotherapy. Topotecan alone was the first approved therapy for second-line treatment for relapsed SCLC. Amrubicin is a promising drug and a variety of trials evaluating its efficacy have been carried out. Amrubicin has shown superiority to topotecan in a Japanese population, but was not superior in a study of western patients. There are some controversial issues for relapsed SCLC, such as treatment for older patients, third-line chemotherapy and efficacy of molecular targeting therapy. This article reviews current standard treatment, recent clinical trials and other topics on relapsed SCLC.

Keywords: chemotherapy, refractory relapse, sensitive relapse, small cell lung cancer

Introduction

Lung cancer remains the leading cause of cancer death, and approximately 13% of all patients with lung cancer are diagnosed as having small cell lung cancer (SCLC) [Govindan *et al.* 2006]. According to recent analyses, there was a modest yet significant improvement in median survival time (MST) and 5-year survival rate of limited stage (LS)-SCLC in North America, Europe, Japan and other countries over the last 30 years. The MST of LS-SCLC is 15–20 months and the 5-year survival rate is up to 15% [Chen *et al.* 2010; Govindan *et al.* 2006]. In terms of extensive stage (ES)-SCLC, a MST of 9.4–12.8 months and 2-year survival of 5.2–19.5% are disappointing [Noda *et al.* 2002; Maalouf *et al.* 2007].

Previously treated patients with SCLC can be divided into two groups: refractory cases are those whose disease progressed during first-line chemotherapy or progressed within 60 days;

sensitive cases are defined as those whose condition responded to first-line chemotherapy and relapsed after a treatment-free interval of at least 60 days. Sensitive cases are more likely to respond to second-line chemotherapy than refractory cases [von Pawel *et al.* 2003]. The standard treatment for relapsed SCLC as third-line treatment is not yet established. Therefore, it is common that physicians have difficulty in treating SCLC after failure of second-line chemotherapy. In general, 80% of older patients (≥ 70 years) with lung cancer generally have complications, such as chronic obstructive pulmonary disease, heart disease, cerebrovascular disease, malnutrition, osteoporosis and dementia [Johnson, 1997]. Evidence-based standard treatment for older patients with relapsed SCLC is also not established. With the advancement of an aging society in the USA, the European Union and Japan, a therapeutic strategy should be considered.

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Table 1. Randomized phase II–III trials of topotecan monotherapy for relapsed SCLC.

Authors [year]	Phase	Regimen	Number of patients	RR (%)	MST (weeks)
Von Pawel <i>et al.</i> [1999]	III	Top	107	24.3	25.0
		CAV	104	18.3	24.7
Von Pawel <i>et al.</i> [2001]	II	Oral Top	52	23.0	32.0
		Intravenous Top	54	15.0	25.0
Eckardt <i>et al.</i> [2007]	III	Oral Top	153	18.3	33.0
		Intravenous Top	151	21.9	35.0
O'Brien <i>et al.</i> [2006]	III	Oral Top	70	7.0	25.9
		BSC	67	–	13.9

BSC, best supportive care; CAV, cyclophosphamide + doxorubicin + vincristine; MST, median survival time; RR, response rate; SCLC, small cell lung cancer; Top, topotecan.

Previous studies reported the efficacy of rechallenge with the same drugs used in initial chemotherapy and it has been justified for sensitive relapsed cases [Rosti *et al.* 2006; Giaccone *et al.* 1987; Postmus *et al.* 1987]. However, refractory relapse is exceedingly chemoresistant and response rates (RRs) of less than 10% are usually attained with single-agent chemotherapy in those patients [Glisson, 2003]. Consequently, although a large number of chemotherapy regimens have been evaluated in clinical trials and some have shown a promising antitumor activity, no evidence-based standard treatment was established for refractory SCLC until 1999. Topotecan, a topoisomerase inhibitor I, is the only drug approved by the US Food and Drug Administration (FDA) for refractory SCLC and is considered standard second-line chemotherapy in several countries [Ardizzoni, 2004; Kim and Mishima, 2011]. A review of 631 relapsed cases treated with intravenous topotecan in six phase II–III studies showed a 20.4% and 4.0% RR in chemotherapy-sensitive and in chemotherapy-refractory cases respectively. These results are disappointing in terms of the risk–benefit balance [von Pawel *et al.* 2003]. Therefore, a variety of antitumor drugs have been studied for patients with recurrent SCLC in the second-line setting; details will be given later in the single-agent chemotherapy section.

Amrubicin, which is also a topoisomerase inhibitor II, has shown better antitumor activity than topotecan. Amrubicin is only approved for use in Japan [Onoda *et al.* 2006; Ohe *et al.* 1989; Inoue *et al.* 2008]. It is important to note that these are phase II noncomparative trials, not designed to determine which agent is better than the other. These results suggested that amrubicin has shown

superiority to topotecan in a Japanese population, but not in a study of western patients.

Molecular target drugs such as gefitinib or erlotinib have been developed and used since 2002. This has led to a paradigm shift in the treatment of advanced non-small cell lung cancer (NSCLC) [Rosell *et al.* 2009; Maemondo *et al.* 2010]. While the standard treatment for advanced NSCLC is dramatically changing, the one for SCLC remains disappointing. More recently, clinical trials of a small molecular inhibitor of several receptor tyrosine kinases have been performed in several countries. In this review, we document issues including the efficacy and safety of second- or third-line chemotherapy and recent prospective studies of cytotoxic agents or molecular targeted agents for SCLC.

Cytotoxic agents

Single-agent chemotherapy

Topotecan, a water-soluble, semisynthetic derivative of camptothecin, is a specific inhibitor of topoisomerase and is the only drug approved as second-line chemotherapy for relapsed SCLC by the FDA. The main studies of topotecan are shown in Table 1.

Von Pawel and colleagues conducted the first phase III study in patients with recurrent SCLC, in which topotecan and cyclophosphamide + doxorubicin + vincristine (CAV) were compared. Patients received either topotecan (1.5 mg/m²) as a 30-min infusion daily for 5 days every 3 weeks or CAV (cyclophosphamide 1000 mg/m², doxorubicin 45 mg/m² and vincristine 2 mg) infused on day 1 every 3 weeks. All the patients had

Table 2. Randomized control trials of single-agent chemotherapy for relapsed SCLC.

Authors [year]	Regimen	Number of patients	RR (%)	MST (months)
Evans <i>et al.</i> [1984]	Etoposide	14	7	2.0
	Etoposide + cisplatin	15	44	4.0
Wolff <i>et al.</i> [1986]	Etoposide*	77	6	4.4
Pallis <i>et al.</i> [2009]	Irinotecan	31	0	4.6
	Irinotecan + gemcitabine	38	24	6.8
*Etoposide was administered at 300, 600 and 900 mg/m ² . MST, median survival time; RR, response rate; SCLC, small cell lung cancer.				

relapsed at least 60 days after completion of first-line chemotherapy. The RR, median time to progression (TTP) and MST were 24.3%, 13.3 weeks and 25.0 weeks in the topotecan arm and 18.3%, 12.3 weeks and 24.7 weeks in the CAV arm respectively. The proportion of patients who experienced symptom improvement was greater in the topotecan arm than in the CAV arm for four of eight symptoms evaluated, including dyspnea, anorexia, hoarseness and fatigue, as well as interference with daily activity. This study showed similar efficacy of topotecan monotherapy compared with the combination with chemotherapy, with an improved rate of symptom control in favor of topotecan [von Pawel *et al.* 1999]. O'Brien and colleagues conducted a phase III study comparing best supportive care (BSC) alone with BSC with an oral topotecan in patients with recurrent SCLC who were unsuitable for intravenous chemotherapy. In the study, BSC with an oral topotecan group showed 7% of RR and 51% of disease control rate (DCR), and MST in the topotecan group was doubled compared with the one in the BSC alone group [O'Brien *et al.* 2006]. Von Pawel and colleagues and Eckardt and colleagues previously reported that the oral formulation of topotecan is similar in efficacy and tolerability to intravenous topotecan, and more convenient than intravenous topotecan by randomized trials [von Pawel *et al.* 2001; Eckardt *et al.* 2007].

A variety of drugs including etoposide (VP-16) [Evans *et al.* 1984; Wolff *et al.* 1986], irinotecan (CPT-11) [Masuda *et al.* 1992; Pallis *et al.* 2009], gemcitabine [Hoang *et al.* 2003], pemetrexed [Jalal *et al.* 2009; Grønberg *et al.* 2009], paclitaxel [Smit *et al.* 1998], picoplatin [Eckardt *et al.* 2009] and bendamustine [Schmitt *et al.* 2007] have been studied as single-agent chemotherapy in the treatment of recurrent SCLC in the

second-line setting. The results of the main trials are shown in Tables 2 and 3. RRs and MSTs were 0–29% and 3.3–7.0 months respectively. Although many drugs have been developed, unfortunately no drugs performed better than topotecan for patients with SCLC as second-line chemotherapy.

Irinotecan is a hemisynthetic product of camptothecin and shows a strong antitumor activity by inhibiting DNA topoisomerase I. In the second-line setting, Pallis and colleagues performed a randomized phase II study comparing irinotecan alone with the combination of irinotecan and gemcitabine [Pallis *et al.* 2009]. The result showed no complete or partial response (PR) was observed in the irinotecan alone group. Its efficacy in the treatment of relapsed SCLC as second-line chemotherapy has not been confirmed yet [Masuda *et al.* 1992].

Pemetrexed, an analogue of folic acid, shows antitumor activity by inhibiting multiple enzymes involved in the metabolic pathway of folic acid as follows: thymidylate synthase (TS), dihydrofolate reductase and glyciamide ribonucleotide formyl transferase [Shih *et al.* 1997]. It has been approved for NSCLC and malignant mesothelioma worldwide [Hanna *et al.* 2004; Jassem *et al.* 2008]. Based on an *in vitro* study which showed growth inhibition of the SCLC cell line, Jalal and colleagues conducted a phase II study of pemetrexed for patients with recurrent SCLC as second-line treatment [Jalal *et al.* 2009]. Pemetrexed was administered at 500 mg/m² intravenously every 3 weeks for up to six cycles. Twenty patients with sensitive relapsed disease and 23 with refractory relapsed disease were enrolled in the study. Finally, one patient achieved PR and three patients had stable disease (SD) in each group. The RR and DCR in the refractory group were

Table 3. Non-comparative trials of single-agent chemotherapy for relapsed SCLC.

Authors [year]	Regimen	Number of patients	RR (%)	MST (months)
Masuda <i>et al.</i> [1992]	Irinotecan	15	47	6.2
Smit <i>et al.</i> [1998]	Paclitaxel	24	29	3.3
Ardizzoni <i>et al.</i> [2000]	Ambamustine	17	0	3.9
Samantas <i>et al.</i> [2000]	Caelyx	14	0	NA
Hoang <i>et al.</i> [2003]	Gemcitabine	27	0	6.4
Schmitt <i>et al.</i> [2007]	Bendamustine	21	29	7.0
Jalal <i>et al.</i> [2009]	Pemetrexed	43	5	3.5
Grønberg <i>et al.</i> [2009]	Pemetrexed	34	3	4.1
Eisen <i>et al.</i> [2009]	Plitidepsin	20	0	4.8
Eckardt <i>et al.</i> [2009]	Picoplatin	77	4	5.2

MST, median survival time; RR, response rate; SCLC, small cell lung cancer.

4.3% and 17.4% respectively. Grønberg and colleagues set a high-dose of pemetrexed (900 mg/m²) with supplementation of vitamin B12 and folic acid [Grønberg *et al.* 2009]. A total of 36 patients were enrolled in the study and 34 received study treatment. The median cycle was 2.5 times. One patient (3%) had a PR, 3 patients (9%) had SD and 29 patients (85%) showed progressive disease. One patient (3%) was not evaluable for response. Median TTP ($n = 33$) was 7.7 weeks (sensitive: 8.4 weeks; refractory: 5.1 weeks). Median overall survival (OS) ($n = 34$) was 17.6 weeks (sensitive: 22.6 weeks; refractory: 15.3 weeks). As for grade 3–4 hematological toxicity, anemia was observed in two (6%) patients, leukopenia in six (18%), granulocytopenia in nine (27%) and thrombocytopenia in three (9%). Febrile neutropenia occurred in six (18%) patients. There were no treatment-related deaths. The authors concluded that a high-dose pemetrexed monotherapy for patients with recurrent SCLC yielded moderate toxicity, however with limited treatment efficacy.

Tanaka and colleagues documented that TS gene expression in primary lung cancer was significantly different according to histologic cell type [Tanaka *et al.* 2011]. Difference in antitumor activity of pemetrexed according to histologic cell

type may be partly explained by very high TS expression in SCLC and high TS expression in squamous cell carcinoma. While pemetrexed inhibits TS activity, it appears small cell or squamous cell lung cancers have too much TS activity for pemetrexed to exert a sufficient tumor suppressive effect. Thus, it is reasonable that pemetrexed showed a minimal antitumor activity for SCLC as well as for squamous cell carcinoma.

Gemcitabine, a novel nucleoside analog similar in structure to cytosine arabinoside, is a pyrimidine antimetabolite and its mechanism of action has well been characterized. In the phase II study conducted by Hoang and colleagues, 27 patients with pretreated SCLC (15 sensitive relapsed and 12 refractory relapsed) received gemcitabine 1250 mg/m² intravenously on days 1 and 8 every 3 weeks. None showed a PR and three patients had SD. RR and DCR for refractory relapsed SCLC were 0% and 8.3% respectively. Median TTP and MST for refractory relapsed SCLC were 5.6 weeks (range 3–24.5 weeks) and 4.2 months (range 1.5–13.0 months) respectively. Although the authors concluded that the efficacy of gemcitabine alone should be limited to recurrent SCLC as second-line chemotherapy [Hoang *et al.* 2003], the data were not sufficient to support this conclusion.

Table 4. Phase II trials of single-agent amrubicin for relapsed SCLC.

Authors [year]	Dose (mg/m ²)	Number of patients	G3/4 neutropenia (%)	G3/4 thrombocytopenia (%)	RR (%)	MST (months)
Kato <i>et al.</i> [2006]	45	34	97	38	53	8.8
		S24			50.0	10.4
		R10			60.0	6.8
Onoda <i>et al.</i> [2006]	40	60	50	12	50.0	10.3
		S44			52.0	11.6
		R16			50.0	10.3
Kaira <i>et al.</i> [2010]	35	29	41	3.4	44.8	12.0
		S10			60.0	12.0
		R19			36.8	11.0
Ettinger <i>et al.</i> [2010]	40	75	67	41	21.0	6.0
		S0				
		R75				

G, grade; MST, median survival time; RR, response rate; SCLC, small cell lung cancer.

Amrubicin is a fully synthetic 9 aminoanthracene, converted in the body to amrubicinol by reduction of the 13-position ketone, possessing higher antitumor activity than the parent molecule. Although classified as anthracycline agents, amrubicin and amrubicinol exert cytotoxic effects as DNA topoisomerase inhibitors, not mainly as DNA intercalators [Onoda *et al.* 2006; Ohe *et al.* 1989; Hanada *et al.* 1998; Noda *et al.* 1998; Noguchi *et al.* 1998a, 1998b; Yana *et al.* 2007; Kato *et al.* 2006]. Amrubicin showed more potent antitumor activity than doxorubicin in several human tumor xenografts implanted in nude mice. While acute toxicity of amrubicin is qualitatively similar to that of doxorubicin, amrubicin shows almost no delayed cardiotoxicity [Noda *et al.* 1998a, 1998b; Kaira *et al.* 2010]. Yana and colleagues performed a phase II study in Japan for patients with previously untreated ED-SCLC. Amrubicin was administered at a dose of 45 mg/m² for 3 consecutive days intravenously every 3 weeks. The RR and MST were 75.8% and 11.7 months, and 1-year and 2-year survival rates were 48.5% and 20.2%, respectively. Grade 3–4 neutropenia, thrombopenia and anemia were seen in 84.8%, 39.4% and 78.8% respectively [Yana *et al.* 2007]. While the antitumor activity of amrubicin was confirmed, more severe and frequent hematologic toxicities concerned clinicians compared with topotecan or irinotecan [Ettinger *et al.* 2010]. Then, a variety of phase II trials have been conducted at different doses of amrubicin for relapsed SCLC as shown in Table 4. In the first trial conducted by Kato and colleagues, 45 mg/m² of amrubicin was administered on days 1–3 every 3 weeks. The

RRs and MSTs in sensitive and refractory cases were 50% and 10.4 months, and 60% and 6.8 months respectively [Kato *et al.* 2006]. In the second study conducted by Onoda and colleagues, 40 mg/m² of amrubicin was administered on the same schedule and 60 patients were enrolled. The RRs and MSTs in sensitive and refractory cases were 52% and 11.6 months, and 50% and 10.3 months respectively [Onoda *et al.* 2006]. In the third study conducted by Kaira and colleagues, 35 mg/m² of amrubicin was administered to both patients with SCLC and NSCLC on the same schedule. The RRs and MSTs in sensitive and refractory cases were 60% and 12.0 months, and 37% and 11.0 months respectively. Grade 4 neutropenia was noted in 71%, 55% and 10% in the first, second and third study respectively [Kaira *et al.* 2010]. While RRs and MSTs were similar among the studies, fewer doses seem to be preferable for patients with relapsed disease, as indicated in previous phase I studies.

Randomized trial of topotecan versus amrubicin for relapsed SCLC as second-line chemotherapy. Table 5 shows previous phase II–III trials conducted comparing topotecan with amrubicin for relapsed SCLC. A first randomized trial of amrubicin *versus* topotecan was performed in Japan. Sixty patients were assigned either to amrubicin (40 mg/m² on days 1–3, every 3 weeks) or to topotecan (1.5 mg/m² on days 1–5, every 3 weeks), and 59 cases (23 refractory and 36 sensitive relapse) were evaluable. The RRs and DCRs were significantly higher in the amrubicin group compared with the topotecan group

Table 5. Randomized phase II–III trials of topotecan *versus* amrubicin for relapsed SCLC as second-line chemotherapy.

Authors [year]	Phase	Regimen	Number of patients	RR (%)	MST (months)
Inoue <i>et al.</i> [2008]	II	Intravenous	30	13	8.4
		Top AMR	29	38	8.1
Jotte <i>et al.</i> [2011a]	II	Intravenous	26	15	7.6
		Top AMR	50	44	9.2
Jotte <i>et al.</i> [2011b]	III	Intravenous	213	16.9	7.8
		Top	S117		9.9
			R96		5.7
		AMR	424	31.1	7.5
			S225		9.2
			R199		6.2

AMR, amrubicin; MST, median survival time; ; R, refractory relapse; RR, response rate; S, sensitive relapse; SCLC, small cell lung cancer; Top, topotecan.

(38% and 79% *versus* 13% and 47%). Median progression-free survival (PFS) rates were 3.5 and 2.2 months, and median OS rates were 8.1 and 8.4 months in the amrubicin and topotecan groups respectively. However, many patients in the topotecan group subsequently received amrubicin and multivariate analysis revealed that amrubicin had more impact on OS than topotecan [Inoue *et al.* 2008].

Subgroup analysis revealed a significantly higher DCR in favor of amrubicin in patients with refractory relapse with performance status 0–1 (Eastern Cooperative Oncology Group). The RR and DCR in all subgroups showed a trend favoring amrubicin. The RR in the amrubicin group which was previously treated with the topoisomerase II inhibitor etoposide was high enough to be comparable to topotecan. Thus, no cross tolerance appears to exist between amrubicin and etoposide. In contrast, no response to topotecan was observed in patients who were previously treated with the topoisomerase I inhibitor irinotecan. A total of 59% of patients received subsequent chemotherapy after the study. Five patients in the amrubicin group received subsequent topotecan and 19 in the topotecan group received amrubicin. Four of the 19 patients (21%) achieved a PR by subsequent amrubicin, whereas no response to topotecan was confirmed after amrubicin. As for adverse events, grade 4 neutropenia (79% *versus* 43%) and febrile neutropenia (14% *versus* 3%) were observed more frequently in the amrubicin group than in the topotecan group [Inoue *et al.* 2008].

A second randomized phase II trial comparing the two drugs also showed a significantly higher RR in the amrubicin arm than in the topotecan arm (44% *versus* 15%). Median PFS and OS also favored the amrubicin arm. Tolerability was similar in both arms. Hematologic toxicity was lower in the amrubicin arm than in the topotecan arm. Grade 3 and 4 neutropenia and thrombocytopenia in the amrubicin arm occurred in 61% and 39% respectively. Grade 3 and 4 neutropenia and thrombocytopenia in the topotecan arm occurred in 78% and 61% respectively [Jotte *et al.* 2011a]. Jotte and colleagues conducted a phase III trial of amrubicin *versus* topotecan as second-line treatment for relapsed SCLC (ACT-1). Six-hundred and thirty seven patients were randomized either to amrubicin 40 mg/m² for 3 consecutive days every 3 weeks or to intravenous topotecan 1.5 mg/m² for 5 days every 3 weeks in the ratio of 2:1. The RRs, DCRs, median PFSs and median OSs were 31.1% *versus* 16.9% (odds ratio 2.223, $p < 0.0001$), 70.0% *versus* 61.5%, 4.1 *versus* 3.5 months ($p = 0.0182$) and 7.5 *versus* 7.8 months ($p = 0.1701$) in the amrubicin arm and the topotecan arm respectively. In terms of grade 3–4 adverse events, neutropenia (41.2% *versus* 51.3%), thrombocytopenia (21% *versus* 54%), anemia (16% *versus* 30%), infections (16% *versus* 10%), febrile neutropenia (10% *versus* 4%), all $p < 0.05$, and cardiac disorders (5% *versus* 5%, $p = 0.84$) were observed in the amrubicin and the topotecan groups respectively. Transfusion rates were 32% and 53% ($p < 0.01$) in the amrubicin and topotecan groups respectively. Amrubicin showed a higher RR and less frequent grade 3–4 hematologic toxicities compared with topotecan.

However, the primary endpoint of OS was not significantly different. An improvement in OS in patients with refractory relapsed disease was confirmed (6.2 months in the amrubicin group *versus* 5.7 months in the topotecan group; hazard ratio 0.766, $p = 0.0469$). In this study, the result concluded that amrubicin is effective in the second-line treatment of relapsed SCLC [Jotte *et al.* 2011b]. A randomized phase II trial of amrubicin *versus* platinum rechallenge as second-line treatment of sensitive relapsed SCLC in Japan (NJLCG0702) and a phase III trial of etoposide and cisplatin *versus* amrubicin and cisplatin as first-line treatment of untreated SCLC in China (China study) are ongoing.

Combination chemotherapy

Several combination therapies have been investigated for relapsed SCLC. The results of the main trials are shown in Table 6 [Figoli *et al.* 1988; Ando *et al.* 2004; Hirose *et al.* 2003; Masuda *et al.* 1998; Ichiki *et al.* 2002; Schuette *et al.* 2005; Groen *et al.* 1999; Kakolyris *et al.* 2001; Goto *et al.* 2004; Kim *et al.* 2006; Faylona *et al.* 1995; Postmus *et al.* 1993; Kosmas *et al.* 2001; Postmus *et al.* 1992; Kubota *et al.* 1997]. The RRs and MSTs were 10–88% and 3.0–11.8 months respectively. While combination therapy of platinum and etoposide, vincristine, paclitaxel or irinotecan seemed to be effective, its efficacy was not high enough to replace the standard single topotecan therapy for relapsed SCLC. Likewise, a variety of phase II trials have investigated irinotecan-based combination therapy in the second-line setting. The results were not promising and no regimens showed a better antitumor effect than topotecan alone as second-line chemotherapy [Ando *et al.* 2004; Hirose *et al.* 2003; Masuda *et al.* 1998; Ichiki *et al.* 2002; Schuette *et al.* 2005; Kim *et al.* 2006; Faylona *et al.* 1995].

Three-drug combination chemotherapies of irinotecan and cisplatin plus etoposide or ifosfamide were studied in phase II trials. Goto and colleagues conducted a phase II trial of cisplatin, etoposide and irinotecan (PEI) for relapsed SCLC in the second-line setting [Goto *et al.* 2004]. Forty patients with sensitive relapsed SCLC received the PEI regimen, which consisted of 25 mg/m² of cisplatin weekly for 9 weeks, 25 mg/m² of etoposide for 3 days in weeks 1, 3, 5, 7 and 9 and 90 mg/m² of irinotecan in weeks 2, 4, 6 and 8 with granulocyte colony-stimulating factor support. Five complete remission and 26 PRs

were observed, and the overall RR was 78%. The MST and 1-year survival rate were 11.8 months and 49% respectively. A phase III trial comparing PEI with nogitecan is currently underway (JCOG0605). In a phase II trial conducted by Kim and colleagues, combination therapy of PEI was administered for patients with refractory relapsed SCLC [Kim *et al.* 2006]. RRs and MSTs were 70% and 7.3 months respectively. While promising RRs were reported in patients with relapsed SCLC, significant toxicity was also observed. These excellent RRs did not seem to reflect longer MSTs. It is important to note that these results cannot be compared directly because they are not randomized clinical trials but non-comparative trials. The results are awaited.

Since both amrubicin and irinotecan were developed in Japan, trials including these two drugs have been conducted mainly in Japan. The results showed that amrubicin had a better antitumor activity than topotecan. After 2006, several studies on amrubicin were conducted outside Japan. As a result, amrubicin failed to replace topotecan as we mentioned above. In contrast, several studies on a variety of drugs including irinotecan have been carried out mainly in western countries. The results showed that none of these drugs replaced topotecan as second-line treatment.

Molecular targeting agents

Angiogenesis is considered one of the major components of tumor progression and metastasis. Vascular endothelial growth factor (VEGF) is a key driver of angiogenesis. SCLC is more vascular than NSCLC, as evidenced by higher microvessel density in tumor tissues [Lucchi *et al.* 2002]. Human SCLC cells express functional VEGF receptor (VEGFR)-2, VEGFR-3 and platelet-derived growth factor receptor (PDGFR)- β [Tanno *et al.* 2004; Ioannou *et al.* 2009]. Patients with SCLC express increased levels of serum VEGF and high pretreatment levels of VEGF are associated with poor response to chemotherapy and reduced survival [Ustuner *et al.* 2008; Tas *et al.* 2006; Salven *et al.* 1998; Zhan *et al.* 2009]. In addition, stem cell factor and its receptor, KIT, are coexpressed in up to 70% of SCLC cell lines and clinical SCLC samples. KIT activation has also been shown to stimulate proliferation of SCLC *in vitro* [Krystal *et al.* 1996]. Thus, inhibition of these kinases represents a rational therapeutic strategy for the treatment of SCLC.

Table 6. Prospective studies of combination chemotherapy for relapsed SCLC.

Authors [year]	Regimen	Number of patients	RR (%)	MST (months)
Figoli <i>et al.</i> [1988]	CDDP + ETP	27	41	6.5
Ando <i>et al.</i> [2004]	CDDP + CPT-11	25	80	7.9
Hirose <i>et al.</i> [2003]	CBDCA + CPT-11	22	68	6.5
Masuda <i>et al.</i> [1998]	ETP + CPT-11	25	71	9.0
Ichiki <i>et al.</i> [2002]	IFM + CPT-11	34	53	7.2
Schuetz <i>et al.</i> [2005]	GEM + CPT-11	35	17	5.8
Groen <i>et al.</i> [1999]	CBDCA + PTX	34	74	7.2
Kakolyris <i>et al.</i> [2001]	CBDCA + PTX	32	25	7.0
Goto <i>et al.</i> [2004]	CDDP + ETP + CPT-11	40	78	11.8
Kim <i>et al.</i> [2006]	CDDP + ETP + CPT-11	30	70	7.3
Faylona <i>et al.</i> [1995]	CDDP + ETP + IFM	42	55	6.8
Postmus <i>et al.</i> [1993]	CPA + DXR + ETP	43	51	5.1
Kosmas <i>et al.</i> [2001]	CDDP + PTX + IFM	33	73	6.5
Postmus <i>et al.</i> [1992]	Caelyx + CPA + VCR	31	10	6.5
Postmus <i>et al.</i> [1993]*	VIMP	25	60	4.4
Kubota <i>et al.</i> [1997]	CODE	17	88	8.2

*Only this is a randomized clinical trial. Other results are noncomparative trials.
 CBDCA, carboplatin; CDDP, cisplatin; CPA, cyclophosphamide; CODE, cisplatin + vincristine + doxorubicin + etoposide;
 CPT-11, irinotecan; DXR, doxorubicin; ETP, etoposide; GEM, gemcitabine; IFM, ifosfamide; MST, median survival time;
 PTX, paclitaxel; RR, response rate; SCLC, small cell lung cancer; VCR, vincristine; VIMP, vincristine + ifosfamide + mesna
 + carboplatin.

Several molecular targeting agents have been investigated for relapsed SCLC. The results of these trials are shown in Table 7 [Han *et al.* 2013; Gandhi *et al.* 2012; Lee *et al.* 2012; Allen *et al.* 2012]. Sunitinib malate is an orally bioavailable, multitargeted, small molecular inhibitor of several receptor tyrosine kinases involved in tumor proliferation and angiogenesis, including VEGFR-1, VEGFR-2, VEGFR-3, PDGFR and KIT. In preclinical models of human SCLC, sunitinib inhibits KIT and PDGFR- β , resulting in significant inhibition of tumor growth [Abrams *et al.* 2003]. However, sunitinib failed to show a significant clinical activity to replace topotecan as second-line

chemotherapy. Han and colleagues conducted a phase II study of sunitinib for relapsed SCLC [Han *et al.* 2013]. The result was that median PFS and median OS were 1.4 months [95% confidence interval (CI) 1.1–1.7] and 5.6 months (95% CI 3.5–7.7) respectively.

Epidermal growth factor receptor tyrosine kinase inhibitor

The vast majority of epidermal growth factor receptor (EGFR) mutations occur in lung cancer, and in particular, adenocarcinoma of the lung [Maemondo *et al.* 2010]. These days, SCLC cases

Table 7. Prospective studies of molecular targeting agents for relapsed SCLC.

Authors [year]	Regimen	Number of patients	RR (%)	MST (months)
Han <i>et al.</i> [2013]	Sunitinib	23	8.7	5.6
Gandhi <i>et al.</i> [2012]	Pazopanib	27	0	ND
Lee <i>et al.</i> [2012]	Alisertib	20	15	ND
Allen <i>et al.</i> [2012]	Top + aflibercept	50	ND	4.6
	Top	46	ND	3.6

MST, median survival time; ND, not described; RR, response rate; SCLC, small cell lung cancer; Top, topotecan.

Table 8. Characteristics of patients with EGFR mutated SCLC and the outcomes.

Case	Age	Sex	Smoking history	Histology	EGFR mutations	EGFR-TKI administered	Outcomes
1	72	Woman	Never	SCLC	Exon19	Gefitinib	PR
2	45	Woman	Never	SCLC	Exon19	Erlotinib	PR
3	81	Man	Ex-smoker	SCLC	Exon18	Gefitinib	PR
4	54	Woman	Never	SCLC	Exon19	Gefitinib	PD
5	73	Woman	Never	SCLC/ Adeno	Exon18	Gefitinib	PR
6	74	Woman	Never	SCLC	Exon18	Gefitinib	PD
Ours	69	Woman	Never	SCLC	Exon19	Gefitinib	PD

Adeno, adenocarcinoma; EGFR-TKI, epidermal growth factor receptor tyrosine kinase inhibitor; Never, never smoker; PD, progressive disease; PR, partial response; SCLC, small cell lung cancer.

with EGFR mutation have sporadically been reported [Shigematsu and Gazdar, 2006]. The epidemiology and standard treatment of SCLC with EGFR mutation are still unknown. We reported an EGFR-mutated SCLC case with a review of the literature, as shown in Table 8 [Asai *et al.* 2013]. Mean RR was 57.1% and there was no SD. In terms of the EGFR mutation type, both exon 19 and 21 are thought to be very sensitive to EGFR tyrosine kinase inhibitor (TKI) [Asai *et al.* 2013]. Two of the four patients (50%) with exon 19 had PR and two of the four patients (50%) showed PD. No severe treatment-related complications were reported in the review. EGFR-TKI might be as effective for patients with EGFR-mutated SCLC as for patients with adenocarcinoma with EGFR mutations.

Tatematsu and colleagues reported that 5 of the 122 patients with SCLC during 7 years were confirmed with EGFR mutations [Tatematsu *et al.* 2008]. A combined type of SCLC and adenocarcinoma were found in three of the five patients. Two of the three were found in resected tumors

and the remaining one was confirmed by trans-bronchial lung biopsy [Asai *et al.* 2013]. Even though a low possibility, EGFR mutations should be examined in women who have never smoked and who are showing a high Carcinoembryonic antigen (CEA) [Shigematsu and Gazdar, 2006]. Note that EGFR-TKI could be optional if EGFR mutation is detected. There is no evidence that EGFR-TKI is effective for relapsed SCLC.

Third-line chemotherapy

Chemotherapy after failing second-line treatment for SCLC is still controversial. While some argued in favor of the efficacy of third-line chemotherapy for SCLC [Park *et al.* 2007; Igawa *et al.* 2007; Asai *et al.* 2012], there is a lack of data showing its efficacy. More studies should be conducted to establish the third-line treatment of relapsed SCLC.

Immunotherapy

Cancer immunotherapy attempts to stimulate the immune system to reject and destroy tumors. The

concept of this treatment started in the USA in the 1980s in randomized controlled studies for various cancers, resulting in reported significant increases in survival and disease-free periods [Kimura and Yamaguchi, 1997; Takayama *et al.* 2000; Kono *et al.* 2002]. Efficacy is enhanced by 20–30% when cell-based immunotherapy is combined with other conventional treatments. In terms of SCLC, although a variety of targeted therapies such as angiogenesis inhibitors, growth factor receptor inhibitors, apoptosis promoters and P53 cancer vaccine have been previously examined for SCLC as first-line treatment, most of the trials failed to show improved PFS and OS [Blackhall and Shepherd, 2007]. To date, no clinical trials have shown any efficacy for relapsed SCLC.

Conclusion

Although a large number of clinical trials of relapsed SCLC have previously been performed, most of the results are disappointing. As a result, topotecan was the only drug approved by the FDA as second-line treatment for relapsed SCLC in 2012. Amrubicin and small molecular targeted drugs are promising and are expected to be evaluated further. Also, third-line treatment could be considered as long as the patient's overall condition is good.

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