Review Article on Small Cell Lung Cancer

Systemic therapy for limited stage small cell lung carcinoma

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Abstract: Systemic treatment in small cell lung carcinoma has been a challenge for oncologists for decades. The high propensity for recurrence is usually due to distant metastasis, which makes systemic treatment an essential component of treatment in small cell lung carcinoma. The regimen of cisplatin and etoposide (established in the mid-1980's) concurrently with thoracic radiotherapy followed by prophylactic cranial irradiation (PCI) remains the standard of care in limited stage disease. Despite numerous trials, this regimen has not been improved upon. The standard combination regimen of cisplatin and etoposide has been compared to alternative platinum-containing regimens with drugs like epirubicin, irinotecan, paclitaxel, topotecan, pemetrexed, amrubicin and belotecan. Non-platinum containing regimens like ifosfamide and etoposide have also been tested. Attempts to intensify therapy have included the addition of a third drug like paclitaxel, ifosfamide, tirapazamine, tamoxifen, and thalidomide. Maintenance therapy following induction with chemotherapy, vandetanib and interferon-alpha have also been attempted. Molecularly directed targeted therapies and immunotherapeutic agents are areas of active research. In this review, we discuss the various systemic therapy options in limited stage small cell lung carcinoma, from the historical regimens to the modern-day therapy and promising areas of research. We also discuss the role of growth factors, the optimal number of chemotherapy cycles, the use of prognostic and predictive factors, the optimal timing of chemotherapy and the treatment of special populations of patients including older patients, and patients with comorbidities.

Keywords: Small cell lung cancer (SCLC); limited-stage; chemotherapy; immune therapy; targeted therapy; radiation; prophylactic cranial irradiation; etoposide; platinum

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Introduction

Small cell lung cancer (SCLC) is an aggressive disease with a rapid doubling time. SCLC accounts for less than 15% of all lung cancers and unlike other types of lung cancer, it spreads early and usually presents with disseminated disease. The median overall survival (OS) in patients with disseminated disease ranges from 7–12 months; recently, survival has been prolonged by a median of 2–3 months with the introduction of immune checkpoint inhibitors in the first-line setting. The 5-year OS is approximately 6.4% (1,2).

Over 60 years ago, the Veterans Affairs Lung Group (VALG) provided a simple and practical staging system for SCLC, which in spite of the more recent recommendation of the International Association for the Study of Lung Cancer (IASLC) to stage SCLC according to the American Joint Committee on Cancer (AJCC) tumor-node-metastasis (TNM) staging system, is still widely followed today. As per the conventional VALG staging, limited stage (LS) SCLC is disease that is limited to one hemithorax and can be encompassed safely within a single radiation portal (3). Using the TNM staging system, LS SCLC refers to any

T (except a tumor with multiple ipsilateral lung nodules that cannot be included in a single radiation portal), any N, but no M., i.e., patients with no distant metastases (4). Approximately 40% of patients with SCLC present with LS disease (5).

SCLC is highly chemosensitive, with responses to chemotherapy often ranging between 60% and 80% (1). Unfortunately, these tumors are quick to recur and metastasize to regional or distant sites and if left untreated, the expected survival is just 2 to 4 months for recurrent or metastatic disease. The doubling time of this tumor is 86 days (range, 25–217 days) (6) and hence the National Institute for Health and Care Excellence (NICE) guidelines recommend that patients with SCLC should be evaluated by a thoracic oncologist within one week after the decision to offer therapy (7).

Contrasting to the tremendous progress that has been made in the therapy of non-small cell lung cancer (NSCLC) and to a lesser degree in extensive stage (ES) SCLC, for the past two decades, there has been very little change in the way we treat LS SCLC, i.e., the combination of platinum and etoposide (EP) with concurrent thoracic radiation therapy (TRT) still remains the most widely used regimen with clinical trials consistently reporting a median OS of 25 to 30 months and a 5-year survival rate of 30% to 35% (8).

In this article, we comprehensively review the systemic therapy options available to treat LS SCLC ranging from the age-old concurrent chemoradiotherapy (CRT) to the latest ongoing immunotherapy trials.

Materials and methods

We searched PubMed using the terms "chemotherapy in small cell lung carcinoma", "treatment in limited stage small cell lung carcinoma", "newer agents in small cell lung carcinoma", "recent advances in treatment of limited stage small cell lung carcinoma", "management of poor performance status lung carcinoma", and "targeted therapies in small cell lung carcinoma". We excluded articles that were about NSCLC and selected those related to SCLC. We then selected the articles that were related to the management and systemic therapy of SCLC. We excluded articles for which the full text was not available, and articles that were not in English. We then searched in Google for details of ongoing trials and the abstracts of scientific meetings, and we also manually looked through the references of the selected articles.

Historical regimens

The journey of systemic therapy in SCLC, as with all solid tumors began with the introduction of nitrogen mustard in the 1940s. One of the earliest studies to evaluate the role of various therapies in lung cancer was by the Veterans Administration Cooperative Study of the Therapy of Lung Cancer (9). They divided 496 patients with lung cancer (81 patients had SCLC) into groups that were treated with nitrogen mustard, steroid hormones (cortisone, diethyl stilbestrol, progesterone, testosterone) and an inert substance (lactose). The proportion of patients who were alive at the end of 90 days in the nitrogen mustard arm was 63%, versus 51% in the inert substance arm and 37% in the cortisone-treated arm. The corresponding median OS were 121, 93 and 56 days respectively.

In 1969, the VALG reported their experience on the use of alkylating agents in patients with lung cancer. They found that nitrogen mustard led to better responses in patients with squamous cell lung cancer while cyclophosphamide was the preferred agent in patients with small cell undifferentiated carcinoma (10). This was the first study that demonstrated a statistically significant survival advantage from cyclophosphamide versus placebo (4 versus 1.5 months).

Subsequently, various other chemotherapeutic agents have been found to have single agent activity in SCLC. These include epipodophyllotoxins like etoposide, platinum compounds, anthracyclines, paclitaxel, docetaxel, gemcitabine, amrubicin, vinorelbine and temozolomide. These have been tested mainly in patients with relapsed/refractory SCLC and have demonstrated modest efficacy (11). One of the major breakthroughs in the treatment of SCLC was the realization that combining multiple non-cross resistant chemotherapy agents led to better results than single agents alone. In 1973, Livingston *et al.* studied the kinetically scheduled combination of vincristine and bleomycin in 15 patients with lung cancer, one of whom had SCLC. This combination was chosen based on the low myelosuppressive potential of bleomycin. The ORR to this regimen was 27% (12). In the subsequent year, Einhorn and colleagues studied the four-drug combination of bleomycin, doxorubicin, cyclophosphamide and vincristine in 29 patients with SCLC; 4 had LS SCLC. All the patients with LS SCLC attained a complete remission (CR), and in 2 patients, the responses were durable; sustained at 52 and 60 weeks. The median OS from the initiation of therapy

was 35 weeks. The major toxicity was leucopenia; 10% patients developed neutropenic infection and there was 1 (3.4%) drug-related death (13).

Despite being a highly chemosensitive tumor, even the combination of multiple agents led to only a short OS as almost all patients relapsed. Relapse in the intrathoracic region occurred in 75–90% of patients treated with chemotherapy alone for LS SCLC (14). Addition of TRT to the first line therapy increased the toxicity, but led to increased remissions, lower risk of local failures and prolonged survival (15,16). Concurrent CRT has now become the current established standard of care for LS SCLC.

Two drug combination regimens

Etoposide with cisplatin (EP) combination

From studies in mice, it was noted that the addition of cisplatin to etoposide led to synergistic effects (17). In 1979, Sierocki *et al.* reported that an induction regimen of EP alternating with cyclophosphamide, doxorubicin and vincristine (CAV) led to ORR of 100% in LS SCLC [52% CR and 48% partial remission (PR)]. The tumors responded rapidly, and responses peaked by 6 weeks. Side-effects included myelosuppression, renal failure, nausea, vomiting and alopecia (18). Subsequently, Evans *et al.* used EP alone as induction therapy in 31 patients with SCLC, 11 of whom had LS SCLC. The ORR was 86% (43% CR and 43% PR). The median duration of response in patients with LS SCLC was 39 weeks, and the median OS in responding LS SCLC patients was 70 weeks (19). Subsequently, EP with concurrent TRT has become the standard of care for LS SCLC.

EP has been evaluated concurrently along with altered fractionation schedules. Altered fractionation could include accelerated regimens, in which the same total dose is delivered in a shorter period, or hyperfractionated regimens in which two or more fractions of a lower dose are delivered in a day. In the pivotal Intergroup 0096 study, 417 patients with LS SCLC were randomly assigned to EP with concurrent 45 Gy of TRT, either delivered once daily over 5 weeks or twice daily over 3 weeks. Grade 3 esophagitis was more common at 27% in the twice-daily radiation arm compared to 11% in the once-daily arm. The median OS, 2-year OS and 5-year OS were significantly better in the twice-daily compared to the once-daily TRT arms at 23 *vs.* 19 months, 47% *vs.* 41%, and 26% *vs.* 16% respectively; P=0.04 (20). However, critics of the study noted that the patients in the standard arm received a suboptimal TRT dose of 45 Gy.

The CONVERT trial (8) was a superiority trial that sought to answer this question; the standard arm was EP with twice-daily TRT based on the Intergroup 0096 study. 547 patients with LS SCLC were randomized to EP for 4 to 6 cycles, concurrent with TRT (starting on day 22 of EP chemo) as either 66 Gy in 33 fractions of 2 Gy each, once daily over 45 days or 45 Gy in 30 fractions of 1.5 Gy each, twice a day over 19 days. Toxicities were similar between the two arms other than a higher incidence of grade 4 neutropenia in the twice-daily TRT arm (49% *vs.* 38%, P=0.05). There was no difference in efficacy endpoints between the two arms: median OS and 2-year OS in the twice-daily TRT *vs.* once-daily TRT arms were 30 *vs.* 25 months (HR, 1.18; 95% CI, 0.95 to 1.45; P=0.14), and 56% *vs.* 51% respectively. Since this was not a non-inferiority trial, the authors concluded that EP with twice-daily TRT should remain the standard of care. However, due to logistic challenges, inconvenience to patients, concerns regarding toxicity and the fact that there was no apparent survival benefit in the twice-daily TRT arm, the most commonly used regimen for LS SCLC continues to be EP with once-daily TRT with standard fractionation: 60 to 66 Gy in 30 to 33 fractions (21,22). The Alliance for Clinical Trials in Oncology is conducting NCT00632853, a Phase III trial comparing once daily radiation (70 Gy in 2 Gy/fraction daily for 7 weeks) or twice daily radiation (45 Gy in 1.5 Gy/fraction twice a day for 3 weeks), combined in both arms with 4 cycles of EP (23).

Epirubicin-based combination regimen

In 2004, the Spanish Lung Cancer group reported a multicenter randomized controlled trial (RCT) that compared high dose epirubicin (Ep, 100 mg/m^2 on day 1 every 21 days) and cisplatin (P, 100 mg/m^2 on day 1 every 21 days) to the standard EP regimen (E, 100 mg/m^2 on days 1 to 3 with P, 100 mg/m^2 on day 1 every 21 days) for 6 cycles in newly diagnosed SCLC patients (24). Of the 402 patients included in the study, 207 (51.5%) had LS SCLC; these patients received TRT; prophylactic cranial irradiation (PCI) was administered to those who attained a CR. The ORRs were similar between the two arms (EP-68.7% *vs.* EpP-74.5%) and there was no difference in OS, which was the primary endpoint (EP-10.1 months *vs.* EpP-10.4 months). Patients with LS SCLC had a better ORR (EP, 78.5%; EpP, 82.0%) and a better median OS (12.9 months in both the arms). Patients in the EpP arm experienced less toxicity, and the difference was significant in patients with LS SCLC (54.7% *vs.* 37%; P=0.005) (24). Thus, EpP is a valid

treatment option for LS SCLC.

Irinotecan-based combination regimens

Han and colleagues at the National Cancer Center in Korea studied the role of irinotecan with cisplatin as induction therapy in a phase II trial in LS SCLC (25). They treated 35 patients with 2 cycles of induction irinotecan (I, 80 mg/m^2) and cisplatin (P, 40 mg/m^2) on days 1 and 8 every 21 days, followed by EP and concurrent twice-a-day TRT. The ORR to induction IP was 97% (9% CR, 89% PR), which increased to 100% after EP CRT. The median PFS was 12.9 months, the median OS was 25 months (95% CI, 19 to 30.9), the 1-year OS was 85.7% and the 2-year OS was 53.9%. Grade 3 and higher neutropenia and febrile neutropenia occurred in 68% and 20% of patients respectively during induction IP, and in 100% and 60% respectively during EP CRT.

A similar phase II study, the CALGB 30206 in 75 patients with LS SCLC evaluated the role of induction IP consisting of irinotecan, 65 mg/m^2 and cisplatin 30 mg/m^2 on days 1 and 8 every 3 weeks for 2 cycles followed by etoposide and carboplatin concurrently with TRT (26). The ORR was 71% (7% CR and 64% PR), which increased to 88% as the best response to all therapy. The median PFS, median OS, 1-year OS and 2-year OS were 12.6 months, 18.1 months, 69% and 31% (95% CI, 22–43%). The preplanned target for 2-year OS of 60% was unfortunately not met.

A phase I dose escalation study found that irinotecan at 60 mg/m^2 on days 1, 8, 15 with cisplatin 20 mg/m^2 on days 1 to 3 and 29 to 31 (IP) concurrently with conventional fractionated TRT, followed by 4 cycles of consolidation chemotherapy was well tolerated with no dose limiting toxicity (27). However, IP administered as a once-in-3-weeks regimen with concurrent TRT was excessively toxic (28). Three phase II studies have evaluated the efficacy and toxicity of IP concurrently with radiotherapy (29-31). The doses of irinotecan in two of the three trials was 60 mg/m^2 on days 1, 8 and 15 every 4 weeks. The ORR ranged from 85% to 93% and the median OS ranged from 20 to 26 months. The common toxicities were gastrointestinal (diarrhea in 20% to 35%), asthenia (67%), pneumonitis (18%), esophagitis (56%) and neutropenia (60% to 80%). There have not been any phase III studies evaluating this regimen in LS SCLC.

The question of the role of consolidation IP after EP-based induction CRT in LS SCLC was answered by the JCOG 0202, which was a phase III multicentric RCT in 281 Japanese patients with untreated LS SCLC (32). All patients received one cycle of EP (E-100 mg/m^2 days 1 to 3; P-80 mg/m^2 on day 1) with accelerated hyperfractionated TRT (1.5 Gy twice a day, 5 days a week for 3 weeks, total 45 Gy). Patients who did not develop progressive disease (PD) were randomized to three cycles of EP or IP (I-60 mg/m^2 on days 1, 8, 15 and P-60 mg/m^2 on day 1). PCI was administered to patients who attained a CR or near-CR. There was no difference in the median OS, which was the primary endpoint of the study; EP-3.2 years versus IP-2.8 years; hazard ratio (HR), 1.07; 95% CI, 0.8–1.46; P=0.7. The 3-year OS in the EP and IP groups were 52.9% and 46.6% and the 5-year OS were 35.8% and 33.7% respectively. During the consolidation chemotherapy phase, the grade 3 and higher toxicities in the EP versus IP arms were neutropenia (95% *vs.* 78%), anemia (35% *vs.* 39%), thrombocytopenia (21% *vs.* 5%), febrile neutropenia (17% *vs.* 14%) and diarrhea (2% *vs.* 10%). Thus, this was a negative trial and EP CRT retained its position as the treatment of choice in LS SCLC.

Other platinum-based regimens

Several other trials have evaluated the role of other two drug platinum-based combination regimens, like paclitaxel + carboplatin (33), topotecan + cisplatin (34), pemetrexed + carboplatin (35), amrubicin + cisplatin (36) and belotecan + cisplatin (37). All these trials have been done in patients with ES SCLC, and there are no data to support the use of these regimens in LS SCLC.

Non-platinum containing regimen

In 1987, Wolf *et al.* reported on a novel non-platinum-based combination regimen, ifosfamide and etoposide (IE), which was compared to the EP regimen in 144 patients with untreated SCLC, both LS and ES. Patients received 6 cycles of either IE or PE at an interval of 3 weeks, followed by TRT (45 Gy) in patients with LS SCLC and PCI in patients who attained a CR. ORRs were similar (IE, 68% *vs.* EP, 65%), but CR rates in LS SCLC were higher in the EP arm (50%) compared to IE (24%). The median OS in patients with LS SCLC was 14.8 months in the EP arm and 11 months in the IE arm; the 2-year OS was also higher in the EP arm at 23% *vs.* 10% in IE arm. The study team concluded that EP was superior to IE in patients with LS SCLC (38).

Addition of a third drug

Cyclophosphamide-epirubicin-vincristine (CEV) regimen

The Norwegian Lung Cancer Study Group conducted

a phase III RCT to compare EP with the CEV regimen in 436 patients with SCLC, 214 (49%) of whom had LS SCLC. The regimens evaluated consisted of 5 cycles of EP (etoposide 100 mg/m^2 IV on day 1, followed by oral etoposide 200 mg/m^2 on days 2 to 4, and cisplatin 75 mg/m^2 IV on day 1) compared to 5 cycles of CEV (epirubicin 50 mg/m^2, cyclophosphamide 1000 mg/m^2 and vincristine 2 mg all drugs administered IV on day 1). The patients with LS SCLC received TRT starting from cycle 3, and all patients who achieved a CR received PCI. The median OS in the LS SCLC was significantly longer in the EP arm at 14.5 months compared to the CEV arm at 9.7 months, P=0.001. The 2-year and 5-year OS were also significantly longer in the EP arm (25% and 10% respectively) compared to the CEV arm (8% and 3% respectively), P=0.0001. Quality of life (QOL) was similar in the two arms. EP CRT continued to remain the treatment of choice for LS SCLC (39).

Ifosfamide-based three drug combination regimen

Glisson *et al.* (40) reported that in a phase II trial in 67 patients with LS SCLC, ifosfamide, cisplatin and oral etoposide with accelerated hyperfractionated TRT resulted in a response rate of 78% (67% CR), median PFS of 12.7 months, median OS of 23.7 months, and 2- and 3-year OS rates of 50% and 39% respectively. Adverse events included grade 4 neutropenia in 55%, grade 4 thrombocytopenia in 26%, febrile neutropenia in 10% and grade 3 and higher esophagitis in 43%. The Hoosier Oncology Group also conducted a phase II trial to evaluate the combination of ifosfamide (with mesna), etoposide and cisplatin with TRT in 53 patients with LS SCLC (41). The response rate was 68% (47% CR), median OS was 15.1 months, 1-, 2- and 5-year OS rates were 69.8%, 35.9%, and 13.2%, respectively. Major grade 3 and higher toxicities included neutropenia in 75%, anemia in 38% and thrombocytopenia in 34%. Fatal toxicities occurred in 7.5% patients. In a phase III study in 171 patients with ES SCLC, the combination of ifosfamide with EP led to superior TTP and OS as compared to EP (42); however, there is no level 1 evidence for its role in LS SCLC.

Taxane-based three drug combination regimens

The Phase II Dutch multicenter trial (43) of paclitaxel, etoposide and carboplatin with TRT and PCI in 38 patients with LS SCLC and the phase II RTOG 9609 trial (44) of paclitaxel, etoposide and cisplatin with accelerated hyperfractionated TRT and PCI in 53 patients with LS SCLC led to promising outcomes. In the Dutch trial, the response rate was 92%, median OS was 19.5 months, 1-, 2- and 5-year OS rates were 70%, 47% and 27% respectively. Hematological toxicities of grade 3 or higher occurred in 57% patients, febrile neutropenia in 24%, esophagitis in 27% with no fatal toxicities. In RTOG 9609 (44), the response rate was 92%, median OS was 24.7 months, 2-year OS was 54.7%; grade 3 and higher toxicities included neutropenia in 75%, esophagitis in 36%, infection in 2% and fatal toxicities in 6%. Hematological toxicities were significant, and the three-drug regimen did not improve on the OS historically reported from the Intergroup study and earlier studies of EP CRT. Therefore, this regimen was not pursued further.

The Greek Lung Cancer Cooperative Group conducted a multicenter randomized study in 133 patients with SCLC [89 (67%) had LS SCLC] to evaluate the addition of paclitaxel to EP (TEP). In the patients with LS SCLC, TRT (50 Gy in 25 fractions) was started after the completion of chemotherapy, and patients who attained a CR were advised PCI. The ORR, time to progression, median OS and 1-year OS in the patients with LS SCLC in the TEP versus EP arms were 55% *vs.* 70%, 12 *vs.* 10 months, 14 *vs.* 12.5 months and 58.6% *vs.* 55% respectively. This trial was prematurely closed due to significantly higher toxicity and mortality in the TEP arm (13% in TEP arm *vs.* 0 in EP at the early interim analysis) without a commensurate improvement in efficacy outcomes compared to EP alone (45).

Other drugs added to EP CRT

Tirapazamine is a benzotriazine di-N-oxide that selectively targets and kills hypoxic cells, and thus could enhance the cytotoxic effects of radiation. A pilot study, S0004, evaluating the addition of tirapazamine to EP and once-daily TRT in LS SCLC reported a median OS of 22 months (46). The phase II study, SWOG 0222 (47), was unfortunately prematurely closed (72 of 85 planned patients were accrued) when a parallelly running study of tirapazamine in patients with head and neck cancer reported excessive toxicity. In the SWOG 0222 study, 46% patients experienced grade 4 toxicities, predominantly hematologic. The ORR was 63%, median PFS was 11 months and the median OS was 21 months. Although tirapazamine was not studied further, the concept of hypoxia-targeted agents in SCLC is attractive.

Based on the preclinical and clinical evidence that tamoxifen enhanced the efficacy of cisplatin-based regimens, the CALGB 9235 conducted a phase III trial comparing

high dose tamoxifen (80 mg orally twice a day for 5 days, starting on day 1 of cisplatin) with standard EP CRT versus EP CRT alone in 307 patients with LS SCLC (48). There was no difference in ORR, failure free survival, OS or toxicities between the two arms.

Lee *et al.* conducted a phase III RCT in 724 patients with SCLC (51% had LS SCLC) evaluating whether the addition of thalidomide to EP improved outcomes (49). The 368 patients with LS SCLC received etoposide and carboplatin for 6 cycles, followed by TRT and PCI in patients who attained a CR or PR. Patients were randomized to receive thalidomide daily for 2 years or placebo. There was no difference in OS between the two arms in the patients with LS SCLC; median OS in the thalidomide and placebo arms was 12.1 and 13.1 months respectively; HR, 0.91; 95% CI, 0.73 to 1.15. Thalidomide doubled the risk of thromboembolism and led to more constipation, rash, and neuropathy.

Thus, in spite of numerous trials evaluating newer and more modern regimens for LS SCLC, EP with concurrent TRT remained the standard of care.

Sequencing of chemotherapy with radiotherapy

The meta-analyses by Pignon *et al.* (16) and Warde *et al.* (50) established that concurrent CRT improved survival and local control over chemotherapy alone in LS SCLC. Pignon *et al.* reported that the addition of TRT to chemotherapy led to a 14% reduction in the risk of death, while Warde *et al.* found that there was a 5.4% absolute improvement in the 2-year survival and a doubling of the local control rate from 25% with chemotherapy alone to 50% after the addition of TRT. The sequencing of chemotherapy with TRT has been extensively studied. The Japan Clinical Oncology Group 9104 study evaluated the optimal timing of TRT with EP chemotherapy. The study enrolled 231 patients with LS SCLC; all patients received 4 cycles of EP and TRT consisting of 45 Gy as 1.5 Gy fractions twice a day over 3 weeks. Patients were randomized to start TRT either on the second day of cycle 1 of chemotherapy (concurrent arm) or after all 4 cycles (sequential). Patients treated with sequential therapy had a median OS of 19.7 months, which improved to 27.2 months in the concurrent arm. The 2-yr and 5-yr OS in the sequential and concurrent arms were 35.1% *vs.* 54.4%, and 18.3% *vs.* 23.7% respectively. Patients treated with concurrent CRT developed more hematological toxicities (51). Several trials and meta-analyses have subsequently confirmed that early initiation of chemotherapy with TRT results in a survival benefit (52-54).

The CALGB 30904 was a pooled analysis of 200 patients from three studies (CALGB 39808, CALGB 30002 and CALGB 30206) that tested the strategy of induction chemotherapy (2 cycles; regimens included topotecan + paclitaxel, etoposide + paclitaxel + topotecan, and cisplatin + irinotecan), followed by concurrent CRT with EP (etoposide + carboplatin) and TRT started on day 43 to a dose of 70 Gy, delivered in once daily 2 Gy fractions. Patients who attained a CR or a very good PR were offered PCI. The pooled ORR from induction chemotherapy was 72%, which increased to 88% post-CRT. Common grade 3 and higher toxicities from induction chemotherapy were neutropenia in 30% of patients, and diarrhea in 10%. During CRT, the common grade 3 and higher toxicities included neutropenia in 80%, leukopenia in 48%, thrombocytopenia in 43%, anemia in 25%, febrile neutropenia in 19%, esophagitis in 23% and dehydration in 15%. The locoregional control was 77%, the pooled median OS was 19.9 months (95% CI, 16.7 to 22.3), the median PFS was 12.3 months, the 2-year and 5-year OS rates were 37% and 21% respectively (55).

An alternating schedule is one in which radiotherapy is delivered on the days that the patient does not receive chemotherapy. The ECOG conducted a pilot study in 34 patients with LS SCLC to evaluate the alternating schedule (56). Patients received EP every 3 weeks for 4 cycles, with TRT as 45 Gy in 1.5 Gy twice daily fractions given for 5 consecutive days after cycles 1, 2 and 3 of chemotherapy. Patients who attained a CR received one additional cycle of consolidation (LI, or late intensification) chemotherapy with cyclophosphamide (4 g/m^2) and etoposide (900 mg/m^2). The decision for PCI was optional. The ORR was 97% (59% CR and 38% PR), median OS was 18 months. Toxicity was as reported from earlier trials, however the LI chemotherapy led to grade 4 neutropenia in all patients, 1 episode of adult respiratory distress syndrome and 2 deaths from sepsis. The investigators concluded that an alternating strategy led to similar outcomes and toxicity as standard concurrent CRT.

The "Petites Cellules" group conducted a trial in 164 patients who were randomized to concurrent CRT in which the radiation (50 Gy in 25 fractions) was started after cycle 2 of chemotherapy on days 30 to 64 versus an alternating schedule in which the radiation was delivered in three courses: 20 Gy in 8 fractions from days 36 to 47 (between cycles 2 and 3), days 64 to 75 (between cycles 3 and 4) and 15 Gy in 6 fractions from days 92 to 101 (between cycles 4 and 5) (57). Chemotherapy consisted of cyclophosphamide

+ doxorubicin or vindesine + etoposide every 4 weeks. There was no significant difference in survival in the two arms (median OS of 13.5 and 14 months in the concurrent *vs.* alternating arms respectively, P=0.15), with higher toxicity in the concurrent arm (6 patients *vs.* 1 patient in the alternating arm, P=0.05).

Following EP CRT, the JCOG1011 evaluated whether dose-intensive weekly chemotherapy (cisplatin, doxorubicin, etoposide, vincristine; CODE) or amrubicin + cisplatin (AP) could result in an improvement in the 1-year PFS (58). The 1-year PFS was 41% in the CODE arm *vs.* 54.3% in the AP arm; neither regimen led to the expected 55% 1-year PFS, and were therefore not felt to be appropriate to take forward for a phase III study.

Despite the unequivocal benefit of concurrent CRT in LS SCLC, in the real world setting only 55% of patients receive both chemotherapy and TRT as the initial treatment. 20.5% receive chemotherapy alone, 3.5% receive radiation alone and 20% receive neither. The major barrier to receiving optimal therapy is financial, and lack of insurance coverage (59).

Optimal number of chemotherapy cycles

The standard of care for a patient with LS SCLC consists of 4 to 6 cycles of chemotherapy concurrently with TRT. In the Intergroup trial, all patients received 4 cycles of EP (20), while in the CONVERT trial, patients could receive 4 to 6 cycles of EP (8). The decision regarding 4 or 6 cycles in the CONVERT study was left to the enrolling center. 32% of the patients in the CONVERT trial were planned for 6 cycles; approximately 20% received 6 cycles. In a recent retrospective study from UK, 188 out of 671 patients had LS SCLC. Of these, 176 patients received 4 cycles and only 12 (6%) received more than 4 cycles (60). Veslemes *et al.* randomized 70 patients with SCLC (both LS and ES) to receive 4 or 6 cycles of EP chemotherapy (61). There was no survival difference between the two arms in the patients with LS SCLC; median OS was 10.5 months in the patients who received 4 cycles of EP versus 12 months in patients who received 6 cycles, P=0.21. Toxicity was also similar in the two arms.

The role of growth factors in LS SCLC

The use of myeloid growth factors concurrently with TRT for patients with LS SCLC is controversial. The SWOG conducted a trial reported by Bunn *et al.* in which 230 patients with LS SCLC were randomized to CRT (6 cycles) with or without granulocyte-macrophage colony stimulating factor (GM-CSF) on days 4 to 18 (62). The primary endpoint, hematologic toxicity was significantly higher in the GM-CSF arm, specifically the frequency and duration of grade 3 and higher thrombocytopenia (91% *vs.* 18%, P<0.001). Additionally, non-hematologic toxicities (pulmonary complications, duration of hospitalization, transfusions and intravenous antibiotic use) and number of toxic deaths (9 *vs.* 1, P<0.01) were higher with GM-CSF. Patients on the GM-CSF arm had a numerically lower CR rate (36% *vs.* 44%; P=0.29), and lower median OS (14 *vs.* 17 months; P=0.15), although these differences did not attain statistical significance. The authors concluded that hematopoeitic growth factors should not be used in patients receiving concurrent EP CRT for LS SCLC.

Forty percent of patients in the CONVERT trial received granulocyte colony stimulating factor (G-CSF). Gomes *et al.* reported that the patients in the CONVERT trial who received G-CSF had twice the frequency of severe thrombocytopenia (29.4% *vs.* 13%; P<0.001) and anemia (20%), but both these numbers were lower than what had been described earlier. Patients required more supportive care measures including transfusion of platelets and blood. There was no increase in pulmonary toxicity, and survival (both PFS and OS) was similar in the two groups. The authors concluded that the use of G-CSF was safe in patients with LS SCLC on concurrent EP CRT (63). G-CSF is probably safer than GM-CSF, and modern radiation techniques are more evolved, with less risk of pulmonary toxicity. However, the study by Gomes *et al.* has only been presented in abstract form so far. In the CONVERT trial, febrile neutropenia occurred in 24% of the patients in twice-daily radiation arm, and in 19% of patients in the once-daily radiation arm. The 2015 ASCO guidelines for the use of growth factors recommend primary G-CSF prophylaxis for regimens that have an expected risk of febrile neutropenia of 20% or higher, however, the guidelines recommend the avoidance of G-CSF in patients receiving concurrent CRT especially if it involves the mediastinum (64). Thus, the role of myeloid growth factors along with concurrent EP CRT for patients with LS SCLC is still unclear.

The choice of platinum therapy

Cisplatin is associated with several adverse events like nephrotoxicity, dyselectrolytemia, neurotoxicity, deafness

and GI side effects. In cisplatin-ineligible patients, i.e., patients with renal dysfunction, hearing loss and poor performance status (PS), carboplatin is used.

The Hellenic Cooperative Oncology Group for Lung Cancer Trials conducted a phase III trial comparing carboplatin (300 mg/m^2 on day 1) to cisplatin (50 mg/m^2 days 1–2), both in combination with etoposide (100 mg/m^2 days 1–3) every 3 weeks for 6 cycles. In the 82 of the 143 patients (57%) who had LS SCLC, TRT was started in the third chemotherapy cycle and PCI was also administered in patients who attained a CR. In the patients with LS SCLC, the ORR in the cisplatin *vs.* carboplatin arms were 76% (44% CR) *vs.* 86% (37% CR). The median OS for patients with LS SCLC was 14.1 months, with no significant difference between those who received carboplatin and cisplatin. However, toxicities were significantly lower in the carboplatin-treated patients, including leucopenia, thrombocytopenia, nausea/vomiting, neurotoxicity, neutropenic infection, and hypersensitivity. Patients who received carboplatin required less hospitalizations. The authors concluded that when combined with etoposide, carboplatin is equiefficacious (in terms of response and survival) but less toxic than cisplatin (65).

Rossi *et al.* conducted an individual patient data meta-analysis of 4 RCTs including 663 patients with SCLC in the first line setting; 32% of the patients had LS SCLC (66). All outcomes were similar between patients treated with cisplatin and carboplatin; ORRs, median PFS and median OS for cisplatin- versus carboplatin-treated patients were 67.1% and 66% (P=0.83), 5.5 and 5.3 months (HR, 1.10; 95% CI, 0.94 to 1.29; P=0.25), and 9.6 and 9.4 months (HR, 1.08; 95% CI, 0.92 to 1.27; P=0.37). There was no evidence of heterogeneity of the treatment effect based on the stage of the disease; the treatment: stage interaction for PFS was P=0.57 and for the OS; P=0.17. The toxicities caused were different: carboplatin led to more myelosuppression, while cisplatin caused more nausea and vomiting, nephrotoxicity and neurotoxicity (66). Thus, carboplatin appears to be an acceptable choice in patients with LS SCLC. However, it must be noted that the pivotal trials (Intergroup and CONVERT) (8,20) that have established the chemotherapy regimens and the TRT schedule for LS SCLC have all used cisplatin-based regimens; while the ongoing NCT00632853 trial (23) comparing accelerated hyperfractionated radiation with standard radiation in combination with chemotherapy permits either cisplatin or carboplatin in combination with etoposide as the concurrent chemotherapy regimen. Several of the ongoing maintenance immunotherapy trials also permit carboplatin as the platinum agent concurrently with radiation (67-70). A retrospective analysis in 73 patients with SCLC [29 (40%) with LS SCLC], found that patients with a high neutrophil to lymphocyte ratio (NLR ≥3.8), had a significantly longer median PFS when treated with cisplatin-based EP as compared to carboplatin (4.6 *vs.* 2.6 months; P=0.021), as well as median OS (cisplatin, 15.7 *vs.* carboplatin, 7.8 months; P=0.042). This difference in PFS was present in the LS SCLC subgroup of patients with high NLR as well; cisplatin, 6.5 months *vs.* carboplatin, 2.8 months; P=0.002 (71). These results are intriguing and worthy of further evaluation.

Prognostic and predictive factors in LS SCLC

Clinical stage is one of the most powerful prognostic factors in patients with SCLC. Within the stage grouping of LS SCLC, patients with no mediastinal lymph node involvement have a better survival. Patients with Stage I and II disease have a better survival compared to those with Stage III disease (median OS with EP CRT, 50 *vs.* 25 months; HR, 0.6; 95% CI, 0.44 to 0.83; P=0.001) (72). Superior vena cava obstruction does not portend a worse prognosis in LS SCLC (73). Kawahara and colleagues categorized 147 LS SCLC patients (enrolled in a randomized study comparing EP, CAV and alternating EP and CAV) into two groups based on the PS and the serum LDH; the group with a normal LDH and PS of 0 or 1 had a median OS of 18.1 months, while the group with an abnormal LDH and PS 2 or 3 had a median OS of 9.9 months; P<0.0001 (74). Xie *et al.* analyzed 383 patients with LS SCLC and reported that the platelet to lymphocyte ratio, age, smoking cessation, chest radiation, chemotherapy, surgery, and PCI were of prognostic significance (75). There is no level 1 evidence to support the role of PET-CT scan in staging of SCLC, and a post-hoc analysis of the CONVERT trial revealed that there was no difference in survival between the patients who were staged with or without a PET scan (72). However, a PET-CT scan, if done, can provide valuable prognostic information. In patients with LS SCLC, at baseline, a higher fluorodeoxyglucose tumor uptake correlates with a worse prognosis (76). Following therapy for LS SCLC, metabolic parameters on a scan including the metabolic tumor volume, the total lesion glycolysis, and the glucose-corrected maximum standardized uptake value (glu-SUV$_{max}$) significantly predicted survival (77).

In a retrospective cohort of 284 patients with LS SCLC, 80% of whom were treated with concurrent CRT, quitting smoking at the time of or after the diagnosis of SCLC decreased the risk of death by 45% (HR, 0.55; 95% CI, 0.38–0.79). Starting TRT within 1 month of the start of chemotherapy had prognostic significance on the univariate analysis, however, it did not retain significance in the multivariate adjusted model, while younger age, concurrent CRT and the delivery of platinum-based chemotherapy significantly impacted survival (78).

Radiotherapy factors that affect prognosis include early initiation of TRT (within 9 weeks of the start of chemotherapy), the use of concurrent CRT, and a short time period between the start of chemotherapy and the end of TRT (SER). (79) Following therapy, platinum-sensitive disease status is strongly associated with longer OS (80). Ding *et al.* reported that in 107 patients with LS SCLC with no evidence of brain metastases on the baseline MRI, who were treated with concurrent EP CRT and no PCI, 46.7% of the patients developed brain metastases, at a median time of 10.7 months (range, 4.8 to 31.1 months) (81). Factors associated with better OS were receipt of ≥ 4 cycles of chemotherapy *vs.* <4 cycles (P=0.015), CR *vs.* PR to initial treatment (P=0.007) and early TRT, i.e., started during cycle 3 of chemotherapy *vs.* late radiation (P=0.017). The factors that predicted a longer time to the development of brain metastases were a lower clinical stage (TNM Stage I or II *vs.* III, P=0.003), CR to initial therapy (P=0.031) and early TRT (P=0.097).

Approximately 60% of patients with LS SCLC have detectable circulating tumor cells (CTC) in the baseline blood sample, prior to initiation of concurrent EP CRT. The presence of CTCs correlates with a more aggressive clinical course and poorer outcomes. Patients with <15 CTC have a better prognosis as compared to those with ≥15 CTC; median OS, 26.7 *vs.* 5.9 months (P=0.001). In patients with ≥15 CTCs at baseline, the median PFS was 5.5 months (*vs.* 19 months for <15 CTCs), 70% had a survival of ≤1 year and 100% had a survival ≤2 years (82).

Recently, a new molecular classification has been proposed for SCLC based on the differential expression of transcriptional regulators, achaete-scute homologue 1 (ASCL1 or ASH1), neurogenic differentiation factor 1 (NeuroD1), yes-associated protein 1 (YAP1) and POU class 2 homeobox 3 (POU2F3) (83). The role of these molecular subtypes, in terms of response to therapy, and impact on outcomes and survival are areas of active research.

The role of adjuvant/maintenance/consolidation therapy in LS SCLC

Vandetanib

Vandetanib is an oral tyrosine kinase inhibitor that targets VEGFR2. The BR .20 trial conducted by the National Cancer Institute of Canada Clinical Trials Group Study (NCIC) was a phase II RCT in 107 patients with SCLC [46 (43%) had LS SCLC] evaluating the role of vandetanib as maintenance therapy in patients who had attained CR or PR following first line therapy (84). Patients on the vandetanib arm had higher incidence of diarrhea, hypertension, QTc prolongation and rash. Overall, this was a negative trial, with no survival advantage noted from vandetanib in PFS or OS. However, in patients with LS SCLC, a trend towards a better survival was noted; the median PFS in the vandetanib arm was 9.99 *vs.* 6.67 months in the placebo arm (HR, 0.8; 80% CI, 0.5 to 1.3) and the median OS in the placebo treated patients was 21.2 months versus not reached in the vandetanib arm; HR, 0.5; 95% CI, 0.2 to 0.9.

Bec2/bacille Calmette-Guerin (BCG) vaccine

The EORTC 08971-08971B Silva Study was a phase III study in 515 patients with LS SCLC who had received concurrent CRT and had a major response (85). Patients were randomized to 5 doses of Bec2/BCG vaccine or observation. The vaccine did not lead to an improvement in QOL, PFS or OS; median OS was 14.3 months in the vaccine arm compared to 16.4 months in the observation arm, P=0.28.

Interferons

The SWOG study evaluated the role of maintenance recombinant interferon alpha-2a (3 million units/m^2 escalated to 9 million units/m^2 subcutaneously 3 times a week for 2 years) in 121 patients with LS SCLC who had an objective response to CRT (86). The median OS in the interferon arm was 13 *vs.* 16 months in the observation arm, P=0.77. Grade 3 and higher toxicities included malaise, fatigue, leukopenia, neutropenia, dyspnea, nausea and respiratory infection. Sixty-seven percent patients discontinued therapy due to toxicities. Various other studies that evaluated whether interferons as maintenance therapy may play a role in improving outcomes in SCLC have also been disappointing (87,88).

Maintenance therapy meta-analysis

A meta-analysis by Rossi *et al.* evaluating 21 RCTs done in 3687 patients with SCLC (both LS SCLC and ES SCLC) showed that overall, there was no statistically significant benefit in terms of prolongation of PFS or OS from the maintenance or consolidation therapy approach (89). The meta-analysis included 11 RCT's that evaluated maintenance chemotherapy, 6 evaluated interferons and 4 evaluated other biological agents (matrix metalloprotease inhibitors, Bec2/BCG vaccination, thalidomide, vandetanib). Maintenance chemotherapy led to a statistically significant prolongation in PFS and OS; however, in absolute terms, this did not appear to be clinically relevant as it translated to an improvement of 2 weeks in OS, and a 4% improvement in 1-year OS from 30% to 34%. Interferon-alpha also led to a significant improvement in PFS and OS; in absolute terms, this was an improvement of 3.5 weeks in OS, and a 9% improvement in 1-year OS (from 30% to 39%). The studies included in the meta-analysis were of low-quality, the data were heterogenous and the analysis was not based on individual patients' data.

Novel therapeutic strategies

Bevacizumab

Bevacizumab is well known angiogenesis inhibitor used in NSCLC, colon cancer, breast cancer and renal cancer. A phase II study in the Sarah Cannon Oncology Research Consortium evaluated the addition of bevacizumab to carboplatin and irinotecan concurrently with TRT and optional PCI, followed by maintenance bevacizumab for 6 months in patients who did not progress. The study was terminated early for safety concerns after 29 patients were enrolled. Two patients developed tracheoesophageal fistulae (one fatal) and one additional patient had fatal aerodigestive bleeding (90).

Immunotherapy

SCLC is strongly associated with smoking and has been shown to harbor a high load of non-synonymous somatic mutations (high tumor mutational burden), both of which features suggest that immunotherapy may be active in SCLC.

The ongoing Phase I NCT02402920 trial is evaluating the addition of pembrolizumab to concurrent CRT in patients with LS SCLC and ES SCLC (67). The combination of the programmed cell death protein 1 (PD-1) inhibitor, nivolumab and the anticytotoxic T-lymphocyte–associated antigen-4 (CTLA-4) inhibitor, ipilimumab, are being evaluated in the maintenance setting after completion of concurrent CRT (Phase II STIMULI trial, NCT02046733) (68). The Phase II/III NCT03811002 trial in 506 patients with LS SCLC is evaluating the addition of atezolizumab to EP CRT (atezolizumab on day 1 or 2 of each chemotherapy cycle), followed by atezolizumab administered every 3 weeks up to 1 year (69). The Phase III ADRIATIC study is a double blind placebo controlled multicenter global study evaluating the role of the anti PD-L1, durvalumab with or without the CTLA4 inhibitor, tremelimumab as consolidation therapy in patients with LS SCLC who have non-progressive disease after concurrent CRT (70). Currently, there are no completed studies that support the role of immunotherapy in LS SCLC. However, immunotherapy has been shown to improve outcomes in extensive stage SCLC in the first line setting (OS improved by atezolizumab with platinum-etoposide in IMpower133 (2), OS improved by durvalumab with platinum-etoposide in the CASPIAN study (91), and PFS improved by pembrolizumab with platinum-etoposide in KEYNOTE-604) (92) as well as in locally advanced NSCLC after completion of CRT (PACIFIC study) (93).

Special patient populations

Chemotherapy in older patients

SCLC commonly occurs in older patients. The median age of patients enrolled in the CONVERT trial was 62 to 63 years; 15% of the patients were over the age of 70 years (8). In a retrospective analysis of two RCTs conducted by the NCIC in 608 patients with LS SCLC, all treated with CAV followed by EP, with TRT and PCI, Siu *et al.* reported that although patients aged 70 years and older received lower overall doses of drugs as compared to the planned doses, yet there was no significant difference in toxicity and increased age was not a poor prognostic factor (94).

Safont *et al.* reported the retrospective analysis of the RCT conducted by the Spanish Lung Cancer Group evaluating high dose EpP in 402 patients with SCLC (95). They found that older patients with LS SCLC received a lower total cisplatin dose (401 *vs.* 508 mg/m^2, P=0.01), but had fewer dose delays (10 *vs.* 15 days, P=0.05). There was no difference in toxicities and a trend to lower TTP and OS in patients over 70 years old.

From the National Cancer Data Base, Corso *et al.* identified 8,637 patients aged ≥70 years with LS SCLC that had been treated with chemotherapy or concurrent CRT (96). They found that there were decreased odds of receiving concurrent CRT with increased age, clinical stage III disease (versus clinical stage I or II), female sex and increasing comorbidities. Concurrent CRT led to a survival benefit over chemotherapy alone; median OS, 15.6 *vs.* 9.3 months; 3-year OS was 22% *vs.* 6.3%; P<0.001.

In the Intergroup 0096 trial, 15 out of 381 (13%) patients were 70 years or over (20). As compared to patients below 70 years, older patients developed more severe hematologic toxicities (grade 4 and higher, 61% *vs.* 84%; P<0.01), similar non-hematologic toxicities and more fatal toxicities (1% *vs.* 10%, P=0.01). There were no differences in ORRs (88% *vs.* 80%; P=0.11), 5-year event free survival rates (19% *vs.* 16%, P=0.18), but 5-year OS rates were higher in the younger patient cohort (22% *vs.* 16%, P=0.05) (97).

In the North Central Cancer Treatment Group study comparing EP with once daily *vs.* twice daily radiation in LS SCLC, older patients (age 70 years and older) had more weight loss and poorer PS at presentation, and experienced more grade 4 and higher pneumonitis (8% *vs.* 0, P=0.008), more fatal toxicities (5.6% *vs.* 0.5%, P=0.03), but similar 2-yr OS (33% *vs.* 48%) and 5-year OS (17% *vs.* 22%), P=0.14 (98).

Most recently, in the CONVERT trial, 67 (out of 490 evaluable) patients were 70 years or older and the median age was 73 years (range, 70 to 82 years) (99). The chemotherapy compliance was similar between the younger and older cohort of patients, but only 73% of the older cohort received an optimal number of radiation fractions versus 85% of the younger cohort, P=0.03. Grade 3 and higher neutropenia was higher in the older cohort (84% *vs.* 70%, P=0.02), but there was no difference in the rates of febrile neutropenia (4% *vs.* 7%, P=0.07) or death (3% *vs.* 1.4%, P=0.67). There was also no significant difference in survivals; median TTP was 18 *vs.* 16 months (HR, 1.04; 95% CI, 0.76 to 1.41; P=0.81) and median OS was 29 *vs.* 30 months (HR, 1.15; 95% CI, 0.84 to 1.59; P=0.38).

Thus, in the trial setting, although older patients overall had more toxicities from standard therapy, efficacy outcomes were similar to those of younger patients. Appropriate patient selection is important. In the real-world setting, often patients are not as fit as those enrolled on trials. Ludbrook *et al.* reported the outcomes of 174 patients with LS SCLC (100). They grouped patients into three age groups: <65 years (n=55, 32%), 65–74 years (n=76, 44%), and ≥75 years (n=43, 25%); and according to the Charlson comorbidity index (CCI) scores 0, 1, and ≥2. They found that older patients had worse PS and more comorbidities, were less likely to undergo diagnostic scans, less likely to receive concurrent CRT, more likely to receive less intensive chemotherapy regimens with fewer cycles and lower total doses, and less likely to receive PCI. Treatment related toxicities were similar, but response rates (91% in <65 years, 79% in 65-74 years and 74% in ≥75 years; P=0.014), median OS (17, 12, and 7 months) and 2-year survival (37%, 22%, and 19%; P = 0.003) were significantly lower with increasing age. However, on multivariate analysis, good PS, normal LDH, absence of pleural effusion, and the receipt of 4 or more cycles of chemotherapy were independently associated with survival while age and the comorbidity index were not.

Patients with comorbidities

Halvorsen *et al.* evaluated the outcomes of 157 patients with LS SCLC with comorbidities enrolled in an RCT comparing EP with two schedules of TRT: 45 Gy/30 fractions twice a day or 42 Gy/15 fractions once a day. When evaluated using the CCI, 40% of the patients had no comorbidity, 34% had CCI-score 1, 15% CCI 2; and 11% had CCI 3–5 (101). When evaluating patients based on the CCI score categories, there were no differences in the rates of completion of chemotherapy, TRT, or PCI; and no significant differences in the development of grade 3 and higher toxicity (P=0.49), fatal toxicities (P=0.36), response rates (P=0.20), PFS (P=0.18) or OS (P=0.09). Thus, the presence of comorbidities does not impact on tolerance to or outcomes of CRT in patients with LS SCLC. However, the drawback of this study is the small sample size, especially in the subgroup of patients with CCI score 3 to 5 (17 patients), making it hard to make definitive conclusions.

Conclusions

In spite of multiple trials attempting to improve the outcomes in patients with LS SCLC, the regimen of EP with TRT continues to remain the gold standard. High dose epirubicin and cisplatin may represent a valid option in combination with TRT. There is no established role for maintenance or consolidation therapy. Multiple mutations exist, but most of the newer drugs have not been found to be effective. Immunotherapy thus far does not have an established role is LS SCLC, but this is an area of active investigation. In older

patients, EP CRT leads to more toxicities but comparable efficacy, and patient selection is key.

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