Recent developments in the treatment of small cell lung cancer

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Shareable abstract (@ERSpublications)
Advances in radiotherapy, targeted treatment and immunotherapy are limited. Progress in treatment options are needed for the treatment of SCLC. Exome sequencing to identify targetable biomarkers could select patients who would benefit from certain therapies. https://bit.ly/3e7ATJ4

Cite this article as: Hiddinga BI, Raskin J, Janssens A, *et al*. Recent developments in the treatment of small cell lung cancer. *Eur Respir Rev* 2021; 30: 210079 [DOI: 10.1183/16000617.0079-2021].

Received: 29 Dec 2020
Accepted: 27 April 2021

Abstract

Small cell lung cancer (SCLC) comprises about 15% of all lung cancers. It is an aggressive disease, with early metastasis and a poor prognosis. Until recently, SCLC treatment remained relatively unchanged, with chemotherapy remaining the cornerstone of treatment. In this overview we will highlight the recent advances in the field of staging, surgery, radiotherapy and systemic treatment. Nevertheless, the prognosis remains dismal and there is a pressing need for new treatment options. We describe the progress that has been made in systemic treatment by repurposing existing drugs and the addition of targeted treatment. In recent years, immunotherapy entered the clinic with high expectations of its role in the treatment of SCLC. Unravelling of the genomic sequence revealed new possible targets that may act as biomarkers in future treatment of patients with SCLC. Hopefully, in the near future, we will be able to identify patients who may benefit from targeted therapy or immunotherapy to improve prognoses.

Introduction

Small cell lung cancer (SCLC) is an extremely aggressive tumour type which accounts for about 15% of lung cancer cases [1, 2]. The cancer originates from neuroendocrine precursor cells and is characterised by its rapid growth and early metastasis, with more than 70% of patients presenting with metastasised disease [3]. Approximately 10–25% of patients have brain metastases at initial diagnosis, and an additional 40–50% will develop them during the course of their disease [3]. First-line treatment in metastatic SCLC consists of a combination of platinum and etoposide [4]. However, the majority of patients experience relapse within the first year of treatment, resulting in poor survival. Several agents or addition of a third drug have failed to show any improvement in outcomes. Even for patients without metastases at diagnosis, the curation rate remains low. Therefore, there is a high unmet need for therapies that could improve survival in patients with SCLC. The guidelines of the European Society of Medical Oncology (ESMO) and the American College of Chest Physicians (ACCP) endorsed by the American Society of Clinical Oncology (ASCO) have not been updated since 2013 [1, 5]. In this manuscript we will address the recent progress achieved in the field of staging, surgery, radiotherapy and systemic treatment, such as immunotherapy, since the landmark reviews published in the beginning of last decade [6, 7].

Eighth tumour-node-metastasis classification

The prognosis of SCLC depends on the tumour stage. Previously, the classifications limited disease (LD-SCLC) and extensive disease (ED-SCLC) were used, where limited disease was defined as disease confined to the ipsilateral hemithorax, which can safely be encompassed within a single radiation field [8]. The Union for International Cancer Control (UICC) tumour-node-metastasis (TNM) staging system was developed for nonsmall cell lung cancer (NSCLC), and edition 8 uses tumour size and the number of metastases and affected organs to estimate prognoses for the different stages of this disease [9]. In clinical

practice, as well as in clinical trials, the distinction between LD-SCLC and ED-SCLC is still useful when deciding on a treatment plan.

Surgery in very limited SCLC

Surgery in SCLC is not widely accepted but can be considered for very small biopsy-proven tumours (very limited disease), cT1N0M0, with confirmed negative mediastinal staging. Most commonly, a surgically removed lung nodule of unknown origin turns out to be a small SCLC. In a systematic review, surgery was not supported in limited SCLC [10]. In several series data about correct staging and adjuvant therapy was unclear. Invasive mediastinal staging is mandatory. There is a tendency towards offering surgery for very small SCLC with negative lymph nodes, but concurrent chemoradiation is an alternative choice. Data about adjuvant radiotherapy and adjuvant chemotherapy are insufficient to offer strong recommendations [1]. Prospective studies are needed to define the role of surgery and adjuvant treatment of very small SCLC.

Radiotherapy in LD-SCLC

For LD-SCLC, which represents around 30% of newly diagnosed SCLC, the standard treatment with curative intent consists of four cycles of platinum-doublet chemotherapy combined with radiotherapy, which improves overall survival compared with chemotherapy alone, even in elderly patients [11]. A concurrent approach is preferred, based on a median survival time of 27.2 months in the concurrent arm, compared with 19.7 months in the sequential arm of a Japanese trial [12]. Timing of radiotherapy is crucial, the shorter the overall treatment time, the better the 5-year overall survival (OS), with the start of radiotherapy preferably coinciding with the first or second cycle of chemotherapy [13, 14]. Despite the older phase 3 trials preferring twice-daily radiotherapy, once-daily radiotherapy is still the standard of care in most centres for practical reasons, and most patients do not qualify for twice-daily radiotherapy due to comorbidity and performance status [15].

The phase 3 trial CONVERT compared once-daily radiotherapy (66 Gy in 6.5 weeks) with twice-daily radiotherapy (45 Gy in 30 fractions in 3 weeks) concurrently with platinum/etoposide chemotherapy in localised SCLC [16]. The study was designed as a superiority trial, with the comparison of OS in both arms as the primary end-point, hoping to demonstrate the benefit of twice-daily irradiation. Of the 547 patients randomised, the two-year OS was 56% in the twice-daily radiotherapy arm *versus* 51% in the conventional arm, which was not statistically significant. No difference in toxicity between both arms was reported.

Encouraged by the assumed noninferiority and safety of twice-daily radiotherapy in SCLC, a Scandinavian phase 2 trial compared the efficacy and tolerability of standard-dose 45 Gy in 30 fractions twice-daily and a high-dose 60 Gy in 40 fractions twice-daily, hoping to improve local control and thus survival [17]. Patients receiving the higher dose had a significantly longer 2-year OS (73% *versus* 46%; p=0.002) and median OS (42 months *versus* 23 months; p=0.027), without – unexpectedly – an increase in toxicity, and comparable tolerance for both arms [18]. The conclusion is that higher dose radiotherapy twice-daily in limited disease SCLC is feasible and tolerable compared with 45 Gy. The currently ongoing CALGB 30610 phase 3 trial is comparing once-daily high-dose thoracic radiotherapy (70 Gy/45 fractions) with standard twice-daily radiotherapy (45 Gy) [19]. The other experimental arm (61.2 Gy) was discontinued at interim analysis.

These trials may shed more light on the issue of the optimal radiation schedule for radiotherapy in locally advanced SCLC.

Radiotherapy in ED-SCLC

Prophylactic cranial irradiation

As the brain is a common site of distant failure in patients with SCLC, prophylactic cranial irradiation (PCI) is recommended in patients after curative treatment for limited stage disease [20]. In an older meta-analysis, the incidence of brain metastases decreased more than 25% 3 years after PCI, with a doubling of survival, 42% *versus* 23% at 2 years [21]. However, these trials predate the current, more sensitive staging with MRI and positron emission tomography (PET) scans.

In a prospective trial, patients with stage IV SCLC with any response to chemotherapy, were randomised to PCI or no further treatment with the time to symptomatic brain metastases as the primary end-point [3]. Patients in the irradiated group had a lower risk of brain metastases at 1 year: the cumulative risk was 14.6% in the irradiated group and 40.4% in controls. The 1-year survival rate was 27.1% in the irradiation group and 13.3% in controls. PCI appeared to be an effective add-on therapy, although the optimal total dose and fractionation schedule remains uncertain. Furthermore, the absence of systematic brain imaging before entering the study did raise concerns about the findings of this study. A Japanese phase 3 trial reassessed the efficacy of PCI in patients with metastasised SCLC with any response to chemotherapy [22]. Patients without

brain metastases on MRI were randomised to PCI (25 Gy in 10 daily fractions of 2.5 Gy) or observation. After a planned interim analysis, the study was closed due to futility. The likelihood that PCI would be superior to observation at the end of the study was minimal. At 12 months follow-up, PCI reduced the incidence of brain metastases (32.9% *versus* 59%) but did not improve OS (48% *versus* 54% at 1 year).

The results of the Japanese PCI study challenge the benefits of PCI. Although PCI is generally well tolerated, patients experience fatigue, nausea, cognitive decline and ataxia [23]. These adverse events may be mild and transient, but could also be progressive and persistent with structural brain damage on MRI. Currently, the guidelines support PCI if patients respond to chemotherapy. The accepted radiation dose is 25 Gy in 10 fractions of 2.5 Gy. There is no role for routine hippocampal sparing [24]. The results of the Japanese trial has led to the dismissal of PCI in many centres. The EORTC Lung Cancer Group is developing a randomised study of PCI *versus* watchful waiting with periodic brain MRI (PRIMALung). A randomised phase III study of the South-West Oncology Group is randomising patients to either MRI surveillance alone, or MRI surveillance with PCI [25].

Consolidation thoracic radiotherapy

Intrathoracic tumour control after chemotherapy remains a problem, as most patients have persistent disease, with disease progression within 1 year. Beneficial effects of thoracic radiotherapy were described in a retrospective series [26]. In a randomised phase 3, after completion of chemotherapy and PCI, thoracic irradiation (30 Gy in 10 fractions) was performed, resulting in an OS at 2 years of 13% *versus* 3% in controls [27]. The authors conclude that thoracic radiotherapy should be considered for patients with advanced disease with any response to chemotherapy. However, in clinical practice this advice is not implemented. Potentially, only patients with presenting symptoms of vena cava superior syndrome, central airway compression, or atelectasis of the lung may benefit from consolidation thoracic radiotherapy [27].

First-line systemic treatment in metastasised SCLC

SCLC is very sensitive to chemotherapy and treatment usually induces rapid responses. The current first-line treatment in ED-SCLC is platinum-based chemotherapy, four to six cycles of cis- or carboplatin plus etoposide in Europe and the United States, and platinum plus irinotecan in Japan [4]. Carboplatin is generally preferred over cisplatin due to its similar efficacy and lower toxicity [28]. However, the majority of patients experience a relapse within the first year of treatment: some of them during treatment (platinum-resistant), some within 90 days from the treatment interruption (platinum-refractory) and others 90 days or more after treatment stop (platinum-sensitive) [29]. In platinum-sensitive relapse, rechallenge with first-line chemotherapy is preferred [1, 5]. Adding a third cytostatic agent to this therapeutic backbone has previously been shown not to result in a better outcome [6].

Second-line therapy in SCLC

Topotecan is the only drug that is formally approved as second-line treatment for SCLC and remains the standard of care. Oral topotecan had a response rate (RR) of 6–17% and a median survival of 25.9 weeks compared with a median survival of 13.9 weeks in a group that was assigned to best supportive care [30].

Immunotherapy

There is great interest in whether immune checkpoint inhibition (ICI) might play a role in the treatment of SCLC. The rationale for combining immunotherapy with chemotherapy in SCLC is the high mutational burden in this tumour, with potentially enhanced immunogenicity. Chemotherapy may stimulate the expression of tumoural antigens, priming the tumour for response to checkpoint inhibitory therapy.

Immunotherapy in adjuvant setting after curative chemoradiotherapy

Despite good initial responses to definitive treatment with curative chemoradiotherapy, outcomes remain poor, with a median progression free survival (PFS) of 15 months and OS of 25 months. The role of adjuvant immunotherapy in this setting was explored (table 1).

The STIMULI phase 2 study of maintenance nivolumab plus ipilimumab in LD-SCLC was conducted to evaluate whether adjuvant immunotherapy might improve outcomes after completion of concomitant chemoradiotherapy and PCI [31]. After randomisation of 153 patients of the 222 planned patients, the study was closed due to slow accrual. It did not meet its primary end-point of improving PFS (10.7 months *versus* 14.5 months). Treatment failure in the immunotherapy arm was mostly due to toxicity; treatment failure in the observation arm was due to disease progression.

In the ongoing phase 3 ADRIATIC trial, 600 patients with at least stable disease after concomitant chemoradiotherapy, with or without PCI, will be randomised 1:1:1 to receive durvalumab plus placebo,

TABLE 1 Immunotherapy trials in small cell lung cancer

Study [ref.]	Trial design	Medication	Number of patients	PFS (months)	OS (months)
Adjuvant in limited disease					
STIMULI [31]	Phase 2, open-label	1) Nivolumab+ipilimumab 2) Observation	153, closed early	10.7	Was not met
ADRIATIC [32]	Phase 3, RCT, double-blind	1) Durvalumab+placebo 2) Durvalumab+tremelimumab 3) Placebo+placebo	600, recruiting		
First-line in metastasised SCLC					
NCT01331525 [33]	Phase 2, RCT, double-blind	1) Carboplatin/etoposide+ipilimumab 2) Carboplatin/etoposide+placebo	42	6.9 1 year PFS: 15.8% (6/35 patients)	17.0
NCT00527735 [34]	Phase 2, RCT, double-blind	1) Carboplatin/paclitaxel+placebo (control arm) 2) Carboplatin/paclitaxel+ipilimumab followed by paclitaxel+carboplatin+placebo (concurrent arm) 3) Carboplatin/paclitaxel+placebo followed by carboplatin/paclitaxel+ipilimumab (phased arm)	130	5.2 3.9 5.2	12.9 9.1 9.9
IDEATE [35]	Phase 3, RCT, double-blind	1) Cisplatin/etoposide+ipilimumab 2) Cisplatin/etoposide+placebo	1132	4.6 4.4	11.0 10.9
IMpower133 [36, 37]	Phase 3, RCT, double-blind	1) Carboplatin/etoposide+atezolizumab 2) Carboplatin/etoposide+placebo	403	5.2 4.3 HR PFS 0.78	12.3 10.3 HR OS 0.73
CASPIAN [39, 40]	Phase 3, RCT, open-label	1) Platinum/etoposide+durvalumab +tremelimumab 2) Platinum/etoposide+durvalumab 3) Platinum/etoposide	268 268 269	4.9 HR PFS 0.84 5.1 HR PFS 0.78	10.4 HR OS 0.82 12.9 HR OS 0.73 10.5
KEYNOTE-604 [42]	Phase 3, RCT, double-blind	1) Platinum/etoposide+pembrolizumab 2) Platinum/etoposide+placebo	453	4.5 4.3 HR PFS 0.75	10.8 9.7 HR OS 0.80
ECOG-ACRIN EA5161 [45]	Phase 2, RCT, double-blind	1) Platinum/etoposide+nivolumab 2) Platinum/etoposide	160	5.5 4.6 HR PFS 0.68	11.3 11.3 HR OS 0.67
REACTION [46]	Phase 2, RCT,	1) Platinum/etoposide+pembrolizumab 2) Platinum/etoposide+placebo		5.4 4.7 HR PFS 0.84	12.3 10.4 HR OS 0.73
Maintenance after first-line chemotherapy					
NCT02359019 [47]	Phase 2, single arm	Pembrolizumab	45	1.4 irPFS 4.7	9.2
Checkmate 451 [48]	Phase 3, RCT, double-blind	1) Nivolumab 2) Nivolumab+ipilimumab 3) Placebo	280 279 275	HR PFS 0.67 HR PFS 0.72	HR OS 0.84 HR OS 0.92
RAPTOR [49]	Phase 2–3, RCT	1) Atezolizumab after response on chemotherapy and atezolizumab 2) Atezolizumab+(extra-)thoracic radiotherapy after response on chemotherapy and atezolizumab	138 phase 2 186 phase 3	Primary end-point PFS in phase 2 Primary end-point OS in phase 3	
Progression after first-line chemotherapy					
Checkmate 331 [50]	Phase 3, RCT	1) Nivolumab 2) Topotecan	569		7.5 8.4
Checkmate 032 [51]	Phase 1/2, open-label	Nivolumab±ipilimumab in different dosages 1) Nivolumab 3 mg·kg^{-1} 2) Nivolumab 1 mg·kg^{-1}+ipilimumab 3 mg·kg^{-1} 3) Nivolumab 3 mg·kg^{-1}+ipilimumab 1 mg·kg^{-1}	216		 1) ORR 10% 2) ORR 23% 3) ORR 19%
Checkmate 032 [52]	Phase 1/2, open-label	Nivolumab monotherapy 3 mg·kg^{-1} beyond third line			ORR 11.9%
KEYNOTE-028 [54]	Phase 1b, single arm	Pembrolizumab	24		9.7 ORR 33%

Continued

TABLE 1 Continued

Study [ref.]	Trial design	Medication	Number of patients	PFS (months)	OS (months)
KEYNOTE-158 [55]	Phase 2, single arm	Pembrolizumab	107	2.0	9.0 (PDL-1$^+$ 14.6 months and in PDL-1$^-$ 7.7 months) ORR 18.7%, ORR in PDL-1$^+$ 35.7% and in PDL-1$^-$ 6.0%
IFCT-1603 [56]	Phase 2, randomised, 2:1	1) Atezolizumab 2) Conventional chemotherapy	49 24	1.4 4.3	9.5 8.7
BALTIC [57]	Phase 2, open-label	Durvalumab+tremelimumab	21		ORR 9.5%
MISP-MK3475 [58]	Phase 2, single-arm, open-label	Paclitaxel+pembrolizumab	26	5.0	9.1 ORR 23.1%

PFS: progression free survival; OS: overall survival; RCT: randomised controlled trial; SCLC: small cell lung cancer; HR: hazard ratio; irPFS: immune-related progression free survival; ORR: overall response rate; PDL-1: programmed death ligand-1.

durvalumab plus tremelimumab, or double placebo for a maximum of 24 months [32]. Primary end-points are PFS and OS for durvalumab, with or without tremelimumab, compared with placebo.

Currently, adjuvant ICI have no role in the treatment of locally advanced SCLC after completion of chemoradiotherapy with or without PCI.

Immunotherapy in first-line metastasised SCLC

Two pivotal phase 2 studies introduced immunotherapy to SCLC, combining the CTLA-4 inhibitor ipilimumab with first-line chemotherapy [33, 34] (table 1). In the first study, the primary end-point of 1-year PFS was not met [33]. The second phase 2 study showed a slightly better outcome for patients treated in the phased ipilimumab *versus* concurrent ipilimumab with chemotherapy [34].

In the large phase 3 study, IDEATE, patients were randomly assigned to receive chemotherapy (platinum/etoposide) plus ipilimumab or placebo every 3 weeks for a total of four doses in a phased schedule [35]. The primary end-point OS was not met, with higher toxicity in the chemotherapy/ipilimumab arm. Ipilimumab may not be effective without corresponding T-cell activation in the tumour environment.

The IMPOWER-133 study was designed to evaluate the safety and efficacy of atezolizumab *versus* placebo in combination with carboplatin/etoposide in 403 treatment-naive participants with metastasised SCLC [36]. The hazard ratio (HR) for disease progression or death was 0.77 (p=0.02). The addition of atezolizumab to chemotherapy in the first-line treatment of metastasised SCLC resulted in a longer OS (33.5% long-term survivors *versus* 20.4% for placebo) and PFS than chemotherapy alone [37]. Although only 43% of tumour specimens were evaluable for programmed death ligand-1 (PD-L1), neither PD-L1 nor the tumour mutational burden (TMB) were found to discriminate long-term survivors. Chemotherapy plus atezolizumab had a comparable safety profile to chemotherapy alone, and did not result in impaired quality of life [38]. Atezolizumab has been approved for registration by both the US Federal Drugs Administration (FDA) and the European Medicines Agency (EMA) [2].

In the phase 3 CASPIAN-trial, the addition of durvalumab and tremelimumab to chemotherapy was also evaluated in treatment-naive patients with metastasised SCLC [39]. Patients were randomly assigned (in a 1:1:1 ratio) to durvalumab plus chemotherapy, durvalumab/tremelimumab plus chemotherapy, or platinum/etoposide alone. First-line durvalumab plus chemotherapy significantly improved OS (22% after 24 months) in patients with advanced SCLC compared with chemotherapy alone. No additional benefit of tremelimumab was observed [40]. However, three times more patients derived long-term benefit when treated with durvalumab plus chemotherapy compared with chemotherapy alone [41]. Patients in all arms with a PFS >12 months had improved overall response rate (ORR), duration of response and OS compared with the PFS <12 months subgroup. Assessment of the characteristics that lead to long-term benefit is ongoing.

In the phase 3 Keynote-604 study, the primary end-point, OS, was prolonged in the pembrolizumab/chemotherapy arm compared with chemotherapy alone [42]. Although PFS improved in the

pembrolizumab arm, the significance threshold was not met (HR 0.8, 95% CI 0.61–0.98). ORR was 71% in the pembrolizumab arm and 62% for placebo. Adding pembrolizumab to chemotherapy did not decrease quality of life [43, 44].

These phase 3 studies showed an improved OS and PFS by adding immunotherapy to first-line chemotherapy, with an acceptable safety profile and quality of life, which supports this regimen as standard of care.

The phase 2 ECOG-ACRIN EA5161-study randomised between platinum/etoposide plus maintenance nivolumab and platinum/etoposide plus observation [45]. The median PFS (primary end-point) and OS were clinically significant, 5.5 months and 11.3 months in the nivolumab plus chemotherapy arm *versus* 4.6 months and 9.3 months in the chemotherapy arm, respectively.

In the phase 2 REACTION-study, chemotherapy with or without pembrolizumab in first-line treatment showed similar results with a not significant PFS of 5.4 months *versus* 4.7 months [46].

Maintenance immunotherapy after first-line chemotherapy

The results of maintenance immunotherapy after completion of first-line chemotherapy are disappointing [47, 48]. In the phase 3 CheckMate-451 trial, patients with responses after completion of first-line chemotherapy were randomised between nivolumab, nivolumab with ipilimumab, or placebo as maintenance therapy [48]. Maintenance immunotherapy did not improve OS, but favourable PFS suggests that some patients could have benefited from maintenance therapy. In a phase 2 study with pembrolizumab, PD-L1 could be assessed in 30 of 45 patients and was positive (PD-L1 expression >1%) in three patients [47], having a PFS of 10, 11 and 13 months. Each unit increase in baseline circulating tumour cells correlated with worse PFS (p=0.052; adjusted for brain metastases, age and sex). Biomarkers to identify the patients most likely to benefit from immunotherapy in the maintenance setting are also lacking.

The RAPTOR trial is evaluating a new strategy of whether thoracic radiotherapy plus maintenance atezolizumab after response on first-line atezolizumab and chemotherapy is better than atezolizumab maintenance alone in patients with metastasised SCLC [49].

Immunotherapy in second-line therapy and beyond

Nivolumab has been investigated in the phase 3 CheckMate-331 trial *versus* topotecan or amrubicin as second-line therapy after progression on standard chemotherapy [50]. The study resulted in a median OS of 7.5 months with nivolumab *versus* 8.4 months with chemotherapy (HR 0.86, 95% CI 0.72–1.04). Immunotherapy in second-line therapy showed no improvement in therapy for SCLC.

Ongoing approaches include combinations of anti-CTLA-4 (ipilimumab and tremelimumab) and anti-PD-(L)1 therapy (nivolumab, pembrolizumab, atezolizumab and durvalumab). In the CheckMate-032 trial, nivolumab/ipilimumab, and nivolumab alone, were evaluated in pretreated patients with SCLC [51, 52]. The responses were fast and durable for patients with relapsed SCLC, regardless of platinum sensitivity or PD-L1 status. Nivolumab monotherapy is approved in the United States as third-line or later based on the pooled data of this trial. In a separate analysis of the pooled nivolumab monotherapy cohort in CheckMate-032, the ORR was 21.3% in patients with a high TMB *versus* 4.8% in those with a low TMB [53]. In the nivolumab plus ipilimumab arm the efficacy was also enhanced in the high TMB group, suggesting TMB may nevertheless have a role as a biomarker for immunotherapy in SCLC, but this has to be further explored.

Several phase 1 and 2 studies evaluated diverse ICIs, which all failed to show efficacy in patients with relapsed SCLC [54–58]. Although in a selected patient category with PD-L1 expression, a slightly better ORR was noted.

Biomarkers in immunotherapy

PD-L1 and TMB are also emerging as biomarkers of response to immune checkpoint inhibitors in various cancer types, including SCLC [53, 59]. Most SCLC tumours seem to lack PD-L1 expression [60]. A recently conducted study speculates that only 2% of patients with SCLC exhibit amplification of the gene CD274, which encodes for PD-L1 expression, and only this small subgroup may be susceptible to ICI [61]. Currently, PD-L1 has no clinical application in SCLC. Some evidence exists that high TMB may be associated with a response to ICI, but large phase 3 studies in patients with first-line metastasised SCLC failed to confirm this [36, 60]. The predictive role of TMB in SCLC has to be defined. The diagnosis of SCLC is made on small biopsies and the evaluation of PD-L1 in tumour tissue is challenging.

Further investigation is ongoing to assess biomarkers such as TMB in tissue and in blood [62]. Liquid biopsies are less invasive for patients [63].

Recommendations in clinical practice

Patients with SCLC still have a poor prognosis and little progress has been made during the last few decades. Surgery for very small SCLC after adequate mediastinal staging seems feasible, but the role of adjuvant chemotherapy is still undecided. Radiotherapy is of additional value in all stages of the disease. For treatment with a curative intent, the proposed radiotherapy schedule of twice-daily irradiation, 45 Gy in 30 fractions seems feasible, and also for elderly patients. From a pragmatic perspective, once-daily radiotherapy should be considered when twice-daily radiotherapy is impractical. After completion of chemoradiotherapy, current guidelines support PCI in case of any response to chemotherapy, with most commonly a radiation dose of 25 Gy in 10 fractions of 2.5 Gy. Discussion about the benefits of PCI, both in the localised and metastasised setting is ongoing. Another option is watchful waiting with periodic brain MRI. Thoracic radiotherapy should be considered for patients with advanced disease who have any response to chemotherapy and present with symptoms such as vena cava superior syndrome, central airway compression and atelectasis of the lung.

Chemotherapy remains the mainstay of the treatment of advanced SCLC. The addition of checkpoint inhibition to the standard backbone chemotherapy has added a modest but significant improvement in outcomes, but predictive biomarkers are yet to come.

Future perspectives

Unravelling the genomics of SCLC and the subsequent discovery of biomarkers is crucial for treatment selection [64]. Whole exome sequencing may help in identifying these biomarkers and targets [65, 66]. For example, in SCLC, loss of TP53 and RB1 occurs most frequently, which results in proliferation and replication stress in SCLC and is associated with early metastasis and rapid resistance against chemotherapy [64]. Amplification of the MYC family of oncogenes occurs in 20% of SCLC and is associated with shorter survival [67]. MYC downregulation suppresses tumour growth.

The clinical relevance of biomarking SCLC lies in preferential targeting of different routes or combinations thereof, or even combining treatment modalities.

Targeting the DNA damage repair pathway

Recent preclinical studies identified predictive biomarkers of response to DNA damage repair (DDR)-targeted therapies in SCLC. Repair proteins such as poly-(ADP)-ribose polymerase (PARP), WEE1, ataxia-telangiectasia-mutated-and-Rad3-related kinase (ATR) and its major downstream effector checkpoint kinase 1 (CHK1) seems attractive to target [68]. PARP, WEE1, ATR and CHK1 prevent entry of cells with damaged or incomplete replicated DNA into mitosis and thus suppress replication stress. Inhibition of these proteins results in cell death. AZD1775 (adavosertib) is a highly selective, potent small molecule inhibitor of WEE1. This small molecule is being tested in several phase 1 and 2 studies, both alone and in combination with PARP inhibition or chemotherapy [69, 70].

Veliparib

Veliparib is a PARP-inhibitor; a small molecule that traps the DNA-repair enzyme PARP on DNA single-strand breaks and blocks its catalytic activity, thus potentially enhancing the damage to DNA caused by chemotherapy. The randomised phase 2 trial of platinum/etoposide plus veliparib or placebo showed a median PFS of 6.1 months *versus* 5.5 months in favour of veliparib [71]. Recent genomic sequencing led to the identification of Schlafen 11 (SLFN11), a predictive biomarker for sensitivity to PARP inhibition in monotherapy in SCLC [72]. SLFN11 expression is high in SCLC and decreases significantly after treatment with veliparib. Prospective validation of the potential of SLFN11 as a predictive biomarker in patients treated with veliparib is warranted.

Temozolomide

Temozolomide (Temodal™) is a triazene derivative causing DNA breakage by adding an alkyl group to the guanine base of DNA. It is an oral drug, well tolerated and not very toxic, with excellent penetration into the central nervous system [73]. Beneficial effects of treatment with temozolomide in patients with SCLC were reported, especially in a subgroup associated with the presence of MGMT promoter methylation, although the difference did not meet statistical significance [74]. The RR in an unselected group was 22% in second-line, 19% in third-line, and 38% in patients with brain metastases. Temozolomide is strongly synergistic with PARP inhibition by preventing the repair of alkylated bases [75]. A phase 2 trial evaluated temozolomide with either veliparib or placebo in patients with relapsed SCLC [76]. Translational objectives

included PARP-1 and SLFN11 immunohistochemical expression, MGMT promoter methylation and circulating tumour cell quantification. Four-month PFS and median OS did not differ between the two arms, but a significant improvement in ORR, which was a secondary end-point, was observed with temozolomide/veliparib compared with temozolomide/placebo (39% *versus* 14%). In patients with SLFN11-positive tumours treated with temozolomide/veliparib a significantly prolonged PFS (5.7 *versus* 3.6 months) and OS (12.2 *versus* 7.5 months) were observed, suggesting PARP-inhibitor sensitivity as a promising biomarker in SCLC. These findings were confirmed in a single-arm trial with olaparib, reporting a lesser effect in platinum-resistant disease [77].

Lurbinectedin

Lurbinectedin is a selective inhibitor of oncogenic transcription, promoting tumour cell death and normalising the tumour microenvironment [78]. In the phase 2 basket trial, 105 patients were treated with lurbinectedin after failure of platinum-based chemotherapy [79]. Activity of lurbinectedin appeared to be greater in patients with a longer chemotherapy-free interval: ORR of 45% *versus* 22% in the platinum-resistant arm. Among all patients, median PFS was 3.5 months (2.6 *versus* 4.6 months) and the median OS was 9.3 months (5.0 *versus* 11.9 months). The most common toxicities were leukopenia and neutropenia. In the phase 3 ATLANTIS-trial comparing lurbinectedin/doxorubicin with either topotecan or cyclophosphamide/doxorubicin/vincristine in second-line metastasised disease, the primary end-point OS was not met [80].

Drug resistance is often a problem of the DDR network. AXL is recognised as the key determinant in both intrinsic and acquired resistance to chemotherapeutic, immunotherapeutic and molecularly targeted agents in SCLC by epithelial-to-mesenchymal transformation (EMT) [81]. High levels of AXL and EMT predict resistance to PARP, ATR and WEE1 targeting. AXL-inhibition induces DNA damage and replication stress and promotes sensitivity to PARP and ATR inhibitors [82, 83]. In addition SLFN11 holds promise as a potential biomarker, while cells with low levels of SLFN11 were more sensitive to AXL/ATR inhibition [84].

Strategies on combinations of DDR-inhibitors or targeting multiple pathways are to be explored. Inhibitors of the DDR pathway confers a synergistic effect on immunotherapy, radiotherapy and chemotherapy; for example, temozolomide [83, 85]. PARP inhibition enhances the effect of radiotherapy in SCLC in a preclinical model [86]. A continuing challenge in SCLC is the intra-tumour heterogeneity. Blocking various routes of growth to tackle the tumour might be the answer.

Targeting the genomic and epigenomic alterations

Potential targetable genomic alterations are mutations in PTEN or RET, and amplifications of fibroblast growth factor receptor 1 (FGFR1) [87–89]. The latter are present in 6% of SCLC [89]. RET mutations are found in 1–2% of SCLC [88]. RET mutated SCLC also seems to express MYC more often. Inactivation of RB1 leads to overexpression of enhancer of zeste homolog 2 (EZH2) which promotes tumour genesis in SCLC [90]. In this process, downregulation of SLFN11 due to overexpression of EZH2 makes SCLC resistant to chemotherapy [91]. The combination of an EZH2 inhibitor and chemotherapy, such as cisplatin or temozolomide, can circumvent resistance by preventing loss of SLFN11. Expression of EZH2 can act as biomarker and therapeutic target in SCLC.

Pazopanib

Pazopanib is a tyrosine kinase inhibitor that inhibits downstream signalling of vascular endothelial growth factor receptor (VEGFR)-1, -2 and -3. These targets are considered interesting given the importance of neoangiogenesis in SCLC and the role of VEGF overexpression in development of resistance to chemotherapy. In a multicentre, single-arm phase 2 trial, 58 patients were treated with pazopanib in second-line [92]. The platinum-refractory cohort was closed early due to futility. Median PFS and OS in cohort the platinum-sensitive cohort were 3.7 months and 8.0 months, respectively, with an ORR of 13.8%. Pazopanib is a tolerable and effective salvage treatment in patients with platinum-sensitive SCLC. However, with its modest effect, pazopanib will likely play no role except in FGFR1-amplified SCLC [93].

Alisertib

Alisertib is a selective oral Aurora kinase A (AURK) inhibitor. AURKs are mitotic regulators required for normal cell proliferation [94]. Errors in mitosis may either lead to cell death, or to aneuploidy and a mitotic dysregulator might offer a therapeutic target with relative sparing of normal cells. A phase 1–2 study in five cancer types reported a promising ORR of 21% for the SCLC arm [95]. This was further explored in a phase 2 trial randomising between paclitaxel plus alisertib (based on preclinical evidence of synergy) or paclitaxel plus placebo, and reported a median PFS of 3.3 months for the alisertib arm, which

was not significantly better than placebo (the ORR of 22% was confirmed) [96]. In a subset of patients with high MYC expression, PFS for the alisertib arm was significantly better (4.6 months *versus* 2.3 months), but as this analysis was not part of the protocol, this will not be further explored. In spite of this discovery of MYC as a potential biomarker in SCLC, development of alisertib was halted.

Targeting the immune system and genomic instability

Defects in the DDR pathway have been associated with enhanced responses to immune checkpoint blockade due to high TMB and genomic instability [97]. Recently, it was found that co-targeting DDR proteins such as PARP and CHK1 can increase expression of PD-L1 and antitumour immune response of anti-PD-L1 in SCLC [98, 99]. These findings suggest that DDR targeting in combination with immunotherapy could be successful.

Drug-delivery challenges

Novel drug-delivery systems such as antibody drug conjugates (ADC) bring medication in the vicinity of the tumour and should help to target tumour cells without damaging healthy cells.

Rovalpituzumab-tesirine

An initially very promising target was delta-like protein 3 (DLL3), a Notch ligand that is highly expressed in about two-thirds of SCLC [100]. Activation of Notch inhibits the growth of SCLC-cells *in vitro*. Rovalpituzumab-tesirine (Rova-T) is an ADC that binds to DLL3, with an ORR of 18% in the phase 1 trial, which increased to 39% in high (⩾50%) DLL3-expressors [101]. The subsequent phase 2 TRINITY trial selected DLL3-expressing tumours in extensively pre-treated patients (at least two lines) but found only an ORR of 12.4% and an OS of 5.7 months, with DLL3-high patients only performing slightly better than DLL3-non high patients [102]. Grade 3–5 toxicity was found in 63%, with 10% grade 5 toxicity. We may conclude that Rova-T is the first targeted agent in SCLC to target DLL3, but results are disappointing. As a result of this, the product was withdrawn and ongoing studies TAHOE (*versus* topotecan) and MERU (maintenance after chemotherapy) closed prematurely [103, 104].

Recently, a definition of four molecular subsets of SCLC have been proposed: acheate-scute homolog 1 (ASCL1), neurogenic differentiation factor 1 (NEUROD1), yes-associated protein 1 (YAP1) and POU domain class 2 homebox 3 (POU2F3) [105, 106]. These molecular subtypes appear to be associated with distinct expression profiles and possible therapeutic sensitivities [107]. For instance, both ASCL1-high and NEUROD1-high neuroendocrine subtypes are characterised by marked expression of insulinoma-associated protein 1 (INSM1), a marker of super-enhanced landscapes in SCLC [105]. SCLC with high NEUROD1 expression have high MYC expression [108]. High MYC expression and amplification predicts sensitivity to AURK and CHK1 inhibitors. In combination with chemotherapy, it strongly suppresses tumour progression and increases survival [67]. MYC activates Notch, so ASCL1 and NEUROD1 subtypes could benefit from DLL3 inhibitors such as Rova-T. The combination of Rova-T and immunotherapy, however, was not well tolerated despite antitumour activity in third-line and beyond [109]. Subtypes with low ASCL1, NEUROD1 and POU2F3 expression act as inflamed SCLC and can benefit from the addition of immunotherapy to chemotherapy [110].

Concluding remarks

The histopathology and tumour biology of SCLC is complex. Simple strategies to target the tumour are not successful in achieving a long survival advantage. Several approaches have the potential to overcome the well-known treatment failures of the last decades.

Firstly, recent studies have shown progress in finding biomarkers to serve as targets for treatment. Extensive exome sequencing in patients with SCLC is the future to create a landscape of predictive biomarkers in SCLC. Epigenetic alterations, gene amplifications and mutations can act as biomarkers in this context. Consequently, biomarker-driven patient selection is needed to stratify patients for treatments. Distinct molecular subtypes appear to be associated with therapeutic sensitivities. The key to success lies in the treatment combination or targeting dual pathways that have additional or synergistic effects. Overcoming intra-tumour heterogeneity is an extra hurdle where combination therapy, concomitantly or sequentially, is probably a “conditio sine qua non”. Secondly, it is expected that adding other treatment modalities, such as radiotherapy or immunotherapy, to biomarker-driven drug combinations will have synergistic effects to overcome resistance mechanisms. Lastly, novel drug-delivery systems should help to target tumour cells while preventing deleterious effects due to interaction with healthy cells.

With possible biomarkers having been discovered, the design of future trials should allow the study of a targeted treatment in a biomarker enriched population. Importantly, referrals of patients for clinical trials with biomarker-selected targeted treatments is warranted to improve the prognosis for patients with SCLC.

Provenance: Submitted article, peer reviewed

Conflict of interest: B.I. Hiddinga has nothing to disclose. J. Raskin reports personal fees from Lilly, Pfizer and BMS, and non-financial support from Roche, outside the submitted work. A. Janssens has nothing to disclose. P. Pauwels has nothing to disclose. J.P. van Meerbeeck has nothing to disclose.

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