Targeted therapies in small cell lung cancer (Review)

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Abstract. Lung cancer is the leading cause of cancer-related mortality. Small cell lung cancer (SCLC) accounted for 12.95% of all lung cancer histological types in 2002. Despite trends toward modest improvement in survival, the outcome remains extremely poor. Chemotherapy is the cornerstone of treatment in SCLC. More than two-thirds of patients who succumb to lung cancer in the United States are over 65 years old. Elderly patients tolerate chemotherapy poorly and need novel therapeutic agents. Targeted drugs have less toxicity than chemotherapy drugs, but no targeted agents have been approved for use in the treatment of SCLC patients to date. Certain new targeted agents, including gefitinib, bevacizumab and Bcl-2 inhibitors, offer a promise of improved outcomes, however negative results are more commonly reported than positive. This review focuses on targeted therapies in SCLC.

Contents

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Abbreviations: SCLC, small cell lung cancer; VALSG, Veterans Administration Lung Study Group; EGFR, epidermal growth factor receptor; LD, limited-stage disease; ED, extensive-stage disease; NSCLC, non-small cell lung cancer; RT-PCR, reverse transcription polymerase chain reaction; PS, performance status; VEGF, vascular endothelial growth factor; CRT, chemoradiation; CR, complete response; PR, partial response; SD, stable disease; DCR, disease control rate; PFS, progression-free survival; OS, overall survival; ORR, objective response rate; MST, median survival time; TTP, time-to-progression; MMP, matrix metalloproteinase; ASCO, American Society of Clinical Oncology; mTOR, mammalian target of rapamycin; AE, adverse event

Key words: small cell lung cancer, targeted therapy, epidermal growth factor receptor, vascular endothelial growth factor, apoptosis, gene

1. Introduction

The most commonly diagnosed types of cancer worldwide are lung (1.61 million, 12.7% of the total), breast (1.38 million, 10.9%) and colorectal cancers (1.23 million, 9.7%). The most common causes of cancer mortality are lung (1.38 million mortalities, 18.2% of the total), stomach (738,000, 9.7%) and liver cancer (696,000, 9.2%) (1). The proportion of small cell lung cancer (SCLC; among all lung cancer histological types) decreased from 17.26% in 1986 to 12.95% in 2002. The proportion of women with SCLC increased from 28% in 1973 to 50% in 2002. There has been a modest but statistically significant improvement in two- and five-year survival. SCLC is nearly universally smoking-related. Possible explanations for the decreasing incidence of SCLC include the decrease in the percentage of smokers and the change to low-tar filter cigarettes. Despite trends toward modest improvement in survival, the outcome remains extremely poor (2).

SCLC is most commonly staged by the Veterans Administration Lung Study Group (VALSG) staging system (3). This system classifies patients as having limited- or extensive-stage disease (LD and ED, respectively). LD is defined as disease confined to one hemithorax, in the absence of a malignant effusion, with disease that can be encompassed in one radiation port. Disease that does not meet these criteria is defined as ED. The TNM staging system is also used for SCLC, especially for patients receiving surgical treatment (4). Approximately one-third of patients diagnosed with SCLC present with LD, which has a median survival time (MST)of 15-20 months. A response to combination chemotherapy is achieved by 80-90% of LD patients, with or without thoracic radiation (5). Of patients with ED SCLC, 60-80% respond to chemotherapy, the MST is eight to ten months and the one- and two-year survival rates are 35 and 10%, respectively (6). SCLC is characterized by its rapid doubling time and high growth fraction. SCLC has a propensity for chemosensitivity, for early hematogenous spread and for association with paraneoplastic syndromes. Chemotherapy is the cornerstone of treatment.

More than two-thirds of patients who succumb to lung cancer in the United States are over 65 years old (7). Elderly

patients tolerate chemotherapy poorly and need novel therapeutic agents. A targeted therapy is a type of medication that blocks the growth of cancer cells by interfering with specific targeted molecules needed for carcinogenesis and tumor growth, rather than by simply interfering with rapidly dividing cells (as with traditional chemotherapy). Targeted drugs have less toxicity than chemotherapy drugs. Certain new targeted agents offer a promise of improved outcomes and negative results are more commonly reported than positive. This review focuses on targeted therapy in SCLC.

2. Growth factor receptor inhibitors

Gefitinib. Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor may be used as a first-line therapy in patients with advanced non-SCLC (NSCLC) with EGFR mutations (8-12). The results of the INTEREST trial (13) suggest that gefitinib provides similar overall survival (OS) to docetaxel in patients across a broad range of clinical subgroups and EGFR biomarkers, including mutation status, may additionally identify which patients are likely to gain greatest progression-free survival (PFS) and objective response rate (ORR) benefit from gefitinib. Tanno *et al* evaluated the effect of gefitinib against the SCLC cell lines NCI-H82, NCI-H209, NCI-H510, NCI-H526 and NCI-H660. The authors found that gefitinib inhibited the phosphorylation of ERK1/2 by EGF addition in cell lines with detectable and undetectable EGFR expression, and suggested that gefitinib is potentially effective against cancers with low EGFR expression, including SCLC (14). Gefitinib has not been recommended for use in SCLC, but some case reports on this subject have been published. A case study concerning a Japanese patient with gefitinib-responsive SCLC reported that the patient had a deletion in exon 19 of EGFR (15). Moreover, another case study also reported that a never-smoking American SCLC patient with an EGFR mutation responded to erlotinib and gefitinib (16). In China, there has also been a case report of an SCLC patient responding to gefitinib, but the status of the mutation is unknown (17). A phase II trial concerning gefitinib in patients with chemosensitive and chemorefractory relapsed SCLC has been performed. A total of 12 patients (63%) had chemosensitive disease and seven (37%) had chemorefractory disease. Two patients had stable disease (SD) and 17 had progressive disease (PD). This study failed to demonstrate a benefit from the use of gefitinib in SCLC patients (18).

EGFR mutation is important for gefitinib and erlotinib therapy in advanced NSCLC, especially in first-line therapy, and it may also be significant in SCLC. Shiao *et al* (19) searched for EGFR mutations in 76 SCLC specimens using reverse transcription polymerase chain reaction (RT-PCR) and direct sequencing. Two specimens (2.6%) tested positive for the EGFR mutation, both deletions in exon 19. The specimens in this study included ten computed tomography-guided biopsy, 17 echo-guided aspiration, 37 echo-guided biopsy, one surgical lobectomy and 11 malignant pleural effusion specimens. Another study (20) analyzed 122 cases of SCLC patients, including 102 specimens obtained by biopsy and 20 from surgical resection, detected by standard RT-PCR coupled with direct sequencing. EGFR mutations were detected in five SCLCs (4%). The patients were mainly light smokers and were in the histological combined subtype. In three tumors of the combined SCLC subtype, both components of adenocarcinoma and SCLC had an EGFR mutation. A partial response (PR) was achieved in a patient (with an EGFR mutation) who was treated with gefitinib. The patients with EGFR mutation were more likely to have SCLC combined with adenocarcinoma compared with the whole SCLC population. We also detected EGFR exon 19 and 21 mutations of 40 SCLC patients who received surgical treatment in Zhejiang Cancer Hospital (Hangzhou, China) between 1998 and 2010 using xTAG technology. Two of 40 cases were found to have a mutation in EGFR exon 19. One patient with EGFR exon 19 mutation was a female non-smoking patient with SCLC combined with adenocarcinoma, and the other was a male smoker with SCLC combined with squamous cell carcinoma. The EGFR mutation is rare in SCLC patients, and EGFR mutation may occur more frequently in combined SCLCs than conventional patients (21). Of SCLC patients who undergo surgical resection, 28% have combined SCLC, and surgical specimens may more accurately reflect the clinicopathological status (22). The low incidence of EGFR exon 19 or 21 mutations may be the cause of the negative result of the study by Moore *et al* (18). We suggest that an EGFR tyrosine kinase inhibitor is a suitable selection for SCLCs with EGFR exon 19 or 21 mutation when relapsed following chemotherapy or in patients who cannot tolerant chemotherapy. Further research concerning SCLC and combined SCLC with regard to EGFR mutation should be performed.

Imatinib. With the success of imatinib mesylate (STI571) in the treatment of c-kit expression and mutation in gastrointestinal stromal tumors, its use in SCLC presented a novel molecular therapeutic approach. The activity of imatinib mesylate is related to the mutation of c-kit in exons 9 and 11 in gastrointestinal stromal tumor (23,24). In the trial performed by Johnson *et al* (25), 19 SCLC patients (9 chemonaïve patients with ED and 10 sensitive relapsed SCLC patients) received 600 mg imatinib on a daily basis. Tumor tissue samples from four (21%) of the 19 patients had the KIT receptor (CD117). No objective responses were observed. In another phase II clinical trial (26), 12 patients with SCLC with c-kit expression and PD after one or two previous chemotherapy regimens received imatinib at 400 mg orally twice daily. No responses were observed, and all patients had disease progression by week four. The trial performed by Dy *et al* (27) also evaluated imatinib for patients with relapsed SCLC with c-kit expression and the result was also negative. Boldrini *et al* studied 60 SCLC samples to determine the mutations of the coding region of the c-kit gene. The expression of c-kit was demonstrated in ~40% of SCLC samples, and two patients with mutations in exon 9 and three patients with mutations in exon 11 were identified. Kaplan-Meier analysis revealed no prognostic significance of c-kit expression for survival (28). We detected c-kit exons 9 and 11 mutation using a pyrosequencing assay in 36 SCLC patients who received surgical treatment in Zhejiang Cancer Hospital between 1998 and 2010. No mutation of c-kit exon 9 or 11 was detected (29).

Other research has focused on imatinib combined chemotherapy or maintenance following chemotherapy. A phase II trial (30) studied irinotecan, carboplatin and imatinib in

patients with untreated ED SCLC. A total of 68 patients received carboplatin [area under the concentration-time curve (AUC) of 4 on day 1], irinotecan (60 mg/m^2 on days 1, 8 and 15) and imatinib (600 mg/day). The treatment cycles were 28 days. Patients remained on imatinib until PD or significant toxicity. The ORR was 66%, median PFS was 5.4 months and MST was 8.4 months. After 1 year, 35% of the patients were alive. Grade 3/4 hematological toxicities included neutropenia (43%), anemia (16%) and thrombocytopenia (9%). Grade 3 non-hematological toxicities included diarrhea (19%), fatigue (24%) and nausea (26%). Irinotecan, carboplatin and imatinib is a safe and generally well-tolerated regimen in patients with SCLC. However, the addition of imatinib did not improve results from those expected with chemotherapy alone. Another phase II trial concerned imatinib maintenance therapy following irinotecan and cisplatin in patients with c-kit-positive ED SCLC. A total of 14 patients were enrolled and imatinib did not appear to delay disease progression following response to chemotherapy (31).

3. Angiogenesis inhibitors

Thalidomide. Tumor growth depends on angiogenesis. Thalidomide has antiangiogenic and immunomodulatory properties. A phase III double-blind, placebo-controlled study (32) on thalidomide in ED SCLC following response to chemotherapy has been performed. A total of 119 patients received two courses of etoposide, cisplatin, cyclophosphamide and 4'-epidoxorubicin (PCDE). Responsive patients who had recovered from chemotherapy toxicity were randomly assigned to receive four additional PCDE cycles plus thalidomide (400 mg daily) or placebo. A total of 92 patients were randomly assigned to placebo (n=43) or thalidomide (n=49). Patients treated with thalidomide had a longer survival compared with those who received placebo (11.7 vs. 8.7 months, P=0.16), although the difference was not statistically significant. Patients with a performance status (PS) of 1 or 2 who received thalidomide had a significantly longer survival (P=0.02) compared to the patients with a PS of 1 or 2 who received the placebo. Neuropathy occurred more frequently in the thalidomide group compared with the placebo group (33 vs. 12%). At present, the regimen of PCDE is not commonly used in SCLC and other chemotherapy regimens, including etoposide and cisplatin combined with thalidomide, are warranted.

Vandetanib. ZD6474 (vandetanib) is an oral receptor tyrosine kinase inhibitor which inhibits both vascular endothelial growth factor (VEGF) and EGFR. A phase II study (33) about vandetanib or placebo in SCLC patients following complete response (CR) or PR to induction chemotherapy with or without radiation therapy has been performed. A total of 107 patients were recruited, including 46 cases of LD and 61 cases of ED. Vandetanib patients experienced more toxicities and required more dose modifications for gastrointestinal toxicity and rash. The OS for vandetanib was 10.6 versus 11.9 months for placebo (P=0.9). Vandetanib failed to demonstrate efficacy as a maintenance therapy for SCLC.

Bevacizumab. Bevacizumab (Avastin) is a humanized monoclonal antibody directed against VEGF. A phase II trial of concurrent chemoradiation (CRT) and bevacizumab in LD SCLC suggested that bevacizumab increases the risk for tracheoesophageal (TE) fistula when administered with and following CRT. Potential mechanisms include enhanced regional tissue injury and impaired mucosal healing (34). A phase II study (35) investigated cisplatin plus etoposide and bevacizumab for previously untreated ED SCLC. A total of 63 patients were treated with bevacizumab (15 mg/kg) plus cisplatin (60 mg/m^2) and etoposide (120 mg/m$^{2)}$, followed by bevacizumab alone until mortality or disease progression occurred. The 6-month PFS was 30.2%, the median PFS was 4.7 months and OS was 10.9 months. The ORR was 63.5% and the most common adverse event (AE) was neutropenia (57.8%). Only one patient had grade 3 pulmonary hemorrhage. The addition of bevacizumab with cisplatin and etoposide in patients with ED SCLC results in improved PFS and OS relative to historical controls who received this chemotherapy regimen without bevacizumab. This regimen appears to be well tolerated and has a minimal increase in toxicities compared with chemotherapy alone. Another randomized phase II study (36) concerned bevacizumab to cisplatin or carboplatin plus etoposide in previously untreated ED SCLC. Bevacizumab to cisplatin or carboplatin plus etoposide for treatment of ED SCLC improved PFS, with an acceptable toxicity profile. However, no improvement in OS was observed.

A phase II trial (37) evaluated irinotecan, carboplatin and bevacizumab in the treatment of patients with ED SCLC. A total of 51 patients with no prior SCLC chemotherapy, no active brain metastases, no hemoptysis and Eastern Cooperative Oncology Group PS 0-1 were enrolled. Treatment consisted of irinotecan (60 mg/m^2) administered intravenously on days 1, 8 and 15, carboplatin (AUC=4) on day 1 and bevacizumab (10 mg/kg) on days 1 and 15 every 28 days for up to six cycles. Patients with no progression received maintenance bevacizumab. ORR was 84%, median time-to-progression (TTP) was 9.13 months, MST was 12.1 months and the one- and two-year OS rates were 51 and 14%, respectively. Grade 3/4 toxicity (≥10%) included neutropenia (39%), thrombocytopenia (22%), dehydration (10%), diarrhea (31%), fatigue (20%) and pulmonary symptoms (10%). No significant bleeding occurred. Another phase II study (38) analyzed cisplatin, irinotecan and bevacizumab for untreated ED SCLC. The results suggest PFS and OS times were longer compared with those of US trials in ED SCLC with the same chemotherapy. Hypertension was associated with improved survival after adjusting for age and PS. The results of a phase II study (39) concerning oral topotecan plus bevacizumab (topo-bev) for second-line treatment of SCLC suggest that the primary efficacy endpoint of improvement in 3-month PFS was not met and that a marginal benefit of this combination cannot be ruled out. The results of another clinical trial (40), which studied paclitaxel plus bevacizumab in patients with chemosensitive relapsed SCLC, suggest that the addition of bevacizumab to paclitaxel does not improve outcomes in these patients.

NGR-hTNF. NGR-hTNF, a selective vascular targeting agent, improves the intratumoral doxorubicin penetration by normalizing tumor vasculature and decreasing tumor interstitial fluid pressure. A phase II trial (41) about NGR-hTNF and doxorubicin in relapsed SCLC was reported at the 2011

annual meeting of the American Society of Clinical Oncology (ASCO). A total of 28 patients were recruited. NGR-hTNF did not increase doxorubicin-related toxicity. The disease control rate (DCR) was 55%, including six cases of PR (22%) and nine cases of SD (33%), and the median PFS was 3.2 months. Over a median follow-up period of 19.3 months, the 6-month and 1-year ORRs were 49 and 34%, respectively. By Cox analyses, PFS and OS did not correlate with age, gender, PS or platinum sensitivity, while only the neutrophil-to-lymphocyte ratio was associated with OS (HR, 0.30). Further development of NGR-hTNF plus doxorubicin in platinum-resistant or -sensitive SCLC is of interest.

Cediranib. Cediranib is a highly potent inhibitor of VEGFR-1, -2 and -3 tyrosine kinases. A phase II study (42) evaluated its safety and efficacy in relapsed/recurrent SCLC. The dose of cediranib was 45 mg *per os* (PO) once a day for the first 12 patients and was reduced to 30 mg PO once a day for the subsequent patients due to intolerance of the higher dose. Cediranib failed to demonstrate objective responses in recurrent or refractory SCLC at the dose and schedule evaluated.

Sorafenib. Sorafenib is a multiple kinase inhibitor of Raf kinase, VEGFR-2, VEGFR-3 and platelet-derived growth factor receptor (PDGFR) β and affects pathways involved in tumor progression and angiogenesis. A phase II trial of sorafenib in platinum-treated ED SCLC patients determined the tumor response rate, toxicity and OS (43). Patients were treated with sorafenib (400 mg PO BID) continuously on a 28-day cycle. Of the 89 patients recruited, 81 were evaluated for toxicity assessment and 79 were evaluated for response. There were no cases of CR, PR was 34% and SD was 32%. MST was 7 (platinum-sensitive) and 5 months (platinum-refractory). Major toxicities included 20 patients (25%) with grade 3 dermatological toxicity, 11 (14%) with grade 3/4 flu-like symptoms and nine (11%) with grade 3/4 metabolic toxicity. A total of 18 patients discontinued treatment due to AEs or side-effects of therapy. Further study of sorafenib in combination with chemotherapy is warranted.

Sunitinib. Sunitinib is a multi-targeted tyrosine kinase inhibitor with direct antitumor and antiangiogenesis activity through targeting PDGFR, VEGFR, KIT and FLT3 receptors. A phase II study of sunitinib in patients with relapsed or refractory SCLC was conducted to evaluate the efficacy and safety of sunitinib (44). Patients received sunitinib (50 mg/day) for four weeks on and two weeks off in a 6-week cycle. A total of 25 patients were enrolled; 24 received treatment and 23 were evaluated for response. The ORR was 9% and the median PFS and OS were 1.4 and 5.6 months, respectively. Grade 3/4 toxicity for sunitinib included thrombocytopenia (63%), neutropenia (25%), asthenia (8%) and anorexia (8%). One or two dose reductions were required by 46% of patients. This approach does not appear to warrant further clinical study.

A phase II study evaluated irinotecan and carboplatin followed by maintenance sunitinib in the first-line treatment of ED SCLC. Patients received up to 6 cycles of irinotecan (60 mg/m^2) on days 1, 8 and 15 and carboplatin (AUC=4) on day 1. Cycles were repeated every 28 days. All patients without progression or intolerable toxicity continued receiving single-agent sunitinib (25 mg orally daily) until progression. A total of 34 patients were enrolled. The median TTP was 7.6 months and the 6-month ORR was 91%. No grade 3/4 toxicities were observed in the four patients who received sunitinib. Maintenance sunitinib was well tolerated following platinum doublet chemotherapy as first-line treatment for ED SCLC (45). Another clinical trial analyzed combination chemotherapy with sunitinib for untreated ED SCLC. The combination of sunitinib (25 mg/day days 1-14) with standard dose cisplatin and etoposide appeared to cause prolonged neutropenia and an unacceptable rate of treatment-related mortality. This combination of chemotherapy and sunitinib is not recommended, even with growth factor support (46).

Marimastat and BAY 12-9566. Matrix metalloproteinases (MMPs) and their tissue inhibitors are important in processes of tumor growth and morphogenesis. The increased tumoral expression levels of MMP-3, -11 and -14 were found to be independent negative prognostic factors for survival in SCLC (47). Synthetic MMP inhibitors may be effective in SCLC, and some clinical trials have evaluated this. Marimastat (BB2516) inhibits MMP-1, -2, -3, -7 and -9 and BAY 12-9566 inhibits MMP-2, -9 and -3. A prospective randomized double-blind placebo-controlled phase III trial of marimastat following response to first-line chemotherapy in SCLC patients has been reported. There were 532 eligible patients (266 marimastat and 266 placebo). The stage of SCLC was limited for 279 patients (52%) and extensive for 253 (48%). The median TTP for the marimastat patients was 4.3 months, compared with 4.4 months for the placebo patients (P=0.81). The MST for marimastat and placebo patients was 9.3 and 9.7 months, respectively (P=0.90). Toxicity was generally limited to musculoskeletal symptoms (18% grade 3/4 for marimastat). Dose modifications for musculoskeletal toxicity were required in 90 patients (33%) on the marimastat arm and 87 (32%) permanently stopped marimastat due to toxicity. Treatment with marimastat following induction therapy for SCLC did not result in improved survival and had a negative impact on quality of life (48). Another phase III randomized, placebo-controlled trial (49) examined the role of BAY 12-9566 in NSCLC and SCLC. BAY 12-9566 did not show any advantage in terms of survival and the incidence of AEs was higher in patients who received BAY 12-9566 compared with the placebo. MMPs are likely to play a smaller role in SCLCs and further clinical trials of MMP inhibitors may be not necessary for SCLC.

4. Apoptosis promoters

G3139. The overexpression of Bcl-2 is found in the majority of SCLCs and is associated with resistance. G3139 is an antisense oligonucleotide complementary to the mRNA encoding Bcl-2. The suppression of Bcl-2 levels through the use of G3139 may increase the antitumor efficacy. A pilot trial (50) evaluated G3139 and paclitaxel in patients with chemorefractory SCLC. A total of 12 patients with chemorefractory SCLC participated in this pilot trial of paclitaxel combined with G3139. The combination of paclitaxel at 150 mg/m^2 and G3139 at 3 mg/kg/day was found to be feasible and well tolerated. No objective responses were observed, but two patients had SD, one remaining stable on therapy for >30 weeks. This study demonstrates that G3139 may be combined with paclitaxel in a cytotoxic dose range. A

phase I study (51) of G3139 combined with carboplatin and etoposide in patients with SCLC suggested that the regimen was well tolerated and results in an encouraging response rate and TTP in ED SCLC patients. A 3:1 randomized phase II study (52) was then performed to evaluate carboplatin and etoposide with (arm A) or without (arm B) oblimersen in 56 assessable patients with chemonaïve ED SCLC. The addition of oblimersen to a standard regimen for this disease did not improve any clinical outcome measure. The additional evaluation of this agent in SCLC is not warranted.

ABT-263. ABT-263 is a novel BH3 mimetic which binds with high affinity ($K_i \leq 1$ nM) and inhibits multiple antiapoptotic Bcl-2 proteins. A study (53) concerning the activity of ABT-263 in a panel of SCLC xenograft models suggested that SCLC is a promising area of clinical investigation with this agent. A phase IIa study of ABT-263 in patients with relapsed SCLC was reported at the ASCO 2010 annual meeting. ABT-263 was administered orally at 325 mg once daily, following a 7-day lead-in dose of 150 mg, on a 21-day cycle until PD or intolerable toxicity. A total of 39 patients were enrolled, 21 discontinued due to PD, four withdrew consent and 14 remained in the study (four with SD). A total of six patients had dose reductions due to AEs and 11 experienced serious AEs. The most common AEs were diarrhea (43%), back pain (43%) and thrombocytopenia (29%). The most common grade 3/4 AE was thrombocytopenia (29%). Four patients had dose interruptions due to AEs. This phase II study revealed that ABT-263 has an acceptable safety profile and the evaluation of tumor response is ongoing in the phase II portion (54).

Obatoclax. Obatoclax is a pan-Bcl-2 antagonist. Langer *et al* (55) reported a randomized phase II study of carboplatin and etoposide with or without pan-Bcl-2 antagonist obatoclax in ED SCLC at the ASCO 2011 annual meeting. A total of 65 patients were randomized and 155 (77 carboplatin, etoposide and obatoclax; 78 carboplatin and etoposide) received treatment. The only grade 3/4 non-hemorrhage AE with >5% increase in absolute frequency in the obatoclax arm was somnolence (8 vs. 0%, obatoclax arm vs. carboplatin-etoposide arm). Grade 3/4 febrile neutropenia was rare (5%, both arms). Grade 3/4 hematological data were similar for each arm (obatoclax arm vs. carboplatin-etoposide arm): anemia, 8 vs. 15%; neutropenia, 61 vs. 58%; and thrombocytopenia, 17 vs. 10%. The obatoclax arm demonstrated a trend for improved ORR, PFS, 12 months survival and OS. Obatoclax markedly decreased the refractory rate to the initial 6 cycles of chemotherapy by 36.5%. Patients with a screening PS of 2 performed poorly in both arms. OS in PS 0-1 patients will be evaluated in a phase III trial comparing carboplatin-etoposide with carboplatin, etoposide and obatoclax (55).

AT-101. AT-101 is an oral, pan-Bcl-2 family protein inhibitor. A phase I/II study of AT-101 in combination with topotecan in patients with relapsed or refractory SCLC following prior platinum-containing first-line chemotherapy was reported at the 2009 ASCO annual meeting (56). A total of 36 patients were enrolled in the study. The recommended phase II dose was AT-101, 40 mg days 1 to 5 with topotecan, 1.25 mg/m^2 days 1 to 5 on a 21-day cycle. In the sensitive-relapsed cohort (n=18), there were no CR, three PR, ten SD and four PD. In the refractory cohort (n=12), there were no CR/PR, five SD and five PD. The median TTP in the sensitive-relapsed cohort was 17.4 weeks and in the refractory cohort was 11.7 weeks. Additional trials of AT-101 in SCLC are ongoing.

5. Other agents

Everolimus. The Akt/mammalian target of rapamycin (mTOR) pathway is frequently activated and plays an important role in SCLC. RAD001 (everolimus) is an orally administered mTOR inhibitor. Kotsakis *et al* reported a phase II study of RAD001 in previously treated SCLC at the 2009 ASCO annual meeting (57). A total of 40 patients were treated with everolimus (10 mg orally daily) until disease progression. A total of 28 patients received two or more cycles of everolimus, seven received one cycle and five did not complete the first cycle. The best response in 35 evaluated patients was one (3%) PR (in sensitive relapse), eight (23%) SD and 26 (74%) PD. DCR at six weeks was 26%. MST was 6.7 months and median TTP was 1.3 months. Grade 3 toxicities included thrombocytopenia (n=2), neutropenia (n=2), infection (n=2), pneumonitis (n=1), fatigue (n=1), elevated transaminases (n=1), diarrhea (n=2) and acute renal failure (n=1). Everolimus was well tolerated but had limited single-agent antitumor activity in unselected previously treated patients with relapsed SCLC. Further evaluation in combination regimens for patients with sensitive relapse may be considered.

BI 2536. BI 2536 is a potent selective inhibitor of polo-like kinase 1, a regulator of mitotic progression. A clinical phase II trial demonstrated that BI 2536 was well tolerated in relapsed SCLC patients, but revealed no convincing antitumor efficacy. BI 2536 should not be assessed further as a single agent in SCLC (58).

R115777. Ras requires farnesylation before it is able to mediate its proliferative functions. R115777 is an oral, non-peptidomimetic farnesyl transferase inhibitor related to cell proliferation and survival and blocks the activity of farnesylated proteins (e.g. ras) involved in signal transduction. A multi-center phase II study evaluated R115777 in patients with sensitive relapsed SCLC. R115777 was administered in 3-week cycles at a dose of 400 mg orally twice daily for 14 consecutive days followed by seven days off treatment, and 22 patients were enrolled. The trial was terminated as no objective responses were observed in the 20 patients evaluable for response (59).

p53 cancer vaccine. Cells become susceptible to DNA damage and dysregulated cell growth if p53 genes are deleted or mutated. Patients with a p53 mutation may be identified as more likely to be resistant to chemotherapy or radiotherapy (60). On this basis, gene therapies targeting p53 have been explored. A trial evaluated the combination of a p53 cancer vaccine with chemotherapy in patients with ED SCLC. This vaccine, consisting of dendritic cells transduced with the full-length wild-type p53 gene, was delivered via an adenoviral vector. A total of 29 patients with ED SCLC were vaccinated repeatedly at 2-week intervals. Most of the

Table I. Completed phase III randomized trials of targeted therapies in SCLC.

Author (ref.)	Study population	Treatment	No. patients	OS (months)	Comments
Pujol JL *et al* (32)	ED SCLC after response to chemotherapy	Thalidomide vs. control	49 vs. 42	11.7 vs. 8.7 P=0.16	Negative, but thalidomide had a significantly longer survival in patients with a PS of 1 or 2
Shepherd FA *et al* (48)	Response to first-line chemotherapy in SCLC patients	Marimastat vs. control	266 vs. 266	9.3 vs. 9.7 P=0.90	Negative
Rigas JR *et al* (49)	Patients in CR and PR	BAY 12-9566 vs. control	327	3.2 vs. 5.3[a] P=0.05	Negative
Bottomley A *et al* (63)	Responding patients with LD SCLC	Bec2 vs. control	515	14.3 vs. 16.4 P=0.28	Negative but a trend toward prolonged survival in patients who developed a humoral response

[a]Time-to-progression. ED, extensive-stage disease; SCLC, small cell lung cancer; CR, complete response; PR, partial response; LD, limited-stage disease; PS, performance status; OS, overall survival.

Table II. Phase II trials of targeted therapies in SCLC with negative results.

Author (ref.)	Study population	No. patients	Treatment
Moore AM *et al* (18)	Chemosensitive and chemorefractory relapsed	19	Gefitinib alone
Johnson BE *et al* (25)	Chemonaïve with ED and sensitive relapse	19	Imatinib alone
Krug LM *et al* (26)	C-kit expression and progressive after 1 or 2 previous chemotherapy regimens	12	Imatinib alone
Dy GK *et al* (27)	Relapsed SCLC with c-kit expression	29	Imatinib alone
Spigel DR *et al* (30)	Untreated ED	68	Irinotecan and carboplatin with imatinib
Schneider BJ *et al* (31)	ED SCLC with c-kit-positive and therapy after irinotecan and cisplatin	14	Maintenance with imatinib
Arnold AM *et al* (33)	After CR or PR to induction chemotherapy	107	Maintenance with imatinib or placebo
Waterhouse DM *et al* (39)	Second-line treatment	50	Oral topotecan plus bevacizumab
Jalal S *et al* (40)	Chemosensitive relapsed	34	Paclitaxel plus bevacizumab
Ramalingam SS *et al* (42)	Relapsed/recurrent	25	Cediranib alone
Han J *et al* (44)	Relapsed or refractory	25	Sunitinib alone
Ready N *et al* (46)	Untreated ED	18	Sunitinib combination chemotherapy
Rudin CM *et al* (52)	Chemonaïve ED	56	Carboplatin and etoposide with or without oblimersen
Kotsakis AP *et al* (57)	Previously treated relapsed	40	Everolimus alone
Gandhi L *et al* (58)	Sensitive relapse	23	BI 2536 alone
Heymach JV *et al* (59)	Sensitive relapse	22	R115777 alone

SCLC, small cell lung cancer; ED, extensive-stage disease; CR, complete response; PR, partial response.

patients received three immunizations. p53-specific T cell responses to vaccination were observed in 57.1% of patients. Immunological responses to vaccination were positively associated with a moderate increase in the titer of anti-adenovirus antibodies, and negatively with an accumulation of immature myeloid cells. One patient showed a clinical response to vaccination whereas most of the patients had disease progression. Clinical response to subsequent chemotherapy

Table III. Studies in SCLC with promising results.

Author (ref.)	Study population	Treatment	No. patients	OS (months)	Comments
Okamoto I *et al* (15)	EGFR mutation	Gefitinib alone	1	Unknown	Gefitinib effective in SCLCs with EGFR mutation
Zakowski MF *et al* (16)	EGFR mutation	Erlotinib or gefitinib alone	1	Unknown	Erlotinib or gefitinib effective in SCLCs with EGFR mutation
Horn L *et al* (35)	Previously untreated ED	Cisplatin plus etoposide and bevacizumab	63	10.9	Improved PFS and OS relative to historical controls
Spigel DR *et al* (36)	Previously untreated ED	Bevacizumab vs. placebo with cisplatin or carboplatin plus etoposide	52	9.4 vs. 10.9	Improved PFS, no improvement in OS
Spigel DR *et al* (37)	ED patients with no prior chemotherapy	Irinotecan, carboplatin and bevacizumab	51	12.1	Warrant to further randomized study
Ready NE *et al* (38)	Untreated ED	Cisplatin, irinotecan and bevacizumab	72	11.6	Improved PFS and OS relative to historical controls
Vigano' MG *et al* (41)	Relapsed	NGR-hTNF and doxorubicin	28	3.2 (PFS)	Further study is of interest
Gitlitz BJ *et al* (43)	Platinum-treated ED	Sorafenib alone	89	Sensitive, 7 Refractory, 5	Comparable with historical controls receiving salvage chemotherapy
Lubiner ET *et al* (45)	First-line treatment of ED	Irinotecan and carboplatin followed by sunitinib	34	7.6 (TTP)	Early assessment of activity is encouraging
Rudin CM *et al* (54)	Relapsed	ABT-263 alone	39	Ongoing	Acceptable safety
Langer CJ *et al* (55)	ED	Carboplatin and etoposide with or without obatoclax	155	10.6 vs. 9.9	A trend for improved OS
Heist RS *et al* (56)	Relapsed or refractory	AT-101 combined with topotecan	36	Ongoing	Warrant to further study

SCLC, small cell lung cancer; EGFR, epidermal growth factor receptor; ED, extensive-stage disease; PFS, progression-free survival; OS, overall survival.

was closely associated with the induction of immunological response to vaccination. This study provides clinical support for an emerging paradigm in cancer immunotherapy, wherein the optimal use of vaccination may be more effective, not as a separate modality, but in direct combination with chemotherapy (61).

Bec2. Bec2 is an anti-idiotypic antibody that mimics GD3, a ganglioside that is expressed on the surface of tumor cells and is of neuroectodermal origin. A phase III study evaluated adjuvant vaccination with Bec2/bacille Calmette-Guerin in responsive patients with LD SCLC. Patients were randomly assigned to receive five vaccinations of Bec2 (2.5 mg)/BCG vaccine or follow-up. The vaccination was administered over a 10-week period. A total of 515 patients were randomly assigned. The primary toxicities of vaccination were transient skin ulcerations and mild flu-like symptoms. There was no improvement in survival, PFS or quality of life in the vaccination arm. The MST from randomization was 16.4 and 14.3 months in the observation and vaccination arms (P=0.28), respectively. Of the vaccinated patients, a trend toward prolonged survival was observed in those (one-third) who developed a humoral response (P=0.085) (62). Quality of life and symptom scores between the two treatment arms were not statistically different at any time (63).

6. Discussion

Targeted therapy drugs are widely used in NSCLC, but there are no targeted drugs approved for use in SCLC. Despite a number of clinical trials investigating SCLC, most of the trials yielded negative results (Tables I, II and III). Imatinib did not demonstrate clinical efficiency even in patients with c-kit expression, and the incidence of c-kit mutations in exons 9 and 11 was low. Vandetanib failed to demonstrate efficacy as a maintenance therapy for SCLC and cediranib failed to demonstrate objective responses in recurrent or refractory SCLC. The maintenance of sunitinib was well tolerated following

platinum doublet chemotherapy as first-line treatment for ED SCLC, but did not demonstrate efficiency in relapsed or refractory SCLC. The combination of chemotherapy and sunitinib caused prolonged neutropenia and an unacceptable rate of treatment-related mortality, so it is not recommended. MMP inhibitors, including marimastat and BAY 12-9566, did not improve survival in SCLC. The combination of G3139 and chemotherapy did not improve any clinical outcome. BI 2536 and R115777 should not be assessed further as a single agent in SCLC.

Despite the low incidence of EGFR exon 19 or 21 mutation, an EGFR tyrosine kinase inhibitor may be effective for SCLC patients with EGFR exon 19 or 21 mutation. The biopsy taken for diagnosis may not accurately reflect the molecular features of SCLC, so more attention should be paid to the molecular mechanisms of SCLC. Further research should be undertaken to evaluate the feasibility of gefitinib in SCLC with EGFR exon 19 or 21 mutations. Angiogenesis may play an important role in SCLC and the results for thalidomide and bevacizumab are promising and need further clinical trials to evaluate efficiency and safety. Further study is warranted in sorafenib or NGR-hTNF in combination with chemotherapy. Further clinical trials concerning Bcl-2 inhibitors ABT-263, obatoclax and AT-101 are ongoing (54-56). Everolimus had limited single-agent antitumor activity in unselected previously treated patients with relapsed SCLC, and further evaluation in combination regimens for patients with sensitive relapsed SCLC may be considered. Further study of a vaccine is warranted.

It is important to seek effective targeted therapies to treat SCLC. Some patterns of gene expression or mutations may render targeted therapies for SCLC invalid. It is useful to classify SCLC by targeted genes. One targeted drug cannot be effective in all SCLC patients, while it may be effective in patients with a specific gene expression pattern or mutation. The low expression or mutation of a gene may have caused the negative results of some clinical trials. We should select suitable SCLC patients in further clinical trials by characterizing the targeted gene and the results of previous clinical trials including the promising results from subgroup analysis. Despite no targeted drugs being approved for use in SCLC, the results of trials on gefitinib, bevacizumab and Bcl-2 inhibitors are promising.

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