Second-line Chemotherapy for Small-Cell Lung Cancer (SCLC)

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Abstract

Although small-cell lung cancer (SCLC) generally shows an excellent response to initial chemotherapy, most patients finally relapse and salvage chemotherapy is considered. Usually, the response to salvage chemotherapy significantly differs between sensitive and refractory relapse. Sensitive relapse is relatively chemosensitive and re-challenge with the same drugs as used in the initial chemotherapy has been used historically, while refractory relapse is extremely chemoresistant and its prognosis has been abysmal. To date, a number of clinical trials have been carried out for relapsed SCLC; however, the number of randomized trials is quite limited. At present, topotecan is the only drug approved by the US Food and Drug Administration for relapsed SCLC, and is considered the standard second-line chemotherapy in many countries. More recently, amrubicin has also shown more favorable antitumor activity, and is the most promising at present. Unfortunately, targeted agents have failed to demonstrate effectiveness for SCLC. Better understanding of the molecular mechanisms is clearly needed.

Introduction

Small-cell lung cancer (SCLC) is strongly associated with tobacco smoking. In recent years, the incidence of SCLC has been gradually decreasing according to the decrease of the smoking population, and it accounts for approximately 13% of all lung cancer cases.[1]

Good sensitivity to chemotherapy and radiotherapy is a feature of SCLC and most patients respond to initial chemotherapy or chemoradiotherapy; however, the majority of patients develop recurrence and the prognosis of such patients is reportedly 2–4 months.[2]

In predicting the efficacy of salvage chemotherapy, both the response and the duration of the response to initial chemotherapy are important.[3,4] Based on these factors, relapsed or refractory SCLC has been classified into 2 groups: patients who respond to the initial chemotherapy and relapse more than 2 or 3 months after the completion of chemotherapy are considered to be 'sensitive relapse' patients, while patients whose tumor is stable or progresses during the initial chemotherapy or who have a recurrence within 2 or 3 months after the completion of chemotherapy are considered to be 'refractory relapse' patients.[5]

Previous studies have reported the effectiveness of re-challenge with the same drugs used in the initial chemotherapy and it has been justified for sensitive relapse[5-7]; however, refractory relapse is exceedingly chemo-resistant, and response rates of less than 10% are usually attained with single-agent chemotherapy in those patients.[8] Consequently, although a number of chemotherapy regimens have been evaluated in

clinical trials and some have shown promising antitumor activity, no standard chemotherapy had been established for relapsed SCLC until recently. Currently, topotecan is the only drug approved by the US Food and Drug Administration for relapsed SCLC, and is considered the standard second-line chemotherapy in many countries.[9] More recently, amrubicin has also shown promising antitumor activity in this setting[10,11]; however, to date it is not approved outside Japan.

Cytotoxic agents

Single-agent chemotherapy (except for topotecan and amrubicin)

Etoposide was composed in 1966 and has been used for the treatment of SCLC. It was initially evaluated in the second-line setting because the combination of cyclophosphamide, doxorubicin, and vincristine (CAV) was the standard first-line regimen for SCLC at the time. In the study conducted by Evans et al., 18 refractory relapse patients were treated with etoposide. Fourteen patients were evaluable for response, and only 1 partial response (PR) was observed.[12] Wolff et al. evaluated the efficacy of etoposide at three different doses in relapsed SCLC: 300, 600, and 900 mg/m^2. Twenty-six, 27, and 26 patients were treated at each dose level; however, only 4 patients achieved PR and the response rate was 6%.[13] These results suggest that single-agent etoposide has only limited activity in the second-line setting.

Irinotecan is a hemisynthetic product of camptothecin and shows strong antitumor activity by inhibiting DNA topoisomerase I. In the first-line setting, the Japan Clinical Oncology Group (JCOG) conducted a randomized phase III study comparing cisplatin-etoposide (PE) with cisplatin-irinotecan (PI) in patients with extensive disease (ED)-SCLC and showed that PI was significantly superior to PE with regard to both

response and survival.[14] Although subsequent studies conducted in the US failed to reproduce the results of the JCOG study, the efficacy of PE and PI was almost identical and both are thought to be standard first-line regimens for ED-SCLC.[15,16] In the second-line setting, Masuda et al. conducted a phase II study of irinotecan. Fifteen patients were given 100 mg/m^2 of irinotecan every week and a response rate of 47% was observed.[17] In the randomized phase II study comparing irinotecan alone with the combination of irinotecan and gemcitabine, however, no partial or complete response was observed (n=31).[18] In the study, 64% of patients had a refractory relapse. Although single-agent of irinotecan is promising in the second-line setting, its efficacy is limited for refractory relapse.

Paclitaxel promotes the assembly of tubulin into microtubules and renders the microtubule resistant to depolymerization, interfering with mitosis, and has demonstrated an antitumor effect against SCLC in both preclinical and clinical studies.[19,20] In the phase II study conducted by Smit et al., 24 heavily pretreated SCLC patients were treated with paclitaxel, 175 mg/m^2 intravenously every 3 weeks. Of 24 patients, 15 had previously received more than 2 regimens, and a 29% response rate was achieved.[21] Although it may be active against drug-resistant SCLC, there is insufficient clinical evidence to use paclitaxel routinely in the clinical setting.

Gemcitabine, a novel nucleoside analogue similar in structure to cytosine arabinoside (ara-C), is a pyrimidine antimetabolite, and its mechanism of action has been well characterized. In the phase II study conducted by Hoang et al., 27 pretreated SCLC patients were treated with 1250 mg/m^2 of gemcitabine intravenously on days 1 and 8, every 3 weeks. Of 27 patients, 15 were sensitive and 12 had a refractory relapse. There were no PR and only 3 patients achieved stable disease (SD). The authors

concluded that single-agent of gemcitabine had only limited activity against previously treated SCLC.[22]

Pemetrexed, a multitargeted antifolate agent, has been approved for non-small-cell lung cancer (NSCLC) and malignant mesothelioma worldwide. Based on an *in vitro* study which showed growth inhibition of the SCLC cell line[23], Jalal et al. carried out a phase II study of pemetrexed in SCLC patients. Pemetrexed was administered at 500 mg/m^2 intravenously every 3 weeks for up to 6 cycles. Twenty sensitive relapse and 23 refractory relapse patients were enrolled; however, only 1 patient had PR and 3 had SD in each group.[24] In the study conducted by Gronberg et al., high-dose pemetrexed (900 mg/m^2) was given with the supplementation of vitamin B12 and folic acid. Among 34 patients who received the study treatment, only 1 patient (3%) achieved PR and 29 (85%) had progressive disease (PD).[25] Pemetrexed was also investigated in the first-line setting. In the study, chemotherapy-naïve patients with ED-SCLC were randomized to receive either carboplatin-pemetrexed or carboplatin-etoposide. The response and survival of carboplatin-pemetrexed was significantly inferior to those of carboplatin-etoposide.[26] Thus, further exploration of pemetrexed is not warranted in SCLC.

Picoplatin is a cisplatin analog designed to avoid the development of platinum resistance, and preclinical data demonstrated that picoplatin overcomes platinum resistance in lung cancer. Eckardt et al. conducted a phase II study of picoplatin in patients with platinum-refractory or –resistant, relapsed SCLC. Seventy-seven patients were treated with picoplatin and 72 were assessable for response. There were 3 PRs (4%), 33 SDs (43%), and 36 PDs (47%).[27] A phase III study comparing picoplatin with best supportive care (BSC) is ongoing.

The efficacy data of single-agent chemotherapy except for topotecan and amrubicin are summarized in Table 1[3,12,13,17,18,21,22,24,25,27-33]

Combination chemotherapy

In the era of CAV, the most intensively investigated second-line regimen was PE. In the study conducted by Evans et al., 15 of 34 evaluable patients had PR (response rate: 44%).[12] In their subsequent study, 78 patients were treated with PE and 43 achieved a marked response (response rate: 55%), including 6 complete responses (CR).[34] In other studies, 40%[35] and 50%[36] response rates were observed for PE; however, there is an issue that the percentages of sensitive and refractory relapse were not presented in those studies. In fact, only a 12% response rate was observed in the study conducted by Batist et al.[37] In the study, the median time since the last chemotherapy was 3 weeks (range, 1–24), suggesting that the majority of patients had refractory relapse. Porter et al. reported a 52% response rate for 29 refractory relapse; however, the definition of 'refractory' in the study was not clear.[38] Recently, in a randomized phase II study comparing PE with the combination of cisplatin, etoposide, and carboplatin, a 19% response rate was noted for refractory relapse in the PE arm.[39] The platin-etoposide combination seems active in sensitive relapse; however, its efficacy is not evident in refractory relapse.

Irinotecan has been extensively investigated in combination with both cisplatin (PI) and carboplatin (CI). Ando et al. examined weekly PI. Twenty-five patients who had previously been treated with etoposide and a platinum-containing regimen were enrolled, and 20 patients achieved PR (response rate: 80%).[40] In this study, even among 16 refractory relapse patients, 13 PR (81%) were observed. Naka et al. conducted a

phase II study of weekly CI, which consisted of an area under the curve (AUC) = 2 of carboplatin and 50 mg/m^2 of irinotecan on days 1, 8, and 15 every 4 weeks. In refractory relapse, 3 of 13 patients had a PR (23.1%), and in sensitive relapse, 6 of 16 had a PR (37.5%), and there was no statistical significance in the response rate between the two.[41] In the study conducted by Hirose et al., patients were treated with CI, AUC = 5 of carboplatin on day 1 and 50 mg/m^2 of irinotecan on days 1 and 8 every 3 weeks. Of 22 evaluable patients, 15 achieved PR, with an overall response rate of 68%. Response rates in sensitive and refractory relapse were 92% and 33%, respectively.[42] Masuda et al. evaluated the effectiveness of combination chemotherapy of etoposide-irinotecan. In their study, 25 patients were treated with 80 mg/m^2 of etoposide on days 1 to 3 and 70 mg/m^2 of irinotecan on days 1, 8, and 15 every 4 weeks, and the response rates were 75% for refractory relapse and 70% for sensitive relapse, respectively.[43] The combination of irinotecan and gemcitabine was also investigated in several studies; however, the response rates for refractory relapse were not promising.[18,44,45]

Three-drug combination of cisplatin, etoposide, and irinotecan (PEI) was investigated separately for both sensitive and refractory relapse. Goto et al. treated 40 sensitive relapse patients with the PEI regimen, which consisted of 25 mg/m^2 of cisplatin weekly for 9 weeks, 25 mg/m^2 of etoposide for 3 days in weeks 1, 3, 5, 7, and 9, and 90 mg/m^2 of irinotecan in weeks 2, 4, 6, and 8 with granulocyte colony-stimulating factor support. Five CRs and 26 PRs were observed, and the overall response rate was 78%. The median survival time (MST) and 1-year survival rate were 11.8 months and 49%, respectively.[46] Grade 3/4 leucocytopenia, neutropenia, and thrombocytopenia were observed in 55, 73, and 33% of the patients, respectively. Non-hematologic toxicities were mild and transient in all patients. No treatment-related

deaths were observed. Considering that this regimen also achieved a 70% response rate in refractory relapse[47], PEI warrants further investigation in the second-line setting.

The combination of carboplatin and paclitaxel (CP) was evaluated for refractory relapse in 2 studies. In the study conducted by Groen et al., 35 refractory relapse patients who were resistant to cyclophosphamide, doxorubicin, and etoposide were treated with CP consisting of 175 mg/m^2 of paclitaxel on day 1 and AUC = 7 of carboplatin on day 1 every 3 weeks. There were 2 CRs and 23 PRs, and the overall response rate was 73%. MST and the 1-year survival rate was 31 weeks and 9%, respectively.[48] In the other study conducted by Kakolyris et al., 22 refractory relapse patients were treated with CP consisting of 200 mg/m^2 of paclitaxel on day 1 and AUC = 6 of carboplatin on day 1 every 3 weeks, with a 25% response rate.[49]

Table 2 shows the results of combination chemotherapy in relapsed SCLC.[12,18,34-61]

Topotecan and Amrubicin

Topotecan, a water-soluble, semisynthetic derivative of camptothecin, is a specific inhibitor of topoisomerase, and has been most intensively evaluated in recurrent SCLC. In the study conducted by Ardizzoni et al., 101 patients were enrolled, and 92 (45 sensitive and 47 refractory) were assessable for response. Among refractory relapse patients, there were 1 CR and 2 PRs, with an overall response rate of 6.4%, whereas in sensitive relapse, there were 6 CRs and 11 PRs, for an overall response rate of 37.8%. MST of sensitive and refractory relapse patients was 6.9 months and 4.7 months, respectively.[62] Combined with other studies, the overall response rate and MST of topotecan were 6.4% to 38% and 6.4 to 8.7 months in sensitive relapse, and 2.4% to

6.4% and 4.1 to 5.1 months in refractory relapse, respectively.[62-66] The results of phase II studies of topotecan are summarized in Table 3.[62-66]

Von Pawel et al. conducted the first phase III study in patients with recurrent SCLC, in which topotecan and CAV were compared. Patients received either topotecan (1.5 mg/m^2) as a 30-minute infusion daily for 5 days every 3 weeks or CAV (cyclophosphamide 1,000 mg/m^2, doxorubicin 45 mg/m^2, and vincristine 2 mg) infused on day 1 every 3 weeks. All patients had relapsed at least 60 days after completion of first-line chemotherapy. The response rate, 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 (p=0.285 for the response rate, p=0.552 for TTP, and p=0.795 for MST, respectively). The proportion of patients who experienced symptom improvement was greater in the topotecan arm than in the CAV arm for 4 of 8 symptoms evaluated, including dyspnea, anorexia, hoarseness, and fatigue, as well as interference with daily activity.[67] The oral formulation of topotecan is similar in efficacy and tolerability to IV topotecan, and more convenient than IV topotecan.[68,69] In the phase III study conducted by O'Brien et al., BSC alone and BSC+oral topotecan were compared in recurrent SCLC patients who were unsuitable for intravenous chemotherapy. In the study, 70 and 71 patients were assigned to BSC alone and topotecan group, respectively. There were 7% PR and 44% SD in the topotecan group, and MST almost doubled (13.9 weeks vs 25.9 weeks).[70] This is the only randomized study in second-line for relapsed SCLC comparing chemotherapy with BSC. Currently, topotecan is the only drug approved by the Food and Drug Administration (FDA) for recurrent SCLC. Randomized studies of topotecan are summarized in Table 4.[67-70]

Amrubicin is a totally synthetic 9-aminoanthracycline, (+)-(7S, 9S)-9-acetyl-9-amino-7-[(2-deoxy- β -D-erythro-pentopyranosyl)oxy]-7,8,9,10-tetrahydro-6,11-dihydroxy-5,12-naphthacenedione hydrochloride, with a chemical structure similar to that of doxorubicin. Amrubicin showed more potent antitumor activity than doxorubicin in several human tumor xenografts implanted in nude mice.[71] Acute toxicity of amrubicin is qualitatively similar to that of doxorubicin; however, amrubicin shows almost no delayed toxicity (e.g. cardiotoxicity).[72-74] Amrubicin is converted to an active metabolite, amrubicinol, by reduction of its C-13 ketone group to a hydroxyl group. *In vitro* cytotoxic activity of amrubicinol was almost equipotent to that of doxorubicin and is 20 to 220 times more potent than its parent compound, amrubicin.[75] Despite their similarity in chemical structure, amrubicin has a different mode of action to doxorubicin. Amrubicin and its active metabolite, amrubicinol, are inhibitors of DNA topoisomerase II. In a phase I–II study of patients with non-small cell lung cancer, amrubicin was administered as a 5-min intravenous infusion for 3 consecutive days. The maximum tolerated dose (MTD) was 50 mg/m^2/day and the dose-limiting toxicities were leukopenia, neutropenia, thrombocytopenia, and gastrointestinal complications. The recommended dose in the phase II study was 45 mg/m^2/day for 3 consecutive days every 3 weeks.[76]

As for SCLC, Yana et al. conducted a phase II study on previously untreated ED-SCLC. Amrubicin was administered at a dose of 45 mg/m^2/day intravenously on days 1 to 3, every 3 weeks. Of the 33 patients, 3 had CR and 22 had PR, with an overall response rate of 75.8%. MST was 11.7 months, and 1-year and 2-year survival rates were 48.5% and 20.2%, respectively; however, hematologic toxicities were severe: Grade 3/4 neutropenia, anemia, and thrombocytopenia were observed in 84.8%, 78.8%,

and 39.4%.[77] For relapsed patients, a phase I study was conducted by Okamoto et al. Fifteen patients were treated with amrubicin at doses of 30, 35, or 40 mg/m^2 on 3 consecutive days every 3 weeks. Grade 4 neutropenia was observed in 67% of patients, and the maximum tolerated dose and recommended dose were determined as 40 mg/m^2 and 35 mg/m^2, respectively.[78] Similarly, Igawa et al. conducted a dose-escalating study of second-line and third-line settings separately. The recommended doses were determined as 40 mg/m^2 for the second-line setting and 35 mg/m^2 for the third-line setting, respectively.[79]

In Japan, 3 phase II studies have been conducted at different doses of amrubicin for relapsed SCLC. In the first study, conducted by Kato et al., 45 mg/m^2 of amrubicin was administered on days 1–3 every 3 weeks. Thirty-four patients were treated with amrubicin, and there were 4 CRs and 14 PRs, with a response rate of 53%. The response rate and MST in sensitive relapse and refractory relapse were 50% and 10.4 months, and 60% and 6.8 months, respectively.[80] In the second study, conducted by Onoda et al., 40 mg/m^2 of amrubicin was administered on the same schedule and 60 patients were enrolled. The response rate and MST in sensitive relapse and refractory relapse were 52% and 11.6 months, and 50% and 10.3 months, respectively.[10] The third study was conducted by Kaira et al. and 35 mg/m^2 of amrubicin was administered to both SCLC and NSCLC patients. In this study, 29 relapsed SCLC patients were enrolled, and the response rate and MST in sensitive relapse and refractory relapse were 60% and 12.0 months, and 37% and 11.0 months, respectively.[81] In the first study, grade 4 neutropenia was noted in 71% of patients; however, the incidence were 55% in the second study and 10% in the third study, respectively. Considering that efficacy data were almost similar, fewer doses seems to be preferable in relapsed patients, as

indicated in previous phase I studies. Recently, the results of the first phase II study conducted outside Japan were presented. In the study, 75 Western patients with refractory relapse were treated with 40 mg/m^2 of amrubicin on 3 consecutive days every 3 weeks. The response rate and MST were 21% and 6.0 months, respectively.[82] The response rate and survival were considerably lower compared with Japanese phase II studies; however, consistent with the results of a Japanese randomized phase II studies comparing amrubicin with topotecan.[11] Table 5 summarizes the phase II studies of amrubicin.[10,80-82]

So far, two randomized phase II studies comparing topotecan and amrubicin have been conducted (Table 6).[11,83] In the first study, conducted in Japan, 60 patients were randomly assigned to either amrubicin (40 mg/m^2 on days 1–3, every 3 weeks) or topotecan (1.0 mg/m^2 on days 1–5, every 3 weeks), and 59 were evaluable. In the study, 36 sensitive relapse and 23 refractory relapse patients were included. Response rates were 13% in the topotecan arm and 38% in the amrubicin arm (p=0.039): in sensitive relapse, 21% for the topotecan arm and 53% for the amrubicin arm; in refractory relapse, 0% for the topotecan arm and 17% for the amrubicin arm. Median progression-free survival times (PFSs) and MSTs were 2.2 months and 8.4 months for the topotecan arm, and 3.5 months and 8.1 months for the amrubicin arm, respectively. However, many patients in the topotecan arm subsequently received amrubicin, and multivariate analysis revealed that amrubicin had more impact on overall survival than topotecan. There was one treatment-related death resulting from neutropenic infection in the amrubicin arm.[11] In the second study, conducted in the U.S., 76 sensitive relapse patients were randomly assigned to either amrubicin (40 mg/m^2 on days 1–3, every 3 weeks) or topotecan (1.5 mg/m^2 on days 1–5, every 3 weeks). The response rate was

significantly better in the amrubicin arm (11.5% vs 44%, p=0.005). Median PFSs and MSTs were 3.3 months and 7.7 months for the topotecan arm, and 4.6 months and 9.3 months for the amrubicin arm, respectively. One patient in the topotecan arm and 4 patients in the amrubicin arm died due to neutropenic infection.[83]

Targeted agents

Imatinib

The c-KIT protein, also known as CD117, is a member of the type III receptor tyrosine kinase (TK) family, and previous studies have shown that ~70% SCLC cells express c-kit. Imatinib is an orally available small molecule that inhibits several protein TK, including c-kit, platelet-derived growth factor receptor (PDGFR), and Bcr-Abl fusion protein, and is effective against chronic myeloid leukemia and gastrointestinal stromal tumors (GIST). Based on these facts, imatinib has been tested for relapsed SCLC in several clinical studies;[84-86] however, none showed the effectiveness of imatinib. One possible explanation is that c-kit expression in SCLC is not correlated with activating mutations in c-kit exon 11, which predict the activity of imatinib in GIST. Further studies of imatinib are not warranted for SCLC.[87]

Anti-angiogenic agents

The microvessel count and vascular endothelial growth factor (VEGF) level were found to significantly affect survival in SCLC patients who underwent primary resection followed by adjuvant chemotherapy.[88] These data prompted us to carry out a clinical study of anti-angiogenic agents for relapsed SCLC.

Bevacizumab is a recombinant, humanized monoclonal antibody against VEGF.

Jalal et al. conducted a phase II study of the combination of paclitaxel and bevacizumab for sensitive relapse SCLC. Thirty-four patients were enrolled and preliminary results were reported in 27 patients: response rate, 11.1%; SD, 55.5%; PD,33.3%; median PFS, 13 weeks; and MST, 21 weeks.[89]

Cediranib is a highly potent inhibitor of VEGFR-1, -2, and -3 TKs. In the phase II study conducted by Ramalingam et al., cediranib was administered at the daily oral dose of 45 mg, reduced to 30 mg because of toxicity, to 25 SCLC patients pretreated with only 1 previous regimen. Unconfirmed PR was reported in 1 patient and SD in 9 patients, with median PFS of 8 weeks and MST of 6 months. Cediranib failed to meet the predefined target (20% response) to continue full accrual to the study.[90]

Sorafenib is a multi-kinase inhibitor affecting the pathways involved in tumor progression and angiogenesis, such as Raf-1, VEGFR-2, VEGFR-3, and PDGFR-β. Sorafenib was administered at the daily oral total dose of 800 mg in 82 patients with SCLC who progressed after 1 platinum-based regimen and were stratified by platinum sensitivity. There were 4 PRs (3 sensitive relapse) and 25 SDs (12 sensitive relapse). Median PFS was 2 months in both groups, and MSTs were 7 months in sensitive relapse and 5 months in refractory relapse, respectively.[91] Overall, anti-angiogenic agents are not promising for SCLC.

Epidermal Growth Factor Receptor Inhibitors

Gefitinib is an orally active inhibitor selective for the TK of epidermal growth factor receptor (EGFR). Although EGFR expression is usually not noted in SCLC cells, there have been 2 phase II studies of gefitinib for relapsed SCLC.

In the study conducted by Moore et al., 19 patients with SCLC pretreated with

1 or 2 previous treatments received oral gefitinib at a daily dose of 250mg; however, there was no complete or partial response.[92] In another study conducted by Langer et al., among 29 patients, only 1 patient achieved PR and the response rate was 3%.[93] The most reliable predictive marker of response with EGFR tyrosine kinase inhibitors, including gefitinib, is somatic mutation of the EGFR gene, and the frequency of mutation is exclusively high in adenocarcinoma histology.[94] Although mutation data are lacking for SCLC, further studies of EGFR inhibitors are not warranted.

Farnesyl Transferase Inhibitor

Ras is a protein requiring farnesylation before it can mediate its proliferative functions, which is critical in carcinogenic processes. Tipifarnib is an oral non-peptidomimetic farnesyl transferase inhibitor that blocks the activity of farnesylated proteins involved in the signal transduction pathways critical for cell proliferation and survival. Heymach et al. conducted a phase II study of single-agent tipifarnib. Twenty-two sensitive relapse patients were enrolled; however, no significant antitumor activity was noted.[95] One possible explanation for the lack of sensitivity to tipifarnib is the absence of activating Ras mutations in SCLC cells.

Conclusions

A large number of clinical studies of relapsed SCLC have been conducted; however, treatment advances are slow. In addition, no targeted agents have proved effective, unlike in NSCLC. Better understanding of the molecular mechanisms is clearly needed, but amrubicin is the most promising at present. A Phase III study comparing amrubicin with topotecan in relapsed SCLC is underway in the EU and US.

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Table 1 Prospective studies of single-agent chemotherapy for relapsed SCLC

Regimen	n*	refractoy pts (%)	RR (%)	RR in refractory pts (%)	MST (months)	MST (months) sensitive/refractory
Etoposide[12]	14	NA	7	NA	2.0	NA
Etoposide[13]	77	NA	6	NA	4.4	NA
Teniposide[3]	44	NA	34	NA	6.9	NA
Irinotecan[17]	15	7	47	NA	6.2	NA
Irinotecan[18]	31	64	0	0	4.6	8.6 / 3.8
ACNU[28]	23	NA	4	NA	NA	NA
Paclitaxel[21]	24	NA	29	NA	3.3	NA
Ambamustine[29]	17	71	0	0	3.9	NA
GI147211[30]	62	45	17	10	NA	NA
Caelyx[31]	14	NA	0	0	NA	NA
Gemcitabine[22]	27	44	0	0	6.4	8.8 / 4.2
Bendamustine[32]	21	NA	29	NA	7.0	NA
Pemetrexed[24]	43	53	5	4	3.5	4.4 / 2.7
Pemetrexed[25]	34	26	3	11	4.1	5.3 / 3.6
Plitidepsin[33]	20	NA	0	0	4.8	NA
Picoplatin[27]	77	92	4	NA	5.2	NA

*number of evaluable patients for response

pts, patients; RR, response rate; MST, median survival time; NA, not available

Table 2 Prospective studies of combination chemotherapy for relapsed SCLC

Regimen	n*	Refractory pts (%)	RR (%)	RR in refractory pts (%)	MST (months)	MST (months) sensitive/refractory
CDDP+ETP[12]	34	NA	44	NA	4.0	NA
CDDP+ETP[34]	78	NA	55	NA	NA	NA
CDDP+ETP[35]	27	NA	41	NA	6.5	NA
CDDP+ETP[36]	18	NA	50	NA	4.7	NA
CDDP+ETP[37]	29	NA	12	NA	3.0	NA
CDDP+ETP[38]	29	100	52	52	NA	NA
CDDP+ETP[39]	31	52	29	19	4.3	NA
CDDP+ETP[50]	59	46	22	15	NA	NA
CBDCA+VCR[51]	22	NA	36	NA	4.2	NA
VIMP[51]	19	NA	53	NA	4.7	NA
VIMP[52]	25	NA	60	NA	4.4	NA
CPA+DXR+ETP[52]	43	NA	51	NA	5.1	NA
CBDCA+DXR[53]	25	NA	64	NA	5.4	NA
CDDP+ETP+IFM[54]	42	NA	55	NA	6.8	NA
CODE[55]	17	NA	88	NA	8.2	NA
CDDP+CPT-11[40]	25	64	80	81	7.9	NA
CBDCA+CPT-11[41]	29	45	31	23	6.1	6.1 / 5.7
CBDCA+CPT-11[42]	22	41	68	33	6.5	8.2 / 6.5
ETP+CPT-11[43]	25	16	71	75	9.0	NA
IFM+CPT-11[56]	34	29	53	33	7.2	NA
GEM+CPT-11[44]	35	43	17	27	5.8	8.7 / 4.5
GEM+CPT-11[45]	71	50	21	11	NA	7.1 / 3.1
GEM+CPT-11[18]	38	47	24	11	6.8	8.6 / 5.7
DXR+PTX[57]	46	30	41	14	5.8	NA
CBDCA+PTX[48]	34	NA	74	NA	7.2	NA
CBDCA+PTX[49]	32	100	25	25	7.0	- / 7.0
CDDP+PTX+IFM[58]	33	61	73	70	6.5	NA
CDDP+ETP+CPT-11[46]	40	0	78	-	11.8	11.8 / -
CDDP+ETP+CPT-11[47]	30	100	70	70	7.3	- / 7.3
ACNU[59]	24	100	25	25	5.8	NA
PTX+GEM[60]	31	32	26	20	7.5	8.3 / 2.5
Caelyx+CPA+VCR[61]	31	29	10	NA	6.5	NA

*number of evaluable patients for response

pts, patients; RR, response rate; MST, median survival time; CDDP, cisplatin; ETP, etoposide; CBDCA, carboplatin; VCR, vincristine; VIMP, vincristine+ifosfamide+mesna+carboplatin; CPA, cyclophosphamide; DXR, doxorubicin; DXR, doxorubicin; IFM, ifosfamide; CODE, cisplatin+vincristine+doxorubicin+etoposide; CPT-11, irinotecan; GEM, gemcitabine; PTX, paclitaxel

Table 3 Phase II studies of single-agent topotecan for relapsed SCLC

Study	Phase	Chemosensitivity	n	Response rate (%)	MST (months)
Ardizzoni et al.[62]	II	S	45	37.8	6.9
		R	47	6.4	4.7
Eckardt et al.[63]	II	S	36	19.0	6.2
		R	38	3.0	4.8
Depierre et al.[64]	II	S	57	14.0	6.0
		R	41	2.4	3.8
Takeda et al.[65]	II	S	50	26.0	8.7
		R	0	-	-
Perez-Soler et al.[66]	II	S	0	-	-
		R	32	11.0	4.7

MST, median survival time; S, sensitive; R, refractory

Table 4 Randomized studies of single-agent topotecan for relapsed SCLC

Study	Phase	Regimen	n	Response rate (%)	MST (weeks)
von Pawel et al.[68]	II	Oral topotecan	52	23.0	32.0
		IV topotecan	54	15.0	25.0
Eckardt et al.[69]	III	Oral topotecan	153	18.3	33.0
		IV topotecan	151	21.9	35.0
O'Brien et al.[70]	III	BSC	67	-	13.9
		topotecan	70	7.0	25.9
von Pawel et al.[67]	III	CAV	104	18.3	24.7
		topotecan	107	24.3	25.0

MST, median survival time

Table 5 Phase II studies of single-agent amrubicin for relapsed SCLC

Study	Phase	Dose (mg/m^2)	Chemosensitivity	n	Response rate (%)	MST (months)
Kato et al.[80]	II	45	S	24	50.0	10.4
			R	10	60.0	6.8
Onoda et al.[10]	II	40	S	44	52.0	11.6
			R	16	50.0	10.3
Kaira et al.[81]	II	35	S	10	60.0	12.0
			R	19	36.8	11.0
Ettinger et al.[82]	II	40	S	0	-	-
			R	75	21.0	6.0

MST, median survival time; S, sensitive; R, refractory

Table 6 Randomized phase II studies comparing topotecan and amrubicin for relapsed SCLC

Study	Regimen	Chemosensitivity	n	Response rate (%)	Median PFS, (months)	Median OS, (months)
Inoue et al.[11]	topotecan	S	19	21.0	3.0	11.7
		R	11	0.0	1.5	5.4
	amrubicin	S	17	53.0	3.9	9.9
		R	12	17.0	2.6	5.3
Jotte et al.[83]	topotecan	S	26	11.5	3.3	7.7
		R	-	-	-	-
	amrubicin	S	50	44.0	4.6	9.3
		R	-	-	-	-

PFS, progression-free survival; OS, overall survival; S, sensitive; R, refractory