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NEW AND EMERGING DEVELOPMENTS IN EXTENSIVE STAGE SMALL CELL LUNG CANCER THERAPEUTICS

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Abstract

Purpose of review—Extensive-stage small cell lung cancer (SCLC) remains a disease with a dismal prognosis, with median survival of approximately 8–10 months. Despite many attempts to develop effective systemic therapies, very little progress has been made in the last several decades. Platinum-based combination chemotherapy remains the standard of care in the first-line setting and is associated with high response rates albeit short-lived. However, there have been advances in the use of radiation therapy, as well as new insights into the biology of SCLC recently.

Recent findings—Some of the most appreciable advances in the last decade have involved the use of local radiation therapy. With the use of new laboratory techniques such as genomic sequencing, there remains promise of rationally targeted drug development. Circulating tumor cell research may also provide insights to SCLC biology and further refine treatment.

Summary—Systemic therapy for SCLC has changed little over the past 30 years with the most significant advances in extensive-stage small cell lung cancer relating to radiotherapy. The effectiveness of prophylactic cranial irradiation and thoracic radiation therapy has renewed interest in therapeutics focused on the modulation of DNA damage or repair. Recent developments in genomic sequencing and immunotherapy may translate to new treatment paradigms for SCLC.

Keywords

genomic sequencing; prophylactic cranial irradiation; small-cell lung cancer

Introduction

Small-cell lung cancer (SCLC) is a virulent malignancy characterized by rapid cellular proliferation, genomic instability, and a predisposition for distant metastatic spread. While SCLC presently accounts for only 10–15% of all lung cancers, it is still responsible for up to 40,000 deaths annually. In the last three decades, the standard for systemic therapy in extensive stage SCLC (ES-SCLC) has remained unchanged. Over that time period, the median survival time for patients with ES-SCLC has remained approximately the same (i.e.,

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8–10 months). It is clear that this is a clinical context of great unmet need and that new treatments are needed. Herein, an update of the most recent developments in SCLC therapeutics is provided, including new targeted and immunotherapeutic approaches that hold promise towards improving outcomes in this disease.

Frontline Therapy

The chemosensitivity of SCLC has been established since methyl-bis-β-chloroethyl amine hydrochloride was recognized to cause tumor regression over 50 years ago[1]. The combination of etoposide with a platinum-based agent, the current standard of care of treatment for ES-SCLC, was first reported to have high response rates in the 1980s[2–4]. Unfortunately, these responses are often short-lived and subsequently the development of chemotherapy resistance is universal. Multiple studies have been conducted to evaluate alternative first-line combination chemotherapy regimens - all of which have sufficiently failed to advance the standard of care.

Initially encouraging results were reported in a Japanese Phase III study comparing etoposide plus cisplatin (EP) to cisplatin and the topoisomerase I inhibitor irinotecan (IP) in 2002[5]. In that trial (Japan Clinical Oncology Group [JCOG] 9511) of only 174 patients, tumor response and patient survival time were significantly higher in the IP group at the initial interim analysis, prompting termination of further accrual. Since this study was done with a limited patient size and in a solely Japanese population, a separate Phase III trial by the Southwest Oncology Group (SWOG 0124) was conducted; this trial closely modeled JCOG 9511 with similar eligibility criteria and treatment parameters[6]. With a trial size of 651 eligible patients, median overall survival for IP and EP was 9.9 and 9.1 months (p=0.71). Thus, this trial demonstrated that EP remains the standard of care for patients with extensive stage disease, at least for non-Japanese (or more accurately, North American) populations. Of note, pre-planned pharmacogenomic studies established that ABCB1 and UGT1A1 were associated with higher irinotecan-related GI toxicity and neutropenia, respectively.

Maintenance Therapy in Extensive Stage SCLC

Since responses to front-line chemotherapy have been short-lived, the role of maintenance therapy in patients with ES-SCLC has also been studied. Historically, an active agent has not been identified in this setting. The mTOR inhibitor temsirolimus was studied in a randomized Phase II trial of 85 patients who had responding or stable disease after induction chemotherapy- this ECOG (E1500) trial failed to show an increase in PFS when temsirolimus was given at a dose of either 25 or 250 mg weekly[7]. Thalidomide was also studied in a small Phase II study of 30 patients with ES-SCLC who had received induction chemotherapy without disease progression; in this limited study, there was a suggestion of benefit, prompting further investigation into anti-angiogenic agents[8]. Vandetinib, a VEGF/EGFR inhibitor, was studied in a randomized Phase II Canadian trial (BR.20) in patients who had a complete or partial response to induction chemotherapy; this trial failed to show a benefit in progression free survival or overall survival for the addition of vandetanib as maintenance[9]. Most recently, a phase II CALGB trial (C30504) evaluated patients with

untreated ES-SCLC, who received etoposide with cisplatin or carboplatin for four to six cycles. Patients without progression were randomized to receive sunitinib (37.5 mg PO once daily) or placebo, with crossover permitted upon progression[10]. Of 138 patients who received chemotherapy, 85 went on to receive either sunitinib or placebo, with median PFS on maintenance of 3.7 months with sunitinib and 2.1 months with placebo (HR: 1.62, 70% CI, 1.27–2.08, one-sided p= 0.02). Median overall survival did not meet statistical significance, however.

Another drug studied in the maintenance setting is saracatinib, a Src-kinase inhibitor. In the Phase II NCCTG trial N-0621, patients were to be enrolled for treatment with saracatinib if they had stable disease or better after 4 cycles of platinum-based chemotherapy[11]. A pre-planned analysis failed to meet PFS endpoint to continue the trial to expansion.

Thus, the body of evidence currently available strongly suggests that an effective maintenance regimen in ES-SCLC is yet to be established.

Radiation Therapy in Extensive Stage SCLC

Perhaps the most important breakthrough of the last decade regarding treatment of ES-SCLC has been the use of prophylactic cranial irradiation (PCI). In a randomized study reported by Slotman et al, patients with ES-SCLC who had a response to systemic chemotherapy underwent either 5–12 fractions of 20–30 Gy PCI or no further therapy[12]. Patients were randomized within 5 weeks of completion of chemotherapy and required to have no evidence of brain or leptomeningeal metastases. Various schedules of PCI were permitted in the trial, with four to five fractions delivered in a week, and biologically equivalent doses ranging from 25 to 39 Gy. Patients randomized to the PCI group were at lower risk of symptomatic brain metastases (HR: 0.27, 95% CI 0.16–0.44, p <0.001), which was the primary endpoint of the trial. Overall survival, a secondary endpoint of the trial, showed an improvement with PCI (6.7 months) vs observation (5.4 months, HR: 0.68, 95% CI: 0.52–0.88, p=0.0003). Disease free survival at six months with PCI was 23.4% vs 15.5% with observation alone. This trial established PCI as standard of care for patients with ES-SCLC with response to frontline platinum-based chemotherapy.

Some concerns have been raised recently regarding the use of PCI in this trial. For example, MRI scanning to evaluate for brain metastases was not required prior to enrollment in the trial. Furthermore, there were variations in radiation doses and schedules and in the induction chemotherapy regimens, including regimens which were non-platinum-based. To address these issues, another Phase III trial was conducted in Japan, reported by Seto et al in abstract form in 2014[13]. In this study, 163 patients were enrolled. Patients were randomized to receive PCI with a pre-defined dose-schedule of 25 Gy in 10 fractions versus observation. The study was stopped early for futility, as it failed to demonstrate a benefit in overall survival for the PCI arm. In fact, median overall survival was 10.1 (95% CI 8.5–13.2) months with PCI vs 15.1 months (95% CI 10.2–18.7) with observation alone (HR 1.38, 95% CI 0.95–2.02), though this difference was not statistically significant. PCI did significantly reduce the risk of development of brain metastases compared to observation alone (32.4% v 38% at 12 months, p <0.001). No statistically significant differences in AEs greater than 2 in

either group were noted. This study does bring some questions as to the standard use of PCI in the treatment of ES-SCLC after induction chemotherapy (see Table 1). However, as the study was conducted exclusively in Japan, the generalizability of the trial remains unclear. The final published report of this trial is eagerly awaited.

The efficacy that has been suggested with PCI led to investigation of the benefit of including thoracic radiation therapy in a consolidative manner after induction chemotherapy. In a randomized Phase III European study called CREST, patients with ES-SCLC were randomized to receive either consolidative thoracic radiotherapy (TRT) or no thoracic radiotherapy[14]. In this trial, 495 patients with ES-SCLC with any response after four to six cycles of platinum-etoposide chemotherapy were randomized to receive 30 Gy of TRT in ten fractions or no TRT within 6 weeks of chemotherapy completion. All patients in the study received PCI. While the primary endpoint, overall survival at 1 year, did not show a statistically significant difference between the two groups, a secondary planned analysis of overall survival at 2 years was performed. This showed a 2-year overall survival of 13% (95% CI 9–19) in the TRT group vs 3% (95% CI 2–8; p=004) in the no TRT group. Similarly, the secondary endpoint of progression free survival was better in the TRT group (24%, 95% CI 19–30) than no thoracic RT group (7%, 95% CI 4–11; p=0.001). Furthermore, intrathoracic progression was significantly lower occurring in 43.7% of patients with TRT v 79.8% of patients with no TRT ($p < 0.001$). These results also held true for intrathoracic progression as the first site of relapse (41.7% v 77.8%, $p<0.001$) and as the only site of relapse (19.8% v 46.0%, $p<0.001$). However, the high rates of initial intrathoracic progression in this study may be atypical in the general ES-SCLC population where widespread metastatic disease is often present upon recurrence. There were no severe toxic effects in the study, with the most common Grade 3 or higher adverse effects being fatigue and dyspnea. The results of this study suggest that TRT should be considered with PCI in patients with ES-SCLC, particularly in patients with persistent intrathoracic disease.

It is remarkable that in a systemic disease such as ES-SCLC, the most impressive advances in recent years have been with the use of localized RT (i.e., PCI or consolidative TRT) rather than with systemic therapies. Nevertheless, the positive results seen with RT trials suggest that there are persistent lethal subclones of SCLC that remain sensitive to DNA-damaging therapy. As such, these observations offer the possibility that DNA damage or repair pathways can be further exploited for systemic drug development in SCLC. To that end, veliparib, a PARP inhibitor which prevents single-strand DNA repair, is under investigation in ES-SCLC. A Phase I trial, E2511, has already been completed, demonstrating the safety of combining veliparib with cisplatin and etoposide in previously untreated ES-SCLC[15]. A Phase II study of this combination is underway. Additional studies in ES-SCLC are planned or ongoing with other PARP and ATR inhibitors.

Second-line Therapy and Beyond

Outcomes for patients failing frontline chemotherapy in ES-SCLC remain suboptimal. Overall prognosis is poor in this patient population, with median overall survival time ranging from 2–3 months in the absence of any therapy. Topotecan was established as a standard treatment for relapsed SCLC in 1999 based on a Phase III trial of intravenous

topotecan compared to cyclophosphamide, doxorubicin, and vincristine[16]. Oral topotecan has also been demonstrated to be effective in second-line treatment based on a Phase III trial of a 141 patients with relapsed SCLC not considered candidates for standard IV chemotherapy[17]. Although topotecan is certainly a reasonable option in the previously treated setting, it is widely held that clinical trial enrollment remains the best approach for patients with relapsed SCLC who have acceptable performance status. It has also been widely held that differential outcomes occur following investigational therapy dependent on platinum-sensitivity status. In those who have failed prior platinum-based therapy, one is considered "platinum-sensitive" if progression occurs > 90 days after last platinum dose, and "platinum-refractory" or resistant when progression occurs <90 days after the last platinum dose. While it was previously thought that there were poorer outcomes in patients with platinum-refractory disease, a recent analysis of the Southwest Oncology Group database of second- and/or third-line ES-SCLC patients receiving novel "targeted therapies" challenges this assumption. In this analysis, 329 patients were evaluated, 151 with platinum-sensitive disease and 178 platinum-refractory. In a multivariate model, platinum-sensitivity was not found to be associated with improved progression-free or overall survival. Instead, elevated LDH, weight loss and a performance status of 1 were the baseline variables independently associated with overall survival[18]. These results suggest that in patients receiving investigational, non-cytotoxic therapy in the second-line (and beyond) setting, platinum sensitivity status may no longer be a clinically relevant consideration.

In the past decade, the newer topoisomerase inhibitor amrubicin was also widely investigated as salvage therapy for SCLC, and in fact is approved for use in Japan for relapsed SCLC. This third generation anthracycline was ultimately tested in a global Phase III study that enrolled 637 patients who had progressed after 1st line therapy and then randomized in a 2:1 distribution to amrubicin 40 mg/m2 IV D1-3 or topotecan 1.5 mg/m2 IV D1-5[19]. The primary endpoint was overall survival. There was a suggestion of benefit in progression-free survival, which was 4.1 months in the amrubicin group v 3.6 months in the topotecan group (HR: 0.83, CI: 0.7–0.99, p=0.041). Amrubicin was also found to have a higher response rate when compared to topotecan (31% vs 17%, HR: 2.22, 95% CI: 1.47–3.36, p=0.0002). Disappointingly, the primary endpoint of overall survival did not reach statistical significance in demonstrating benefit to treatment with amrubicin. Interestingly, overall survival in platinum-refractory patients did demonstrate a slight advantage with amrubicin over topotecan (6.2 v 5.7 months, HR: 0.77, 95% CI 0.59–1.0, p=0.047), but this difference was small and part of a subset analysis.

Like topoisomerase inhibitors, temozolomide also creates DNA damage, as a non-classic oral alkylating agent. It has been studied in glioblastoma multiforme, and in that setting, promoter methylation of MGMT, a gene which encodes for a DNA repair protein, predicts response to temozolomide. In a Phase II single arm study of 64 patients with refractory or relapsed small-cell lung cancer, patients were treated with temozolomide 75 mg/m2 PO qdaily D1-21 of a 28-day cycle until progression[20]. The overall response rate for the study was 22% (95% CI, 9–40%) as second-line treatment, and 19% (95% CI, 7–36%) as third-line treatment. 38% of patients with target brain lesions had a complete or partial response (95% CI, 14–68%). There was also a suggestion of better response to therapy in patients with methylated MGMT compared to patients with unmethylated MGMT. A smaller study

of 25 patients with refractory or relapsed small-cell lung cancer evaluating temozolomide in a standard dosing scheduled (75 mg/m2 qdaily for 5 days every 28 days) demonstrated a response rate of 12% (95% CI, 3–31%)[21]. While these results are discouraging, temozolomide combined with the PARP inhibitor, veliparib, is also under investigation in a Phase II study in relapsed or refractory small-cell lung cancer.

Given the use of combination chemotherapy in the front line setting for SCLC, the use of combination therapy in the second-line setting has also been considered. A Japanese Phase III randomized trial of 180 patients with platinum-sensitive SCLC compared the combination of cisplatin, etoposide, irinotecan with single-agent topotecan[22]. Growth factor support was used in the combination arm of the trial. Overall survival, the primary endpoint of the trial, was longer in the combination arm compared to single-agent topotecan (HR=0.67, 90% CI 0.51–0.88, p= 0.0079). Median survival time was 18.2 months for cisplatin, etoposide and irinotecan vs 12.5 months with topotecan alone. However, Grade 3 & 4 AEs were greater with the combination compared to topotecan alone, most notably with anemia (84.4% vs 27.8%), thrombocytopenia (41.1% vs. 27.8%), diarrhea (7.8% vs. 0%) and febrile neutropenia (31.1% vs 6.7%). The generalizability of the trial has not been established given that the trial only enrolled Japanese patients who were highly selected patients, more likely to respond to another platinum-based regimen. This toxicity profile also brings to question the tolerability of this combination in the palliative setting.

Recent Developments in SCLC Therapeutics

Attempts to develop more effective therapies have thus been largely unsuccessful in SCLC. However, there have been promising leads with continued investigation into the genetics of SCLC and the advent of advanced genomic analysis, which have helped to shed more light into the molecular phenotypes associated with SCLC. In preclinical models, inhibiting the expression of Aurora-A genes can prevent cell proliferation and induce G2/M phase arrest in human SCLC lines[23]. This has led to trials evaluating aurora A kinase inhibitors in SCLC, including a Phase I/II trial of alisertib which was recently reported[24]. In this five-arm study, patients were treated with alisertib, an oral Aurora A kinase inhibitor (50 mg PO twice daily for 7 days followed by 14 day break). One of the arms of this study enrolled 60 patients with relapsed or refractory small-cell lung cancer. Of the patients with response-assessable disease with SCLC in the trial, 21% (95% CI, 10–35) had an objective, partial response on therapy. These promising results have prompted a phase II trial in platinum refractory ES-SCLC studying alisertib in combination with paclitaxel due to preclinical synergy observed with the combination.

A study sequencing SCLC exomes, genomes and transcriptomes confirmed the very high mutational burden in SCLC[25]. As expected, TP53 and RB1 were frequently inactivated. Recurrent mutations were also seen in CREBBP, EP300 and MLL genes, all of which encode histone modifiers. This work implicates histone modification as a potential target for future drug development. Indeed, histone deacetylase inhibitors have been pursued as treatments in ES-SCLC; to date, romidepsin failed to demonstrate a benefit in relapsed ES-SCLC in a Phase II trial[26]. However, panobinostat and vorinostat are still under investigation.

Another group of investigators evaluated exome, transcriptome and copy-number alteration data from primary human SCLC and normal tissue pairs, matched small-cell lung cancer with lymphoblastoid cell lines, as well as primary tumors and small-cell lung cancer cell lines[27]. They reported 22 significantly mutated genes involving kinases, G-protein coupled receptors, and chromatin-finding proteins. Among these were several members of the SOX family of genes. In fact, SOX2 amplification was noted in ~27% of samples studied. SOX2 appears to play a critical role in maintaining pluripotency and self-renewal of stem cells. In the study, short hairpin RNA (shRNA) against SOX2 stopped proliferation of cell lines in SOX2-amplified lines, suggesting a potential therapeutic avenue that has not yet been evaluated in clinical trials.

Most recently, clinical data on the clinically actionable nature of delta-like protein 3 (DLL3) were reported[28]. Part of the Notch signaling pathway, DLL3 is important to tumor-initiating cells' biologic function and survival, and is highly expressed in SCLC cells. A novel agent, rovalpituzumab tesirine, an antibody-drug conjugate designed to bind to DLL3, has recently been investigated in a Phase Ia/Ib trial in SCLC. In 29 DLL3-positive patients with SCLC who had progressed after first-line or second-line therapy, 34% of patients had a partial response to therapy and 31% achieved disease stability. The duration of response in patients with a partial response or stable disease was more than 178 days, with no cases of disease progression. Patients had to have sufficient tumor sample to confirm high expression of DLL3, which can be a challenge in SCLC. This drug will need to be studied further, but these early results are quite promising.

Immune checkpoint inhibition is an area of great promise in the treatment of tumors with high mutational burden, and thus it is also a new target of interest in SCLC. Preliminary results from the KEYNOTE-028 trial were recently presented[29]. In this Phase Ib trial, 135 patients with ES-SCLC which had progressed on platinum-based chemotherapy were screened for PD-L1 expression, with 27% testing positive. Ultimately, 17 patients were enrolled and received the PD-1 antibody pembrolizumab leading to 25% of patients with a partial response, 7% with stable disease and a disease control rate of 31%. Responses were durable at >16 weeks, but the trial is still ongoing. The drug-related AE rate was high, however, at 53%, though only 1 patient reportedly had a drug-related AE ≥ Grade 3.

Another area of recent interest is the application of circulating tumor cells (CTCs) in this disease, as the availability of sufficient amounts of tumor tissue for molecular characterization is notoriously poor in SCLC and has hindered the development of targeted therapies. Thus, alternative sources of readily accessible tumor – such as CTCs – would provide a transformational change. In a recent study, blood samples from 97 patients with SCLC receiving chemotherapy were analyzed pre- and post-treatment to quantitate CTCs and circulating tumor microemboli (CTMs)[30]. CTCs are highly prevalent in SCLC and were present in 85% of SCLC patients. Those with ≥ 50 CTCs/7.5 mLs of blood were found to have an overall survival of 5.4 months while overall survival of 11.5 months was noted with patients with < 50 CTCs/7.5 mLs before chemotherapy (HR: 2.45, 95% CI 1.39–4.30, p = 0.002). The presence of CTMs was also an independent prognostic factor, with presence of <1 CTM/7.5 mL of blood correlating with better overall survival compared to ≥ 1 CTMs/7.5 mL. While CTCs did involve apoptotic and proliferating subpopulations, CTMs did not

exhibit these subpopulations. This suggests that the presence of CTCs may guide susceptibility to systemic therapy, whereas the presence of CTMs suggests inherent mechanisms to develop relative resistance to cytotoxic chemotherapy and to evade anoikis.

Conclusion

Systemic therapy for SCLC has changed little over the past 30 years with the most significant advances in extensive-stage small cell lung cancer relating to radiotherapy. The effectiveness of PCI and thoracic RT has led to development of systemic therapies involved in DNA damage or repair. The recent remarkable advances in the treatment of non-small cell lung cancer with targeted therapy and immunotherapy have not translated to similar paradigm shifts in SCLC. However, with recent developments in genomic sequencing and immunotherapy, this may be changing. As these new techniques lead to more insights into SCLC biology, identifying more promising targets, like DLL3 and the Notch pathway, may be possible. Comprehensive molecular and immune analysis, either in tissue or circulating tumor cells, may also be vital to developing effective systemic therapies and improving outcomes for this uniformly fatal disease.

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Key points

- Despite numerous clinical trials and investigations, prognosis remains poor for patients with extensive-stage small-cell lung cancer, with etoposide in combination with a platinum-based agent the standard of care for induction therapy.
- The most promising advances in the last decade in extensive-stage small cell lung cancer involve the use of radiation therapy, with benefits demonstrated with the use of prophylactic cranial irradiation after initial induction chemotherapy. More recently, the use of consolidative thoracic radiation therapy has also conferred significant benefit.
- Recent advances in genomic sequencing as well as further insights into the biology of small-cell lung cancer may translate to identification of actionable targets for new therapies.
- The use of circulating tumor cells may allow a better understanding of the heterogeneity of small-cell lung cancer, and may identify patients likely to respond to therapy.

Table I

Phase III studies evaluating the use of Prophylactic Cranial Irradiation (PCI) in Extensive Stage SCLC

	EORTC (Slotman)	**WJOG (Seto)**
Patient population	• Any response to systemic chemotherapy • No known brain or leptomeningeal metastases	• Any response to platinum-based chemotherapy • MRI-proven absence of brain metastases
N	286	163 (stopped early)
PCI Treatment	• 20 Gy in 5 or 8 fractions • 24 Gy in 12 fractions • 25 Gy in 10 fractions • 30 Gy in 10 or 12 fractions	• 25 Gy in 10 fractions
Primary endpoint	Development of symptomatic brain mets	Overall survival
Results		
Risk of brain metastases (at 12 months) *	14.6% PCI 40.4% control HR: 0.27 (95% CI, 0.16–0.44) p <0.001	32.4% PCI 58% control P<0.001
Median overall survival	6.7 months PCI 5.4 months control HR: 0.68 (95% CI, 0.52–0.88, p = 0.003)	10.1 PCI 15.1 control HR: 1.38 (95% CI, 0.95–2.01, p = 0.0091)
Progression free survival	14.7 weeks PCI 12 weeks control HR: 0.76 (95% CI, 0.59–0.96, p=0.02)	8.8 weeks PCI 9.6 weeks control HR: 1.12 (95% CI, 0.82–1.54)

* Defined as symptomatic brain metastases in EORTC trial, any brain metastases in WJOG trial