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The ostracism of radiotherapy in contemporary immunotherapy clinical trials of extensive–stage small cell lung cancer

Abstract

Small–cell lung cancer (SCLC) traditionally has been described as either limited-stage (LS–SCLC) or extensive–stage (ES–SCLC) based on whether the tumor fits in a radiation portal. Until recently, ES–SCLC treatment consisted of 4–6 cycles of platinum-based doublet chemotherapy, optionally followed by thoracic consolidation and prophylactic cranial irradiation (PCI) in patients with partial or complete response. However, survival was poor, and no significant improvements in outcomes were achieved during the past decades. Recently, the addition of atezolizumab, an immune checkpoint inhibitor, to chemotherapy in the first-line setting (IMpower 133 trial) resulted in improved progression-free survival and overall survival compared to chemotherapy alone. Similar results were obtained by the addition of durvalumab to chemotherapy in the CASPIAN trial. In both studies, thoracic radiotherapy was not allowed, and the utilization of PCI was low. In this short review, we follow the ES–SCLC treatment algorithm's evolution and ponder whether radiation therapy's decaying role is justified.

Keywords: extensive-stage small cell lung cancer, radiotherapy, immunotherapy, immune checkpoint inhibitors

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Introduction

SCLC accounts for approximately 13–15% of all lung carcinomas.[1] Tobacco use is the primary cause, and in 90% of cases, the diagnosis involves current or former smokers, with the risk being related to the duration and intensity of smoking.[2] SCLC originates from neuroendocrine–cell precursor cells and is archetypically described as either limited or extensive stage, based on whether the gross tumor fits within one radiation portal. It is biologically characterized by high aggressiveness and early widespread metastasis, resulting in most patients diagnosed with extensive-stage disease. Despite the high initial response rates to first-line platinum-based chemotherapy, ES–SCLC invariably relapses and metastasizes, showing poor response to subsequent systemic treatments. For patients responding to first-line chemotherapy, thoracic radiotherapy consolidation[3-5] and prophylactic cranial irradiation[6-8] may be considered based on randomized clinical trial data.

Recently, the addition of atezolizumab, an immune checkpoint inhibitor (ICI), combined with chemotherapy, was shown to improve overall survival (OS) in an unselected patient population (IMpower 133 trial).[9] Similar results were obtained with the addition of another ICI, durvalumab, in the planned interim analysis of the CASPIAN trial.[10] In both of these studies, radiation therapy was explicitly forbidden.[11,12] Traditionally, radiotherapy (RT) was associated with immunosuppression due to the inherent radiosensitivity of lymphocytes and the use of large radiation portals.[13] In the past few years, though, it was realized that irradiated cancer cells die via diverse modes, whose immunological effects can trigger immune-related systemic responses.[14,15] In this mini-review, we follow the evolution of ES–SCLC treatment algorithm and contemplate the declining role of radiation therapy in the contemporary era.

Immunotherapy in SCLC

Rationale

SCLC constitutes a "loss–of–function" malignancy due to frequent loss of tumor suppressor genes, such as TP53 and RB1, which unfortunately are not targetable.[16-19] Also, with approximately 8.88 somatic mutations per megabase, SCLC is second only to melanoma with regard to the tumor's mutational burden (TMB).[20] Presumably, highly mutated tumors are more likely to form neoantigens. Hence, they are potentially immunogenic and capable of inducing immune-mediated antitumor reactions. TMB has been shown to correlate with patient response to both anti–cytotoxic T–lymphocyte-associated protein 4 (CTLA–4) and anti-programmed cell death–1 (PD–1) treatments.[21,22] SCLC is the most common cancer histology associated with paraneoplastic syndromes.[23] These are induced when the immune system identifies shared antigens between SCLC tumor cells and normal tissues. For instance, in the Lambert Eaton syndrome, common antigens between the tumor cells and healthy neurons lead to antibody-mediated (anti–Hu) cross-reactions. Provocatively, in retrospective studies, patients with Lambert–Eaton syndrome had more frequent complete responses to therapy (55.6% vs. 19.6%) and improved OS (14.9% vs. 10.2%) compared to those without it.[24-26] Last, preclinical data support the view that SCLC tumor cells may downregulate local and systemic immune responses through CD4(+) T–cell-mediated immunosuppression.[27] Therefore, for the reasons above (high TMB, the existence of paraneoplastic syndromes, and T–cell-mediated immunosuppression), SCLC is considered an ideal candidate for immunotherapy strategies.[15]

Proof of concept

The first ICI investigated in ES–SCLC combined with platinum-based doublet chemotherapy was ipilimumab, an anti–CTLA–4 monoclonal antibody. In a phase III study, 1132 patients with newly diagnosed ES–SCLC were randomized to platinum (cisplatin or carboplatin) and etoposide plus ipilimumab 10mg/kg or placebo every three weeks for a total of 4 doses, followed by maintenance of ipilimumab or placebo every 12 weeks(28). The study's outcome was disconcerting as median OS equaled 11.0 months for chemo–IO and 10.9 months for chemotherapy plus placebo (hazard ratio (HR), 0.94; 95% CI: 0.81 to 1.09; p=0.3775), failing to meet its primary endpoint. Nonetheless, it demonstrated the attainability of combining chemotherapy and ICI in ES–SCLC, blazing a trail in the use of anti–

PD–1 and anti-programmed death-ligand 1 (PD–L1) antibodies in this notoriously treatment-refractory disease.

First-line treatment

In the first-line setting, the combination of platinum doublet chemotherapy and the PD–L1 inhibitor atezolizumab has demonstrated improved outcomes. IMpower 133 was a double-blind trial of 403 patients with untreated ES–SCLC receiving either carboplatin/etoposide combined with atezolizumab or placebo, followed by maintenance until progression or loss of clinical benefit.[9] The two primary endpoints were progression-free survival (PFS) and OS in the intention–to–treat population. PD–L1 testing was not required. After a median follow–up of 13.9 months, the median OS was 12.3 months in the atezolizumab arm vs. 10.3 in the placebo arm (HR 0.70, p=0.0069). The 1–year OS was 51.7% and 38.2%, respectively. The 12–month PFS rate increased from 5.4 to 12.6%, and the combination was well tolerated. In a subgroup analysis, assessments of TMB with a blood-based assay did not correlate with treatment outcomes. IMpower133 was the first pharmacological study in over 20 years to show a clinically meaningful improvement in OS. Following the publication of these data, atezolizumab was approved by the Food and Drug Administration (FDA)(29) and was included in the National Comprehensive Cancer Network (NCCN) guidelines.

Second–line and later–line

CheckMate 032 was a large (N=216) phase I/II study of pre-treated, with at least one previous platinum-containing regimen, limited-stage (LS) or ES–SCLC patients, receiving either nivolumab alone 3mg/kg or nivolumab 1mg/kg plus ipilimumab 3mg/kg for four cycles, followed by nivolumab monotherapy 3mg/kg until progression or unacceptable toxicity.[30] Response rates were 10% for nivolumab 3mg/kg, 23% for nivolumab 1mg/kg + ipilimumab 3mg/kg and 19% for nivolumab 3mg/kg + ipilimumab 1mg/kg. Grade 3/4 toxicity rates were 13%, 30%, and 19%, respectively. When attained, responses were durable in the nivolumab monotherapy arm (≥6 months in 77%, ≥12 months in 62%, and ≥18 months in 39%)(45). PD–L1 expression did not appear to predict response.

Strikingly, nivolumab monotherapy provided durable responses even as a third– or later–line treatment for recurrent SCLC.[31] In the CheckMate 032 study, 109 patients began receiving third– or later–line nivolumab monotherapy, and despite low objective response rates (ORR, 11.9%), at a follow–up of 28.3 months, the median duration of response was 17.9 months. The 12– and 18–month overall survival rates were 28.3% and 20.0%, respectively, and grade 3 to 4 treatment-related adverse events were infrequent. Based on the demonstration of nivolumab's durable overall responses in patients with ES–SCLC with progression after platinum-based chemotherapy and at least one other line of therapy, the FDA gave an accelerated approval.[32]

A pooled analysis of KEYNOTE–028 (phase Ib)[33] and KEYNOTE–158 (phase II)[34] led NCCN to also include pembrolizumab as a treatment option for relapsed SCLC regardless of PD–L1 status. These studies reported an ORR of 19.3% (95% CI, 11.4–29.4) and a median OS of 7.7 (95% CI, 5.2–10.1) months.[35]

Second-line IO vs. chemotherapy

CheckMate 331 investigated nivolumab vs. topotecan or amrubicin in 569 patients with relapsed SCLC after one prior chemotherapy line for ES–SCLC or chemoradiation for LS–SCLC, good performance status, and no central nervous system (CNS) metastases. The study did not meet the primary endpoint of OS.[36] In the IFCT–1603 phase II trial, patients were randomized to atezolizumab or second-line chemotherapy (topotecan or re-challenge with platinum/etoposide). Neither did this study meet its primary endpoint of ORR at six weeks, and naturally, there was no difference in OS between the two arms (median OS 9.5 vs. 8.7 months, adjusted HR of atezolizumab 0.84, 95% CI: 0.45–1.58, p=0.60).

Maintenance phase

The results of ICIs in the maintenance phase have been discouraging. In a phase II study of 45 patients who responded or had stable disease after induction with first-line platinum doublet chemotherapy, pembrolizumab 200mg every three weeks was given as maintenance therapy after.[37] Pembrolizumab did not appear to constitute an improvement compared with historical data given the median PFS of 1.4 months. However, the 1–year PFS rate of 13% and OS rate of 37% suggest a subset of patients who benefited from pembrolizumab. CheckMate 451, a double blind phase III maintenance study, also failed to show an OS benefit of ICIs vs. placebo. In this trial, 834 patients who had a complete or partial response or stable disease after four cycles of platinum-based chemotherapy for ES–SCLC were randomized to nivolumab 1mg/kg plus ipilimumab 3mg/kg every three weeks for four cycles followed by a flat dose of nivolumab (240 mg every 2 weeks) or nivolumab alone at the same flat dose or placebo. The study's primary endpoint was OS, and it did not differ significantly between treatments, at a median of 9.2 and 9.6 months, respectively, and a nonsignificant HR of 0.92.[38]

Role of radiotherapy in contemporary immunotherapy clinical trials

First-line

In IMpower133, for patients to be included in the trial, they had to be treatment–free for at least six months since last chemo/radiotherapy (among those treated with curative intent) for limited-stage SCLC. Also, no consolidative thoracic radiotherapy was allowed during the maintenance phase. Although PCI was permitted, only 22 patients in each group received it.[39] In these patients, CNS–related events (headache, asthenia, dizziness, insomnia, and fall) were more common in the atezolizumab arm. Seven patients received palliative thoracic radiotherapy (3 in the atezolizumab arm, 4 in the placebo arm). In the CASPIAN study,[12] exclusion criteria included any radiotherapy history to the chest preceding systemic therapy and planned thoracic consolidative RT (palliative care outside of the chest was allowed). Table 1 shows the ongoing trials in ES–SCLC with ICIs and whether radiotherapy is allowed.

Maintenance phase

In the maintenance trial with pembrolizumab of Gadgeel et al., both thoracic radiation and PCI were permitted.[37] Unfortunately, we do not have data on the number of patients that underwent radiotherapy. According to the protocol, pembrolizumab had to be started within eight weeks of the start of the last cycle of chemotherapy. It is not clear whether in this two–month interval, thoracic consolidation or PCI were given and how long it took between the end of radiotherapy and the start of immunotherapy. This might prove to be a critical piece of information for the following reason. In the PACIFIC trial, initially, completion of the last radiotherapy session had to occur between days 1 and 14 before randomization (to durvalumab maintenance vs. placebo). The protocol was subsequently amended to facilitate patient management, and the criterion changed to 1 to 42 days, creating heterogeneity among the study participants. The HR for patients randomized within 14 days of chemoradiation completion was 0.39 (95% CI, 0.26–0.58) compared to 0.63 (95% CI, 0.49–0.80)

for randomization between 14 and 42 days.[40] This disparate effect may be explained based on a synergy between chemoradiation and immunotherapy, given their temporal proximity. Alternatively, it may represent a case of selection bias, i.e., patients more fit were more likely to undergo immediate randomization after the completion of concurrent therapy.[41] In the Checkmate 451 trial of nivolumab and ipilimumab maintenance, consolidative chest radiation constituted an exclusion criterion.[42]

Table 1 Studies for ES–SCLC with immunotherapy

NCT Registry Number	Phase	Immune Checkpoint Inhibitor	Estimated enrollment (participants)	Thoracic Radiotherapy Permitted	PCI Permitted
03568097 (PAVE trial)	Phase 2	Avelumab	55	NS	NS
3923270	Phase 1	Durvalumab	54	Yes	NS
03971214 (PICARES trial)	Phase 1	JS–001 (PD–1 inhibitor)	6	Yes	Yes
02538666 (CheckMate 451)	Phase 3	Nivolumab, Ipilimumab	1327	No	NS
3382561	Phase 2	Nivolumab	150	No	NS
3994744	Phase 2	Sintilimab	68	No	NS
1331525	Phase 2	Ipilimumab	42	NS	NS
2402920	Phase 1	Pembrolizumab	80	Yes	NS
3043599	Phase 1/2	Ipilimumab, Nivolumab	21	Yes	NS

Role of thoracic consolidation radiotherapy

The data currently available for the role of thoracic irradiation in ES–SCLC date back to 1999 when a randomized trial by Jeremic et al. was conducted.[3] In a total of 210 patients that were treated with three cycles of platinum/etoposide, those who achieved a CR at both the primary and distant disease sites (CR/CR) or a PR at the chest and distant CR (PR/CR) received thoracic accelerated hypofractionated RT (54 Gy in 36 fractions over 18 treatment days). Radiotherapy was combined with chemotherapy, followed by two additional chemotherapy cycles *vs.* four additional cycles of chemotherapy alone. Patients with inadequate responses were treated nonrandomly. Also, all patients with distant CR received prophylactic cranial irradiation with 25 Gy in 10 fractions. The median overall survival was nine months, and the 5–year survival rate was 3.4%. Patients in the combined modality had significantly better survival rates than those treated with chemotherapy alone (17 vs. 11 months; 5–year survival rate, 9.1% vs. 3.7%, respectively; p=0.041). Local control was also better in the former group, but the difference was marginally not significant (p=0.062). There was no difference in distant metastasis-free survival between groups.

CREST trial was a phase 3 randomized controlled multicenter trial conducted across 42 hospitals. In total, 498 patients with WHO performance score 0–2 and confirmed ES–SCLC who responded to chemotherapy were randomly assigned to receive either thoracic consolidative radiotherapy (30 Gy in 10 fractions) or no thoracic radiation therapy (TRT). All patients received prophylactic cranial irradiation with 25 Gy in 10 fractions. Although the overall survival at 1–year was not significantly different between groups, in secondary analysis, the 2–year overall survival was 13% (95% CI 9–19) for thoracic radiotherapy arm versus 3% (95% CI 2–8; p=0.004) for the control arm. At 6 months, progression-free survival was 24% (95% CI 19–30) versus 7% (95% CI 4–11; p=0.001). In a subsequent secondary analysis of the CREST trial, additional data regarding the sites and numbers of metastases were collected from 260 patients' records at the top 9 recruiting centers.[43] The PFS (p=0.04) and OS (p=0.02) were significantly better in patients with no more than two metastases. Also, the presence of liver (p=0.03) or bone metastases (p=0.04) negatively affected OS. These findings may provide indirect evidence and guide future trials regarding which patients are more likely to benefit from thoracic irradiation.

Palma et al. conducted a meta-analysis of the previous studies, including a total of 604 patients (302 TRT; 302 non–TRT).[44] The delivery of thoracic consolidative radiotherapy was associated with improved overall survival (HR, 0.81; 95% CI, 0.69–0.96; p=0.014) and progression-free survival (HR, 0.74; 95% CI, 0.64–0.87, p<0.001). Regarding treatment-related side effects, esophageal toxicity (grade 3 or higher) was 6.6% in the TRT arm and 0% in the non–TRT arm (p<0.001), and pulmonary toxicity (grade 3 or higher) was similar in both groups (≤2%). The analysis concluded that chest radiotherapy improves OS and PFS in patients with ES–SCLC, at the cost of a small incremental risk of esophageal toxicity.

RTOG 0937 was a randomized phase II trial comparing PCI vs. PCI plus consolidative radiation therapy (cRT) to both intrathoracic disease and extracranial metastases from ES–SCLC.[5] The primary endpoint was 1–year overall survival and eligible patients had one to four extracranial metastases after a complete or partial response to chemotherapy. PCI consisted of 25 Gy in 10 fractions and cRT of 45 Gy in 15 fractions (both primary and extracranial disease). Regrettably, in 97 randomized patients, the 1–year OS did not differ: 60.1% (95% CI: 41.2–74.7) for PCI and 50.8% (95% CI: 34.0–65.3) for PCI plus cRT (p=0.21). The 3– and 12–month rates of progression were 53.3% and 79.6% for PCI and 14.5% and 75% for PCI plus cRT, respectively. Time to progression favored PCI plus cRT (hazard ratio = 0.53, 95% CI: 0.32–0.87, p=0.01), albeit at the cost of increased treatment-related toxicity.

Given that contemporary immunotherapy clinical trials of ES–SCLC (namely IMPower 133 and CASPIAN) did not allow for thoracic irradiation, we lack data on the efficacy of radioimmunotherapy combinations in this setting. Priming with chemotherapy alone generates mediocre neoantigen expression and inadequate responses.[15,45] Therefore, the omission of radiation may represent a missed opportunity to enhance immunogenicity and treatment outcomes.[45]

Fortunately, following the PACIFIC trial's breakthrough that proved both the safety and efficacy of integrating radiotherapy and immunotherapy in NSCLC, ongoing trials test similar combinations in limited-stage SCLC. In Europe, the phase II randomized multicenter STIMULI study compares standard chemoradiation and PCI, followed by either observation or four cycles of ipilimumab and nivolumab followed by maintenance nivolumab for patients with LS–SCLC.[46] In the NCT03811002 trial, thoracic chemoradiation with or without atezolizumab will be tested in the LS–SCLC setting.[47] Similarly, in NCT02402920, researchers from MD Anderson Cancer Center are testing dose–escalation of pembrolizumab on top of platinum-based doublet chemotherapy and radiotherapy in LS–SCLC and ES–SCLC.[48] The NCT02701400 trial conducted by Emory University was a randomized phase II study evaluating tremelimumab and durvalumab with or without hypofractionated RT or stereotactic body radiation therapy (SBRT) in patients with relapsed SCLC. Unfortunately, the study did not show sufficient efficacy for ICIs with or without SBRT in relapsed SCLC.[49] Besides its small sample size (N=17), patients had relapsed disease, and up to two lines of prior chemotherapy might explain the negative results. Presumably, the earlier the combination of radioimmunotherapy is delivered, the better.

Role of prophylactic cranial irradiation

SCLC appears to have a high propensity for the central nervous system. In the Auperin meta-analysis,[6] brain metastasis incidence, without PCI, was 58.6%. In Slotman[7] EORTC 08993–22993, the incidence of symptomatic brain metastasis at one year was 40.4%, and in Takahashi[8] 59.0%. These data were challenged by a Japanese, phase 3, multi-institutional study randomized patients with ES–SCLC who had any response to platinum-based doublet chemotherapy and a normal baseline MRI to receive PCI (25 Gy in 10 fractions) or observation.[8] It was required that all patients had regular brain MRIs at 3–month intervals up to 12 months and at 18 and 24 months after enrolment. Between 2009 and 2013, 224 patients were randomly assigned. The PCI arm experienced a lower rate of brain metastases (40.1% at 18 months vs. 63.8% at 18 months in the surveillance arm). Patients who did not receive PCI and subsequently developed brain metastases received salvage brain RT in 83% of the cases. The median overall survival was 11.6 months (95% CI 9.5–13.3) in the PCI group and 13.7 months (10.2–16.4) in the observation group (hazard ratio 1.27, 95% CI 0.96–1.68; p=0.094). Given these disconsonant results, the National Comprehensive Cancer Network guidelines were relaxed and now include both PCI consideration and imaging surveillance. Particularly older patients (>60 years old) with pre-existing neurocognitive deficits are at increased risk for neurological sequelae after PCI. How do we reconcile these data with the other studies? In the EORTC trial, there was no requirement for routine brain MRI during staging or follow–up. Only symptomatic patients would undergo imaging. Hence, it is plausible that some patients with occult CNS disease were randomized to PCI and had received "therapeutic" rather than prophylactic RT at the time of enrollment.

Recently, in the NRG CC001 phase III trial, 512 patients with brain metastases were randomized to whole-brain radiotherapy (WBRT)+memantine (M) or Hippocampal Avoidance (HA)+WBRT+M. The use of HA reduced neurocognitive function failure risk (adjusted HR=0.74, p=0.02) and patient-reported symptoms while achieving similar intracranial control and survival.[50] As far as the overall incidence of hippocampal metastases (defined as lesions inside hippocampus plus 5mm) in SCLC is concerned, the rates are low and provide preliminary evidence for the safety of HA–WBRT in clinical trials.[51] Whether HA–WBRT will prove to be a valid approach also in the PCI setting is the subject of another trial.[52] Last, an ongoing randomized study aimed at toxicity reduction is the ENCEPHALON trial, which will compare WBRT alone versus radiosurgery for patients with 1–10 brain metastases from small cell lung cancer.[53]

The central nervous system is an "immune–privileged" site that may restrain immunotherapy drugs' therapeutic efficacy.[54] Although ICIs appear to exhibit intracranial activity when there are brain metastases,[55-57] it is unclear if they could penetrate, given their molecular size, an intact blood-brain barrier (BBB), and act preventively. Besides, even if they manage to cross the BBB, whether activated T lymphocytes can infiltrate brain lesions is debatable since the trafficking of immune cells into the CNS is very tightly restricted by the BBB.[54,58] Other interfaces, such as cerebrospinal fluid and choroid plexus, may provide means of accessing CNS.[59]

In IMpower 133, 8.7% of the enrolled patients had treated brain metastases.[9] Unfortunately, the study did not describe the incidence of new brain lesions. Therefore, it is impossible to deduce the effect of atezolizumab on the rate of intracranial progression and whether it could act prophylactically. However, in the PACIFIC trial, durvalumab maintenance following chemoradiotherapy reduced the incidence of brain metastases in patients with newly diagnosed stage III, unresectable, non–small lung cancer (NSCLC) (6.3% vs. 11.8%).[40] To the extent that extrapolating from NSCLC to SCLC is valid, we hypothesize that ICIs may exert a prophylactic effect in CNS.

As systemic therapies in SCLC continue to evolve and survival rates are improved, the disease's intracranial control will become a pressing issue depending on how much CNS penetrant the new drugs will be (less of an issue if they penetrate enough, more if they do not). If brain relapses turn out to be frequent, this, along with the technological advancements in radiation techniques (e.g., HA–WBRT PCI), will transform the risk-benefit ratio in favor of PCI. On the other hand, for patients living longer, PCI could put them at risk for delayed RT–associated neurotoxicity.[60] Ultimately, the better the extracranial control of the disease due to systemic treatments, the more PCI might be needed, and the less toxic it needs to be in order to maintain a favorable risk-benefit ratio.

A note on biomarkers

Although PD-L1 and Tumor Mutational Burden (TMB) have materialized as predictive biomarkers of response to immune checkpoint inhibitors in various cancer types, most SCLC tumors seem to lack PD-L1 expression, leaving a small subgroup of patients likely to benefit from ICIs.[61] Currently, PD-L1 has no role in the decision making and treatment algorithm of SCLC. Also, the lack of actionable biomarkers has made it challenging to develop more effective treatments.[62]

Conclusion

ES–SCLC is a profoundly aggressive disease that lacked for years any meaningful pharmacological advances. In this sense, the debut of immunotherapy drugs represents a long-awaited breakthrough. Radiotherapy has traditionally been perceived as immunosuppressive, but this concept is being aggressively challenged by numerous studies outlining its safety and its synergy with immunotherapy agents. The stake is that radiotherapy may be eliminated by the therapeutic algorithm simply through blocking it from the modern clinical trials. We resolutely believe that the next generation studies will build upon the PACIFIC trial's successful paradigm in NSCLC.

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Conflicts of interest

Authors declare that there is no conflict of interest.

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