Treatment options for relapsed small-cell lung cancer

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Small-cell lung cancer is a chemo-sensitive disease with a response rate ranging from 70 to 90% for first-line treatment; however, relapses are very common and as a result long-term survival is poor. Chemotherapy has demonstrated a benefit over the best supportive care, even in patients who have relapsed after initial treatment with a platinum-based regimen. Agents currently being used in salvage therapy include topotecan, cyclophosphamide, doxorubicin and vincristine regimen. In the last 5 years, several drugs have shown promise in initial evaluation; however, randomized phase III trials would be needed to answer this question. Our understanding of the biology of small-cell lung cancer has improved dramatically over the past few years and this has translated into the developments of new therapeutic targets for this disease. Agents affecting several targets, including bcl-2, matrix metalloproteinases, epidermal growth factors and angiogenesis, are being studied currently and have the potential to change the treatment paradigms of this otherwise fatal malignancy. This review focuses on the various current and future options, including cytoxic and targeted agents, for salvage therapy in patients with this disease. *Anti-Cancer Drugs* 18:255–261 © 2007 Lippincott Williams & Wilkins.

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Introduction

Small-cell lung cancer (SCLC) represents approximately 15% of lung cancer, which is the leading cause of cancer-related death in the world [1]. In spite of being an extremely chemo-sensitive tumor with a high response rate, the vast majority of patients (> 90%) die from their disease within 2 years [2].

Chemotherapy has been shown to improve survival even in extensive-stage SCLC [3]. Combination chemotherapy [cyclophosphamide, doxorubicin and vincristine (CAV)] was found to be superior to single-agent chemotherapy and became the standard of care in the 1980s [4]. The introduction of etoposide and the subsequent proven advantage of the etoposide/cisplatin (EP) regimen over the CAV regimen led to a generalized acceptance of EP as the standard first-line therapy in patients with SCLC [5–7]. Despite the excellent response rates seen with EP, relapse rates are high and many of these patients are candidates for second-line treatment [6]. The factors predicting response to the second-line treatment include performance status, whether the disease is relapsed or refractory to first-line therapy and the extent of the tumor (limited vs. extensive stage) [8,9].

In this review, we will discuss the different treatment options for patients with relapsed or refractory SCLC in addition to the role of targeted therapy and future directions.

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Cytotoxic chemotherapy for relapsed/refractory small cell lung cancer

Anthracyclines

Doxorubicin/epirubicin

CAV or CEV (cyclophosphamide, epirubicin and vincristine) was commonly used in treatment-naïve patients with SCLC before the development of the platinum–etoposide combination [6]. Although EP was shown to be superior to CEV in limited stage disease (LD) in terms of median survival (14.5 vs. 9.7 months; $P = 0.001$) and 2- and 5-year survival (25 and 10% vs. 8 and 3%; $P = 0.0001$), there were no significant survival differences between both regimens in the setting of extensive stage disease (ED) [7]. Thus, this combination was tried in patients who had failed the platinum–etoposide regimen. Phase II data in patients with relapsed/refractory disease, using CAV, have suggested a 13–30% response rate, depending on whether the disease was chemosensitive or not [10,11]. Interestingly, patients with a primary refractory disease and who were crossed over to the alternative regimens, were more likely to respond to EP than to CAV. Although the response rates have been higher with EP compared with CAV (15–23 vs. 8%), no differences on overall survival have been reported even in this setting [6,12]. Given this modest activity in patients with relapsed/refractory disease, and the potential for cardiotoxicity in older patients [13], the search for better and safer regimens is underway.

Topoisomerase I inhibitors

Topotecan

Topotecan is a water-soluble, semisynthetic derivative of camptothecin that has demonstrated antitumor activity in both chemosensitive and chemoresistant SCLC [14,15]. The major toxicity of topotecan includes myelosuppression.

The efficacy and safety of topotecan in patients with recurrent SCLC has been demonstrated in several multicenter studies. In these early studies, topotecan was administered intravenously (i.v.) at a dose of 1.5 mg/m^2 daily for the first 5 days of a 21-day cycle. These studies demonstrated the efficacy of topotecan in patients with both chemosensitive and refractory disease. Chemosensitive patients had response rates ranging from 14 to 38%, with an additional 16–31% of patients showing evidence of stable disease. Median survival in these studies was 25–36 weeks. Response rates in patients with chemorefractory disease were lower at 2–7%, with stable disease being seen in 5–40% of patients. The median overall survival in this group of patients was 16–21 weeks [14–17].

In a randomized phase III multicenter study, 210 patients with SCLC, who had relapsed at least 60 days after completion of first-line therapy, were randomized to receive either CAV or topotecan [15]. Both CAV and topotecan demonstrated similar response rates (18.3 vs. 24.3%), time to progression (TTP) (12.3 vs. 13.3 weeks) and median survival (24.7 vs. 25 weeks). Patients randomized to topotecan, however, experienced greater symptom control as regards dyspnea, anorexia, hoarseness, fatigue and decreased interference with daily activities ($P < 0.044$). As far as other toxicities were concerned, severe neutropenia was significantly less common with topotecan (38 vs. 51%), but severe thrombocytopenia (9.8 vs. 1.4%) and anemia occurred more frequently (17.7 vs. 7.2%) than with CAV.

Topotecan combinations have been tried in the salvage setting, but toxicity concerns have tempered their use in these patients. The European Organization for Research and Treatment of Cancer (EORTC) combined topotecan and cisplatin in a phase II trial of 110 patients [18]. Sixty-one percent of patients had a chemo-sensitive relapse; 43 and 87%, respectively, had received platinum and etoposide previously. Patients with a chemo-resistant relapse demonstrated a response rate of 24% (95% confidence interval, 12.1–39.4%); however, toxicity was considerable with more than half of the patients developing grade 4 neutropenia and/or thrombocytopenia.

To decrease the myelotoxicity associated with the standard dosage schedule of topotecan (1.5 mg/m^2 daily intravenous infusion for 5 consecutive days), a better toxicity profile was witnessed with the weekly administration at a dose of 4 mg/m^2 [19] and the use of the oral preparation [17].

Irinotecan

Irinotecan inhibits the activity of the enzyme topoisomerase I, which relieves torsional strain during DNA replication, by inducing reversible single-strand breaks [20]. Irinotecan binds to the topoisomerase I–DNA complex and interacts with the replication, thereby arresting DNA replication and leading to lethal double-stranded DNA breaks [21]. The activity of irinotecan has been demonstrated in preclinical studies in a variety of mouse tumors and human tumor xenografts, including drug-resistant tumors [22,23].

The initial studies conducted in Japan showed response rates of 47% following therapy with single-agent irinotecan in patients who were refractory to cisplatin and etoposide [24,25]. The addition of cisplatin to irinotecan demonstrated superiority over the standard EP regimen in the first-line setting in a Japanese phase III trial [26]. Data from Germany [27] showed similar results, with a longer progression-free survival with irinotecan and carboplatin compared with etoposide and carboplatin (9 vs. 6 months). Data from the United States Intergroup study, however, failed to confirm this survival advantage for irinotecan–cisplatin over EP in treatment-naïve patients [28].

The role of irinotecan combinations in the treatment of relapsed/refractory patients is currently being evaluated. In a multi-center phase II study, Agelaki *et al.* [29] treated 31 patients with refractory or relapsed SCLC using a combination of irinotecan and gemcitabine. They noted partial responses in three patients (overall response rate of 10%) and stable disease in seven patients (22%). Toxicities were tolerable and there were no toxic deaths. Ando *et al.* [30] evaluated the combination of cisplatin and weekly irinotecan in 25 patients who had previously failed EP. They found that this combination was active with a partial response rate of 80% and median TTP and median survival of 3.6 and 7.9 months, respectively. The regimen was well tolerated with the major toxicity being myelosuppresion.

Taxanes

In preclinical models, response to paclitaxel has been observed in tumors known to have p53 mutations [31]. In breast cancer, a normal P53 status was shown to be associated with resistance to paclitaxel, whereas response was supported by deficient p53 [32]. As mutated p53 is among the commonest molecular mutations seen in SCLC, the correlation between p53 mutation and response to paclitaxel might serve in optimizing the use of paclitaxel in this setting.

Addition of paclitaxel to EP has been shown to be associated with improved survival in patients with LD [33], and although this improvement was not seen in patients with extensive disease [34], it was sufficient to evince interest in its role in the relapsed/refractory setting. In a phase II study, Groen *et al.* [35] treated 35 patients, refractory to cyclophosphamide, doxorubicin and etoposide, with paclitaxel 175 mg/m^2 and carboplatin AUC 7 once every 3 weeks for five cycles. Of the 34 patients who were assessable for response, they noted a complete response in two patients and partial response in 23 patients (overall response rate 73.5%). One-year survival was 9% and toxicities were tolerable.

In another similar study, 32 patients who were refractory to first-line therapy with either CAV or EP were treated with a combination of paclitaxel (200 mg/m^2) on day 1 and carboplatin AUC 5 on day 2 repeated every 4 weeks [36]. Of the 29 patients evaluable for response, responses were seen in eight patients (one complete response and seven partial response) for an overall response rate of 25%. In addition, seven (22%) patients had stable disease. The median duration of response and the median TTP were 3 and 5.5 months, respectively, and the median overall survival was 7 months. Grade 3–4 neutropenia was observed in 12 (37%) patients but there were no toxic deaths. The results of these two studies would suggest that patients refractory to front-line therapy could still benefit from a second-line regimen comprising paclitaxel.

In contrast, the results with the other taxane commonly used, docetaxel have been disappointing. Two studies combined docetaxel with gemcitabine with no responses [37,38]. The reason for the difference in responses between paclitaxel and docetaxel is unclear, although one of the reasons could be the absence of a platinum agent in the docetaxel combinations studied.

Cytotoxic agents under investigation

Amrubicin

Amrubicin (SM-5887) is a totally synthetic anthracycline and a potent topoisomerase II inhibitor. Amrubicin is converted into an active metabolite, amrubicinol, which is selectively distributed in tumor tissue. Amrubicinol is 10–100 times more cytotoxic than amrubicin [39], and may be responsible for the superior antitumor activity of amrubicin compared with doxorubicin in animal and preclinical studies [40,41]. Furthermore, the cardiotoxicity in preclinical studies seemed to be milder with amrubicin compared with doxorubicin [42].

Early studies with amrubicin have demonstrated excellent response rates. In a phase I–II study of seven patients with extensive stage SCLC treated with cisplatin and amrubicin, Ohe *et al.* [43] demonstrated a response rate of 88%, median survival of 13.6 months and a 1-year overall survival of 56%. Two recent phase II trials evaluated the role of amrubicin in patients with relapsed or refractory SCLC. The results of both these studies were similar, with response rates of approximately 50% and median survival ranging from 8.8 to 11.7 months [44,45]. The dose-limiting toxicity seen in these studies was myelosuppresion, seen in more than 75% of patients.

BAY 38-3441

This compound is a topoisomerase I inhibitor that has a peptide–carbohydrate moiety attached to the camptothecin (CPT) toxophore [46]. The main difference between BAY 38-3441 and other topoisomerase I inhibitors like topotecan and irinotecan is its increased water solubility and stability of the CPT lactone ring, which is essential for topoisomerase I inhibition. Clinical activity of the topoisomerase I inhibitors seems to correlate with the level of CPT lactone present in human serum [47]. In humans, irinotecan and topotecan undergo nonenzymatic hydrolysis of the lactone ring to generate an open-ring hydroxyl carboxylic acid, which is at least 10-fold less active as an inhibitor for topoisomerase I [48]. As BAY 38-3441 has a more stable lactone ring, it may have a superior efficacy compared with topotecan and irinotecan.

In animal models, BAY 38-3441 caused $\log_{10}$ cell kill and tumor growth delays that were more than double than those of topotecan in the MX-1 mammary tumor model. Phase I data have shown that renal toxicity is the dose-limiting toxicity of BAY 38-3441. The recommended dose for this compound is a 3-day schedule of 320 mg/m^2/day as 30-min infusions [49].

Targeted therapy

We seem to have reached a plateau as far as the beneficial effects of cytotoxic chemotherapy on overall survival is concerned. Our increasing knowledge and understanding of the molecular biology and immunology of SCLC is leading to studies of more targeted therapies for this disease. Although none of these have yet demonstrated survival benefit in patients with SCLC, it is hoped that these agents, in combination with the conventional cytotoxic agents, will lead to future breakthroughs that will eventually result in improved outcomes from SCLC.

c-Kit

Almost one-third of the patients with ED SCLC have a c-kit overexpression by immunohistochemistry [50,51]. With this background, Johnson *et al.* [52] enrolled 19 patients with extensive disease, who were either treatment-naïve or had a chemo-sensitive relapse in a phase II trial using imatinib 600 mg daily for 1 year. Although imatinib did not demonstrate any activity in this group of patients, a major drawback of this study was that 79% of the enrolled patients lacked c-kit expression. The Cancer and Leukemia Group B refined this study design and

conducted a similar trial [53] using imatinib mesylate at a dose of 400 mg twice daily, now, in patients with c-kit overexpression. Despite the selection of patients who demonstrated the c-kit overexpression, the results were similar to those obtained by Johnson *et al.* [52], with no observed responses and only one patient with stable disease for 31 weeks. One of the proposed reasons for the inactivity of imatinib in SCLC was that the putative cells of the origin of SCLC are not developmentally dependent on c-kit [54], as opposed to cells like mast cells, germ cells and hematopoietic stem cells, which depend on the normal activity of the stem cell factor/KIT axis for development.

Bcl-2

The oncogene bcl-2 plays a major role in suppressing apoptosis, and thus, in inhibiting responses to therapy [55]. Therefore, suppression of bcl-2 in tumors in which it is expressed may increase therapeutic efficacy [56]. Bcl-2 is expressed in 83–90% of SCLC [57] and thus represents a potential therapeutic target in this disease.

G3139, or oblimersen, is an 18-base antisense phosphorothioate oligonucleotide complementary to the bcl-2 mRNA in the region encoding the first six amino acids of bcl-2 [58]. Preclinical and clinical studies have demonstrated that intravenous administered G3139 can be taken up by tumor cells and can result in the reduction of bcl-2 protein production [59]. The combination of oblimersen and paclitaxel was tested in a small trial enrolling 12 patients with chemo-refractory SCLC [60]. No objective responses were found, but four patients experienced stable disease. The low yield of this small study was attributed to the relatively low doses of both agents. The dose of oblimersen chosen may have been insufficient to suppress the expression of the target gene bcl-2, and paclitaxel was given at a dose of 150 mg/m^2 every 3 weeks, which is clearly below that routinely used.

Antisense inhibition of bcl-2 expression may increase the therapeutic efficacy of cytotoxic agents and hence may be more beneficial in a chemo-responsive setting, rather than a chemo-refractory one. On the basis of this hypothesis, Rudin *et al.* [61] conducted a trial testing the role of oblimersen as first-line treatment in combination with etoposide and carboplatin. Sixteen patients with extensive stage SCLC received oblimersen, carboplatin and etoposide. This combination yielded promising results with reasonable toxicity. The CALGB is currently conducting a trial comparing EP to EP with oblimersen in ED to define an exact role for this molecule.

Matrix metalloproteinase inhibitors

Matrix metalloproteinases (MMPs) are involved in extracellular membrane degradation [62], which is a key process that enables the cancer cell to metastasize. Therefore, use of protease inhibitors to limit extracellular matrix proteolysis by malignant cells and thereby interfere with tumor cell invasion would be an attractive therapeutic target. In SCLC, elevated expression of MMP has been identified as a negative predictor of survival [63]. In a retrospective analysis, Michael *et al.* [63] demonstrated the tumor expression for MMP-11 and MMP-14 was an independent negative prognostic factor for survival.

Marimastat, a synthetic orally administrated inhibitor of MMPs, is a broad-spectrum MMPI with activity against collagenases, gelatinases and stromolysins [64]. The National Cancer Institute of Canada–Clinical Trials Group and the EORTC conducted a randomized placebo-controlled trial of marimastat in 532 patients with SCLC who had responded to first-line chemotherapy [65]. The addition of marimastat after induction chemotherapy did not result in improved survival and had a negative impact on the quality of life. One of the reasons for these disappointing results may be patient selection, as MMP expression was not studied in these patients. Another possibility would be the broad-spectrum activity of marimastat. Given the results of Michael *et al.* [63], in which the proteinases MMP11 and MMP14 were expressed, a more selective MMPI targeting these two proteins would arguably be more beneficial.

Epidermal growth factor receptor family

Epidermal growth factor receptor (EGFR) is overexpressed in nonsmall-cell lung cancer in approximately 40–80% of patients and may represent a factor predicting for metastatic spread [66,67]. In contrast to nonsmall-cell lung cancer, although EGFR expression has been reported to be low in SCLC, gefitinib, an oral EGFR tyrosine kinase (TK) inhibitor, has been shown to inhibit EGFR signaling in SCLC cell lines [68]. Anecdotal evidence has suggested tumor regression in patients with extensive stage SCLC following treatment with gefitinib [69,70]. This would suggest a potential role for gefitinib and other agents targeting the EGFR pathway in this disease.

HER-2/*neu* expression in SCLC has been less well studied. Studies have demonstrated overexpression of HER-2/*neu* by immunohistochemistry, in approximately 13–30% of patients with extensive stage SCLC [71–73]. These studies also found that HER-2/*neu* expression was associated with a poor prognosis for patients with advanced disease. On the basis of these findings, the antiHER-2/*neu* monoclonal antibody trastuzumab may be useful as a therapeutic agent in SCLC.

Vaccines

Ganglioside (GD3) is a cell surface glycosphingolipid antigen with limited expression in normal tissues, being

largely restricted to cells of neuroectodermal origin and to a subset of T lymphocytes [74]. Studies on SCLC cell lines, however, suggest that these cell lines may express significant levels of GD3. The antiidiotypic antibody BEC-2, which mimics the structure of the GD3 ganglioside, showed promising results in a pilot study [74]. On the basis of these results, the EORTC performed a randomized phase III study in 515 patients with LD-SCLC, who were randomized to receive BEC-2 or not as a maintenance following standard induction chemotherapy [75]. Although there was no improvement in survival, progression-free survival or quality of life in the vaccination arm, there was a trend towards prolonged survival in patients who developed a humoral response. The authors concluded that vaccination strategies may be warranted with vaccines that were more potent in inducing a humoral immune response.

Another approach towards vaccination therapy is to target p53. Mutations in the p53 have been demonstrated in approximately 90% of patients with SCLC [76,77]. Wild-type p53 protein is present in very low levels in normal cells, whereas mutant p53 is present in much greater quantities in tumor cells because of its prolonged half-life. This differential expression between normal and tumor cells could provide a basis for vaccine therapy. Antonia *et al.* [78] conducted a study on 29 patients with extensive stage SCLC, who were vaccinated with a vaccine consisting of dendritic cells transduced with the full-length wild-type p53 gene delivered via an adenoviral vector. In this study, although only one patient showed a clinical response, there was a high rate of objective clinical responses to chemotherapy (61.9%) that immediately followed vaccination. This clinical response to subsequent chemotherapy was closely associated with the induction of immunologic response to vaccination. Hence, it is likely that vaccine therapy would serve as an adjunct to chemotherapy, rather than a primary treatment modality in this setting.

Vascular endothelial growth factor

Vascular endothelial growth factor (VEGF) is a key factor in the development of new blood vessels that increases the permeability of microvessels [79]. It promotes angiogenesis by increasing vascular permeability and stimulating endothelial cell division. VEGF-TK inhibitors have been shown to inhibit downstream signaling pathways that are activated following ligand binding to the VEGF receptor. Multiple agents with VEGF-TK inhibitory activity are being tested for their utility in therapy for various malignancies. A number of small molecules that inhibit VEGF-TKs are in development, including ZD6474, PTK787/ZKI222584 (vatalanib), AZD2171, BAY 43-9006 (sorafenib), SU11248 (sunitinib) and AMG706 [80]. Trials incorporating SU11248, a multi-targeted TK inhibitor, are currently being planned in SCLC.

Other targets

Transforming growth factor-β (TGF-β) has been shown to have a complex but definite role in mediating or regulating several events that occur virtually in all human cancers [81]. These include resistance to growth inhibitory factors, proliferation in the absence of exogenous growth factors, invasion and metastasis, limitless replication potential, evasion of apoptosis, recruitment of blood supply through angiogenesis, and finally evasion of destruction by the immune system. In SCLC, resistance to the growth inhibitory effects of TGF-β have been shown to be mediated through decreased or absence of TGF-β receptor II [82]. Therefore, increasing receptor expression could serve as a potential target for the tumor. The ubiquitin/proteasome pathway represents one of the models having a role in regulating TGF-β receptor expression and therefore proteasome inhibitors such as bortezomib might have a potential role in treating SCLC [83].

Conclusions

The treatment of relapsed or refractory SCLC has mainly revolved around second-line cytotoxic chemotherapy. Our understanding of the molecular pathways that regulate the development of this malignancy has increased tremendously in the past decade. Novel therapeutic agents including various combinations of cytotoxic agents, targeted agents and immunologic strategies hold the promise of improving outcomes in this disease.

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