review articles

Radiation and Systemic Therapy for Limited-Stage Small-Cell Lung Cancer

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abstract

Progress in the overall treatment of small-cell lung cancer (SCLC) has moved at a slower pace than non–small-cell lung cancer. In fact, the standard treatment regimen for limited stage SCLC has not appreciably shifted in more than 20 years, consisting of four to six cycles of cisplatin and etoposide chemotherapy concurrent with thoracic radiotherapy (TRT) followed by prophylactic cranial irradiation (PCI) for responsive disease. Nevertheless, long-term outcomes have improved with median survival approaching 25-30 months, and approximately one third of patients now survive 5 years. This is likely attributable in part to improvements in staging, including use of brain magnetic resonance imaging and fluorodeoxyglucose–positron emission tomography imaging, advances in radiation treatment planning, and supportive care. The CONVERT and CALGB 30610 phase III trials failed to demonstrate a survival advantage for high-dose, once-daily TRT compared with standard 45 Gy twice-daily TRT, although high-dose, once-daily TRT remains common in practice. A phase III comparison of high-dose 60 Gy twice-daily TRT versus 45 Gy twice-daily TRT aims to confirm the provocative outcomes reported with 60 Gy twice daily in the phase II setting. Efforts over time have shifted from intensifying PCI, to attempting to reduce treatment-related neurotoxicity, to more recently questioning whether careful magnetic resonance imaging surveillance may obviate the routine need for PCI. The addition of immunotherapy has resulted in mixed success in extensive-stage SCLC with modest benefit observed with programmed death-ligand 1 inhibitors, and several ongoing trials assess programmed death-ligand 1 inhibition concurrent or adjuvant to chemoradiotherapy in limited-stage SCLC. Major advances in future treatment will likely depend on a better understanding and exploiting of molecular characteristics of SCLC with increasing personalization of therapy.

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INTRODUCTION

Small-cell lung cancer (SCLC) is an aggressive smoking-related malignancy accounting for approximately one seventh of all lung cancers.[1] Tumors typically metastasize early resulting in bulky hilar and mediastinal lymph node involvement and distant disease. Approximately one third of patients present with limited-stage disease, with tumor confined to one hemithorax, with ipsilateral supraclavicular lymph node involvement permitted if all sites of disease can be encompassed within a single radiation portal.[2] Limited-stage small-cell lung cancer (LS-SCLC) trials generally exclude patients with contralateral hilar and, or contralateral supraclavicular nodal spread. TNM staging is prognostic, although most clinical decisions are still based on the original Veterans Administration Lung Study Group classification.[3]

Progress in the treatment of SCLC has moved at a slower pace than non–small-cell lung cancer (NSCLC), with only modest benefit from immune checkpoint inhibitors (ICIs) in extensive-stage disease.[4-6] In fact, the treatment regimen for LS-SCLC has not appreciably shifted in more than 20 years, with standard therapy consisting of 4-6 cycles of cisplatin and etoposide chemotherapy (PE) concurrent with thoracic radiotherapy (TRT) followed prophylactic cranial irradiation (PCI) in responsive disease. Nevertheless, long-term outcomes have improved for this population of patients with median survival approaching 25-30 months, and approximately one third of patients now survive 5 years.[7,8] This is likely attributable in part to improvements in staging with increased use of brain magnetic resonance imaging (MRI) and 18-fluorodeoxyglucose positron emission tomography (PET), advances in radiation treatment planning, and better supportive care.

INTEGRATION OF TRT

Although SCLC is very responsive to systemic chemotherapy upon initial diagnosis, there is a preponderance of both local and systemic relapse even in cases presenting with limited disease. The value of including TRT was addressed in two meta-analyses published in 1992, which demonstrated improvements in overall survival (OS) and/or local tumor

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CONTEXT

Key Objective

Although standard treatment for limited-stage small-cell lung cancer (LS-SCLC) has not appreciably shifted in more than 20 years, outcomes have improved with median survival approaching 25-30 months, and approximately one third of patients now survive 5 years. This review examines current management, recent advances, and ongoing research in LS-SCLC.

Knowledge Generated

Recently completed and ongoing phase III studies of thoracic radiotherapy, prophylactic cranial irradiation (PCI), and systemic therapy aim to define best practices in LS-SCLC. The role of high-dose daily thoracic radiotherapy remains unsettled. Ongoing studies are geared toward reducing PCI-related neurotoxicity and questioning whether magnetic resonance imaging surveillance may obviate PCI. Trials integrating immune checkpoint inhibitors assess whether the benefits seen in extensive disease apply to LS-SCLC.

Relevance

Outcomes in LS-SCLC are promising with state-of-the-art combined modality therapy. Future progress may depend on refinement of local and systemic therapy with increasing personalization of treatment.

control, albeit at the expense of increased toxicity, with the addition of radiotherapy to chemotherapy.[9,10] The impact of local TRT may have been underestimated as included studies used antiquated staging and treatment techniques and used systemic therapy that would currently be considered suboptimal.

TRT TIMING AND SEQUENCING

Alternating or sequencing chemotherapy and TRT were common in early European trials, but administering TRT concurrent with chemotherapy has been adopted as standard practice, given the relatively favorable outcomes with this approach. The JCOG-9104 phase III trial strongly supported concurrent over sequential therapy in the setting of modern chemoradiotherapy, although OS differences did not quite reach statistical significance (median survival of 27 months compared with 19.7 months, $P = .08$).[11]

Although the long-standing debate regarding the optimal timing for TRT in LS-SCLC has not been completely settled, most guidelines and practice patterns are in line with TRT starting with the first or second cycle of chemotherapy.[12,13] Earlier TRT should result in better outcomes by reducing the time for resistant tumor clones to develop after initiating systemic therapy. The majority of studies directly addressing TRT timing are underpowered and further hampered by outdated staging and treatment methods. The primary trial supporting late TRT, CALGB 8083, was conducted before the routine utilization of cisplatin chemotherapy.[14] However, the classic National Cancer Institute of Canada study supporting early TRT used hypofractionated TRT and antiquated techniques including spinal cord (and potentially tumor) blocking.[15] While cycle 2 TRT bested cycle 6 TRT in the National Cancer Institute of Canada study, the benefit was attributed to fewer brain metastases with cycle 2 TRT, as local tumor control appeared similar in both cohorts.

Meta-analyses assessing TRT timing suggest benefit from early TRT with some caveats. The most comprehensive report, published in 2016, did not find an OS benefit for earlier or shorter TRT when data from nine studies including 2,305 patients were analyzed with median 10 years of follow-up.[16] However, the importance of maintaining chemotherapy intensity was emphasized as earlier TRT was beneficial among trials with a similar proportion of patients who were compliant with chemotherapy. This analysis is somewhat confounded by the inclusion of JCOG 9104, where early TRT was concurrent but late TRT was sequential following chemotherapy,[11] and the Intergroup (INT) 0096 trial, where TRT was initiated with cycle 1 in both arms and thus studied intensity of TRT, not simply timing.[17]

As a matter of clinical practice, it has become challenging to routinely initiate TRT with initial chemotherapy because of the complexity of modern radiotherapy treatment planning. There was a consensus to mandate cycle 1 TRT when CALGB 30610 (C30610) initiated, but the trial was amended early because of slow accrual and $< 50\%$ of patients received TRT with cycle 1 chemotherapy.[7] TRT was started with the second chemotherapy cycle in CONVERT,[8] and begins with cycle 2 chemotherapy in the ongoing NRG LU-005 assessing atezolizumab (NCT03811002). Early TRT is favored in our practice, but some clinical circumstances may dictate consideration of delaying TRT. Outcomes from select cooperative group studies dating back to INT-0096, including several initiating TRT with chemotherapy cycle 3 or 4, are detailed in Table 1.

TRT DOSE AND FRACTIONATION

Traditionally, modest doses of TRT (40-50 Gy) with conventional fractionation were thought to be effective for LS-SCLC, given the high tumor response rate. However,

TABLE 1. Prospective Clinical Trials of Concurrent Chemoradiation in LS-SCLC

Trial	Years	N	Chemotherapy	TRT	TRT Duration (weeks)	TRT Start	SER (days)	Med OS (months)
INT-0096[17]	1989-1992	417	PE	45 Gy once daily	5	Cycle 1	33[a]	19
				45 Gy twice a day	3	Cycle 1	19[a]	23
NCCTG[18]	1990-1996	262	PE	50.4 once daily	5.5	Cycle 4	101	21.9[b]
				48 Gy twice a day split	5	Cycle 4	93	19.9[b]
CALGB 9235[19]	1993-1999	307	PE	50 Gy once daily	5	Cycle 4	96	20.6
			TamPE	50 Gy once daily	5	Cycle 4		18.4
RTOG 9609[20]	1996-1998	55	PET	45 Gy twice a day	3	Cycle 1	19	24.7
ECOG 2596[21]	1997-1998	61	PET	63 Gy	7	Cycle 3	89	15.7
SWOG 9713[22]	1998-1999	87	PE—TC	61 Gy	6.5	Cycle 1	45	17
CALGB 39808[23]	1999-2000	75	TTpo—CE	70 Gy	7	Cycle 3	89	22.4
SWOG 0222[24]	2003-2006	68	TpzPE—PE	61 Gy	6.5	Cycle 1	45	21
CALGB 30002[25]	2001-2003	65	TETpo—CE	70 Gy	7	Cycle 3	89	20
RTOG 0239[26]	2003-2006	72	PE	61.2 Gy CB	5	Cycle 1	33	19
CONVERT[8]	2008-2013	547	PE	45 Gy twice a day	3	Cycle 2	40	30
				66 Gy once daily	6.5		66	25
Scandinavian[27]	2014-2018	170	PE[c]	45 Gy twice a day	3	Cycle 2	40	22.6
				60 Gy twice a day	4		47	37.2
CALGB 30610 RTOG 0538[7]	2008-2019	638	PE (81%) CE (19%)	45 Gy twice a day	3	Cycle 1 or 2	19-40	28.5
				70 Gy once daily	7		47-68	30.5

Abbreviations: C, carboplatin; E, etoposide; Irin, irinotecan; LS-SCLC, limited-stage small-cell lung cancer; OS, overall survival; P, cisplatin; PE, etoposide and cisplatin; SER; approximate time from start of chemotherapy to end of radiotherapy; T, paclitaxel; Tam, tamoxifen; Tpo, topotecan; Tpz, tirapazamine; TRT; thoracic radiotherapy.

[a]May have been longer in some patients, and radiation therapy was permitted to start during cycle 1, not necessarily on day 1 of cycle.

[b]Includes only those without disease progression who were randomly assigned after third cycle of PE.

[c]Carboplatin substitution for cisplatin for toxicity concerns in some patients, per protocol.

ultimate local tumor control is suboptimal following conventional TRT as best demonstrated by the outcomes after 45 Gy once-daily radiotherapy from INT-0096, as the majority of patients had a component of thoracic tumor relapse.[17]

An accelerated twice-daily regimen was developed in the 1980s in an effort to enhance TRT efficacy. INT-0096 tested both fractionation and TRT intensity in comparing 45 Gy once-daily TRT over 5 weeks with 45 Gy twice-daily (twice a day) TRT over weeks. OS was significantly improved on the twice a day arm as 5-year OS increased from 16% to 26% with twice a day TRT, creating a paradigm shift toward more routine consideration of accelerated hyperfractionation.[17] The main tradeoff in the experimental arm was a doubling of severe acute esophageal toxicity. INT-0096 was one of the few trials (in any disease) to demonstrate altering the intensity of radiotherapy in a chemotherapy-sensitive disease could ultimately affect OS. Nevertheless, the impact on clinical practice was muted in part because of concerns about treatment-related toxicity and logistical considerations with treating patients twice a day. Only 25% of recently surveyed radiation oncologists favored twice a day radiation therapy (RT).[28]

One criticism articulated regarding INT-0096 was the relatively low dose of once-daily TRT used, and the (unproven) widely held assumption that higher-dose once-daily TRT would be as effective as twice a day TRT. The advent of advanced radiotherapy planning facilitated the utilization of high-dose daily radiotherapy in multiple prospective trials in NSCLC and LS-SCLC. Even before conformal radiotherapy, phase I data from the CALGB noted the maximum tolerated dose for daily fractionation to be at least 70 Gy in 35 fractions.[29] A subsequent phase II CALGB trial using 70 Gy daily RT suggested promising outcomes, particularly since TRT was initiated with the third cycle of chemotherapy and a carboplatin backbone was used.[23] Two major phase III trials have now been reported assessing whether high-dose once-daily TRT would improve OS compared with standard 45 Gy twice a day TRT.[7,8] In the CONVERT trial, conducted in Europe and Canada, high-dose once-daily (66 Gy in 33 fractions) was not superior to 45 Gy twice a day. Median OS was 30 and 25 months, and 5-year OS was 34% and 31% in the twice a day and once-daily arms, respectively. Although the hazard ratio favored twice a day TRT, the difference did not reach statistical significance ($P = .14$). CONVERT investigators concluded twice a day regimen

should remain the standard of care and noted that more patients assigned to twice a day completed TRT. Regardless, the subsequently designed LU-005 trial permits either 66 Gy once-daily or 45 Gy twice a day. Initial results of the C30610/RTOG 0538 were recently presented. Once again, once-daily TRT, this time 70 Gy once-daily in 35 fractions over 7 weeks, was not superior to 45 Gy twice a day in 3 weeks.[6] The median and 5-year OS were 30.5 months and 34% with 70 Gy once-daily TRT and 28.5 months and 29% with 45 Gy twice a day, respectively. While not designed to assess noninferiority, the favorable outcomes for the 70 Gy cohort provides the strongest evidence supporting high-dose once-daily TRT in LS-SCLC. In contrast to the INT-0096 trial, most toxicities were comparable between treatment arms in both the CONVERT and CALGB trials with similar rates of esophageal toxicity.

The lack of an OS benefit with high-dose once-daily TRT in the CONVERT and CALGB trials coupled with the outright negative results of high-dose once-daily TRT in NSCLC have called into question the role of conventional dose escalation in the face of chemoradiotherapy for lung cancer.[7,8,30] Although outcomes with 70 Gy cohort in the initial report of the CALGB study seem favorable, direct evidence supporting a dose response for once-daily TRT is lacking. Further dosimetric analysis from recent randomized trials may provide insight regarding the therapeutic index for high-dose once-daily TRT, with particular attention given to the impact of high TRT doses to normal structures.

Alternative approaches to improve TRT efficacy have included studying whether accelerating the treatment course may be just as effective using hypofractionated TRT (larger once-daily fractions). In a Norwegian phase II study, 45 Gy twice a day resulted in more complete responses and numerically longer median OS compared with 42 Gy in 15 fractions, both completed over 3 weeks.[31] This group more recently reported provocative results with higher-dose twice a day TRT, 60 Gy in 40 fractions, as 2 years OS reached 74% in a phase II setting. A phase III comparison with 45 Gy twice a day is ongoing to determine whether the benefit of 60 Gy twice a day TRT will hold up.[27] A hybrid concomitant boost approach, mixing once-daily and twice a day TRT, was studied in RTOG-0239 and initially included in the C30610 trial.[26] This arm was dropped from the study during a planned interim analysis,[32] but long-term outcomes from this cohort will soon be available.

TRT PLANNING

Advances in radiotherapy planning coupled in part with a shift in treatment philosophy away from treating clinically uninvolved regional nodal regions have contributed to an improved therapeutic ratio. Seminal trials such as INT-0096 electively targeted the bilateral mediastinal lymph nodes (at a minimum). Implementation of fluorodeoxyglucose-PET imaging for treatment planning may identify unsuspected regional nodal metastasis up to 25% of patients. Several reports suggest treatment of clinically uninvolved mediastinal nodal regions may safely be omitted in PET staged patients.[33-35] CONVERT and C30610 did not include elective mediastinal irradiation, although the ipsilateral hilum was included in the C30610.

Many treatment planning considerations for LS-SCLC mimic the NSCLC setting. Accounting for tumor movement is critical, and four-dimensional computed tomography should be routinely used to encompass target motion, with expansions for clinical target volume and planning target volume. If chemotherapy has been initiated before TRT, target volumes should be designed to account for response to chemotherapy though initially involved nodal regions should be targeted. Image guidance preferably with cone-beam computed tomography is preferable and may be particularly helpful in detecting rapid changes in tumor volume during therapy in patients with bulky SCLC. Adaptive replanning should be considered in cases of major response and/or significant anatomic changes during therapy, and was included as an option on the 70 Gy arm of C30610. Intensity-modulated radiotherapy (IMRT) often results in superior dosimetric plans compared with 3D conformal radiation therapy, with the suggestion of improved outcomes from a post hoc analysis of RTOG-0617.[36] Cardiac dosimetry was independently associated with OS, underscoring the importance of heart avoidance. Approximately half of C30610 patients were treated with IMRT, and analysis is planned with particular focus on cardiac dose and other organs at risk.

As bulky mediastinal adenopathy is common in SCLC, meeting traditional metrics used for planning NSCLC, particularly volume of lung receiving 20 Gy (V20), can be challenging. V20 lung was predictive of pulmonary toxicity in a review 100 patients treated to 70 Gy on phase II CALGB SCLC trials. Although V20 lung exceeded 40% in 30 patients, only three patients developed grade 3 toxicity, with no grade 4-5 events.[37] These data support consideration of aggressive treatment of LS-SCLC even when traditional metrics cannot be strictly met (ie, V20 $<$ 35%-40%). Otherwise, organ at risk constraints parallel those for NSCLC when conventional fractionation is used. With 45 Gy twice a day TRT, less data are available to guide normal tissue constraints, although particular attention should be given to spinal cord dosing.

CURRENT STATE OF PCI

PCI has been a mainstay of treatment in SCLC for decades. A meta-analysis from the late 1990s demonstrated a significant reduction in intracranial metastases (IM) and a 5.4% improvement in survival at 3 years after complete tumor response in patients with mostly LS-SCLC.[38] The observation that higher doses of PCI resulted in a lower rate of IM led to development of trials comparing high-dose PCI, 36 Gy either once-daily or twice a day, to standard 25 Gy in

10 fractions.[39,40] Unfortunately, higher-dose PCI was associated with both higher late neurotoxicity and reduced OS. Concerns over the late neurocognitive effects of PCI have underpinned the design of recent trials. NRG CC003, which builds upon the experience with hippocampal-avoidant whole-brain RT in the IM population, compares standard whole-brain radiotherapy (WBRT) with hippocampal-avoidant-IMRT (NCT02635009) with primary end points of neurocognitive decline and intracranial relapse. More recently, the benefit of PCI as a routine component of initial therapy has been directly challenged in large part to results of a Japanese trial in extensive-stage (ES)-SCLC, which suggested that with strict MRI staging and surveillance, PCI does not improve OS.[41] The substantial reduction in incidence of IM (69% *v* 48%) with PCI did not lead to an OS difference. Although this trial did not include patients with LS-SCLC, it was noted that trials included in the classic meta-analysis demonstrating an OS benefit with PCI were performed before routine availability of MRI. A recently activated phase III noninferiority study (SWOG 1827 aka MAVERICK) compares PCI with MRI surveillance in both LS-SCLC and ES-SCLC (NCT04155034). A key secondary end point is the rate of cognitive failure–free survival. Moreover, recent data challenge the long-held axiom that, given the concern of subsequent rapid intracranial relapse, WBRT is necessary in treating brain metastases in SCLC.[42] Radiosurgery is currently being studied as an alternative to WBRT (NCT04804644), and if radiosurgery is ultimately deemed an acceptable strategy for managing SCLC BM, it may provide further ammunition to modify routine practice of PCI.

Although the role of PCI has been questioned in LS-SCLC, the majority of prospective data emanate from trials including PCI. For the time being, there are insufficient data to abandon the practice, and PCI remains a standard recommendation on the active LU-005 trial.

SYSTEMIC THERAPY

Systemic chemotherapy for lung cancer dates back to the first half of the 20th century including a Veterans Affairs comparison of various agents including nitrogen mustard, diethylstilbestrol, testosterone, progesterone, and cortisone to treat inoperable bronchogenic malignancies, including SCLC.[43] The observation that using multiple non–cross-resistant chemotherapy agents lead to better outcomes than using single-agent chemotherapy led to the use of multidrug regimens such as cyclophosphamide, doxorubicin, and vincristine; cyclophosphamide, epirubicin, and vincristine; and etoposide and cisplatin (PE).[44] Etoposide was noted to particularly be active in SCLC, and synergistic when combined with cisplatin, with complete response rate of 52% and partial response rate of 48% in patients with limited-stage disease.[45] PE also became the preferred regimen for SCLC because of toxicity profile and the ability to safely integrate with TRT. Various PE dosing regimens are used in LS-SCLC, including cisplatin 60 mg/m^2 on day 1 and etoposide 120 mg/m^2 on days 1-3 as used in INT-0096, with alternative

TABLE 2. Ongoing Phase II and Phase III Studies of ICI in LS-SCLC

Agent	Mechanism of Action	Phase	Sample Size	Primary End Point	NCT
Concurrent with chemoradiation and as consolidation					
Durvalumab	Anti–PD-L1	2	51	PFS	NCT03585998
Durvalumab (DOLPHIN)	Anti–PD-L1	2	105	PFS	NCT04602533
Pembrolizumab concurrent followed by pembrolizumab ± olaparib (KEYLYNK-013)	Anti–PD-1 and PARP inhibitor	3	672	PFS, OS	NCT04624204
Atezolizumab (NRG LU-005)	Anti–PD-L1	2 or 3	506	PFS or OS	NCT03811002
Sintilimab induction plus platinum-etoposide, followed by chemoradiation and sintilimab consolidation	Anti–PD-1	2	140	PFS	NCT04189094
Consolidation following chemoradiation					
Toripalimab	Anti–PD-1	2	170	PFS	NCT04418648
SHR-1316	Anti–PD-1	2	60	PFS	NCT04647357
Atezolizumab (ACHILES)	Anti–PD-L1	2	212	2 year OS	NCT03540420
Ipilimumab and nivolumab (STIMULI)	Anti–CTLA-4 and anti–PD-1	2	174	OS, PFS	NCT02046733
Durvalumab plus or minus tremelimumab (ADRIATIC)	Anti–PD-L1 and anti–CTLA-4	3	724	PFS, OS	NCT03703297
Atezolizumab ± tiragolumab	Anti–PD-L1 and anti–TIGIT	2	150	PFS	NCT04308785

Abbreviations: CTLA-4, cytotoxic T-cell lymphocyte-4; ICI, immune checkpoint inhibitor; LS-SCLC, limited-stage small-cell lung cancer; OS, overall survival; PD-L1, programmed death ligand-1; PFS, progression-free survival.

TABLE 3. Outcomes of Patients With Early-Stage SCLC Treated With Local Therapy With or Without Chemotherapy

Author (date)	Type	N	Stage(s)	Local Treatment	Chemotherapy	Survival
Yu et al (2010)[52]	SEER	205[a]	I	Surg	NR	5 years 50%
		38[a]		Surg plus RT		5 years 57%
Takei et al (2014)[53]	Retrospective	168	I	Surg	76%[b]	5 years OS IA: 64%-72% IB: 46%-61%
Yang et al (2016)[54]	NCDB	954	I	Surg	57%	5 years 47%
Verma et al (2017)[55]	Multi-inst retrospective	74	I	SBRT	56%	3 years 34% MS 31 months (w/CT) 14 months (w/o CT)
Paximadis et al (2018)[56]	NCDB	943	I	Surg	54%	3 years 62%
		140		SBRT	51%	3 years 40%
		1,595		EBRT	93%	3 years 44%
Salem et al (2019)[57]	CONVERT RCT	35	I-II	45 Gy twice a day	100%	MS 72 months
		51		66 Gy once daily		MS 39 months
Newman et al (2019)[58]	NCDB	239	I	SBRT	35%	MS 2.2 years 5 years 27%
		1,139		EBRT	89%	MS 2.1 years 5 years 26%
Raman et al (2021)[59]	NCDB	1,948	I	Surg	36%	5 years OS Wedge: 31% Segm: 35% Lobe: 45%

Abbreviations: Adj, adjuvant; cIA/B, clinical stage IA/B; CT, chemotherapy; EBRT, fractionated external beam radiotherapy; IND, induction; MS, median survival; NCDB, National Cancer Database; NR, not reported; OS, overall survival; pIA/B, pathologic stage IA/B; PORT, postoperative radiotherapy; RCT, randomized controlled trial; SBRT, stereotactic body radiotherapy; SCLC, small-cell lung cancer; Surg, surgical resection; w/, with; w/o, without.

[a]Selected patients who underwent lobectomy.

[b]Of entire reported population (stage I-III). Chemo receipt NR for individual stage groups.

regimens of cisplatin 75 mg/m^2 on day 1 and etoposide 100 mg/m^2 on days 1-3, or cisplatin 25 mg/m^2 on days 1-3 and etoposide 100 mg/m^2 on days 1-3, both of which were permitted on CONVERT.[8,17] Four cycles of chemotherapy are recommended, and the use of myeloid growth factors is not recommended during concurrent chemoradiation because of potential severe toxicity.[12,46]

Attempts to improve outcomes with the inclusion of more intensive systemic therapy, newer-generation chemotherapy, and systemic targeted therapy have been unsuccessful in improving the therapeutic index. For example, the addition to paclitaxel to PE with 45 Gy twice a day increased acute toxicity without improving outcomes in the phase II RTOG 9609 study and a pilot SWOG 0222 trial demonstrated the hypoxic cell sensitizer tirapazamine increased toxicity without clear benefit.[20,24] Although there was substantial initial enthusiasm for anti–vascular endothelial growth factor agents in SCLC, the addition of bevacizumab to chemoradiotherapy resulted in severe local toxicity including tracheoesophageal fistula.[47] Treatment with irinotecan and cisplatin resulted in improved OS compared with PE in ES-SCLC in a Japanese experience, but the JCOG 0202 study did not show a benefit for including consolidation irinotecan and cisplatin in LS-SCLC.[48,49]

Carboplatin is often substituted for cisplatin in clinical practice, given underlying comorbidities in many patients with LS-SCLC. Carboplatin is generally better tolerated, although hematologic toxicity may be greater. A meta-analysis of four randomized studies comparing first-line cisplatin versus carboplatin included two trials of patients with LS-SCLC.[50] Response rate, progression-free survival (PFS), and OS were similar in both chemotherapy groups. Although most LS-SCLC prospective studies have been restricted to PE, C30610 was amended to allow carboplatin to enhance accrual, and the active LU005 trial allows either carboplatin or cisplatin. When used in LS-SCLC, the recommended dosing is carboplatin area under the curve 5-6 on day 1 and etoposide 100 mg/m^2 on days 1-3.

The addition of ICIs to first-line chemotherapy has resulted in mixed success in ES-SCLC. Although programmed death ligand-1 (PD-L1) inhibitors modestly improve survival, improved outcomes have not been observed with cytotoxic T-cell lymphocyte-4 inhibition in the front-line setting.[4-6] Consolidation ipilimumab and nivolumab did not improve 2-year PFS in the STIMULI phase II trial, although long-term OS may be a better metric for ultimate efficacy of ICIs.[51] Ongoing phase 2 or 3 clinical trials evaluating the role of

TABLE 4. Transcriptional Subtypes of LS-SCLC and Therapeutic Vulnerabilities

Subtype	Hallmarks	Frequency, %	Therapeutic vulnerability
SCLC-A	High ASCL1 expression, DLL3 expression	36	BCL2 inhibition, DLL3 antibody-drug conjugates, DLL3 BiTE
SCLC-N	High NEUROD1 expression, MYC expression, high expression of somatostatin receptor 2 (SSRT2)	31	Aurora kinase A inhibition, somatostatin analog, antibody-drug conjugates targeting SSRT2
SCLC-P	High POU2F3 expression	16	PARP inhibition, antimetabolite
SCLC-I (inflamed subtype)	Lack ASCL1, NEUROD1 and POU2F3 expression High expression of genes related to immune cell infiltration, immune checkpoints, HLA genes, interferon gamma activation High expression of Bruton tyrosine kinase	17	Immune checkpoint inhibitors Bruton kinase inhibitors

Abbreviations: BiTE, bispecific T-cell engager; LS-SCLC, limited-stage small-cell lung cancer; PARP, poly (ADP-ribose) polymerase; SCLC, small-cell lung cancer.

ICIs concurrent or adjuvant to chemoradiation LS-SCLC are listed in Table 2.

SPECIAL CONSIDERATIONS

Although early-stage (node-negative) disease only represents approximately 5% of SCLC, debate regarding optimal local management has grown in recent years with increased utilization of stereotactic body radiotherapy (SBRT) as well as advances in thoracic surgical techniques. There is limited prospective surgical evidence in SCLC, although National Comprehensive Cancer Network guidelines include surgical resection for patients with T1-2 N0 patients following mediastinal staging.[12] This is supported by contemporary database studies describing encouraging outcomes. SBRT has also been proposed as an attractive option for this population, as underlying lung disease renders many patients with SCLC medically inoperable, and is included in updated guidelines.[13] Analogous to surgery, supporting data are limited to retrospective or database series. Table 3 summarizes select reports in early-stage SCLC, recognizing limitations in the data regarding the relative value of surgery and radiotherapy. The CONVERT study provides particularly provocative prospective data for chemoradiotherapy in early-stage SCLC with median OS of 50 months for all stage I-II patients, reaching 72 months for those in the twice a day TRT cohort.[57] As such, treatment with chemoradiation should not be dismissed as a consideration for appropriate patients with early disease. Regardless of local therapy, adjuvant chemotherapy should be considered for node-negative patients, best illustrated by a National Cancer Database analysis of 954 patients, where adjuvant chemotherapy was associated with improved median OS from 42 to 66 months after R0 resection.[54] Prospectively, the addition of atezolizumab to neoadjuvant chemotherapy is being evaluated in surgical patients (NCT04696939). Striking improvements in OS have also been reported with the use of chemotherapy in patients treated with SBRT.[55,60] Current guidelines suggest consideration of adjuvant mediastinal radiation therapy for pathologic N2 disease, although data are limited.[12,61] The use of PCI in early-stage disease is controversial and has been particularly questioned in surgical patients with N0 disease.[62]

TREATMENT OF OLDER PATIENTS

Relatively little prospective evidence is available to guide therapy for elderly patients with LS-SCLC, although the median age at diagnosis approaches 70 years. Given the abysmal prognosis without therapy, undertreatment is a major concern in elderly patients, and 40% of patients age 70 years or older in a National Cancer Database analysis did not receive TRT.[63] Multivariate analysis suggested treatment with combined therapy had the greatest impact on OS, even for patients $>$ 80 years, and the benefit held for the population with defined comorbidity. Evidence from prospective clinical trials also suggests patients benefit from aggressive treatment regardless of age. Similar response rates and event-free survival were observed with older and younger patients on INT-0096, with a suggestion of improved outcomes with twice a day TRT.[64] The recent CONVERT trial provides even more promising evidence for treatment of older patients with modern therapy as median OS (29 months *v* 30 months) and PFS (18 months *v* 16 months) were essentially equivalent in patients older and younger than 70 years, respectively.[65] Older patients may be at increased risk for treatment-related toxicities, often meriting careful patient selection including the use of formal geriatric assessment tools, using measures to mitigate toxicity, and ensuring close monitoring. In the CONVERT trial, chemotherapy compliance was similar regardless of age, although older patients were less likely to complete optimal TRT. Deciding whether older patients should receive PCI is particularly complex, as studies suggest neurotoxicity may be directly related to age, yet clinical trial analysis suggest that fit older patients may still benefit from PCI.

FUTURE DIRECTIONS

There is ample opportunity to move beyond the standard treatment approach for LS-SCLC defined last century by

INT-0096—through optimization or intensification of local therapy, challenging traditional thinking about the role of PCI (with critical attention toward quality of life), and particularly developing more effective systemic therapy. Radiotherapy advances such as adapting TRT intensity to metabolic tumor response and treatment with proton therapy are of interest but may not be widely applicable to patients with LS-SCLC, although tailoring TRT according to disease extent, underlying patient characteristics, and tumor biology should be an area of focus in the future.

In contrast to NSCLC, identifying actionable therapeutic targets and valid biomarkers to direct systemic therapy in SCLC has remained challenging. PD-L1 expression and tumor mutational burden do not necessarily correlate with the OS benefit observed with ICIs in ES-SCLC, and treatment benefit might depend on other factors related to the tumor microenvironment. Although active phase III trials will help determine whether ICIs have magnified benefit in LS-SCLC, perhaps because of lower (micro)metastatic tumor burden or interrelationship between ICIs and TRT, additional strategies will be needed for the majority of patients with LS-SCLC. To that extent, other agents including DNA damage response inhibitors and TIGIT targeting antibodies (NCT04624204 and NCT04308785) are being studied in combination with PD(L)-1 inhibitors (Table 2). Gay et al, using tumor expression data mostly derived from resected LS-SCLC, recently suggested a framework for a personalized approach with the classification of four distinct SCLC subtypes. Hallmarks of these subtypes and potential therapeutic vulnerability are shown in Table 4.[66] Of particular note is an inflamed subtype, most likely to respond to ICIs, which was seen in only 17% of patients. Additional molecular changes inherent to SCLC may potentially be exploited including loss of tumor suppressor genes *TP53* and *Rb1*.[67] The novel p53 reactivator eprenetapopt has shown promise in hematologic malignancies and is being studied in solid tumors along with pembrolizumab (NCT04383938).[68,69] *FGFR1* alterations may also be present in SCLC, and a phase I trial is evaluating anlotinib, an FGFR 1-3 multikinase inhibitor, concurrent with chemoradiation in LS-SCLC (NCT04882033).[67]

In the end, it will also be essential to gain a better understanding of the interdependence of local and systemic therapy to optimize management of LS-SCLC. Both the sequence and intensity of TRT may ultimately affect response to novel therapeutics, while newer systemic agents may affect thoracic and CNS relapse as demonstrated in trials assessing ICIs in NSCLC,[70] potentially influencing decisions regarding TRT and/or shifting the therapeutic ratio of PCI.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Radiation and Systemic Therapy for Limited-Stage Small-Cell Lung Cancer

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