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Lung Cancer

Small Cell Lung Cancer: Have We Made Any Progress Over the Last 25 Years?

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LEARNING OBJECTIVES

After completing this course, the reader will be able to:

1. Discuss the currently available SCLC treatment options.
2. Describe the benefits of integrating thoracic radiotherapy into SCLC treatment.
3. Identify the limitations of current SCLC treatment options and explain how future clinical trials are addressing these limitations.

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ABSTRACT

Twenty-five years ago, small cell lung cancer was widely considered to be the next cancer added to the list of "curable cancers." This article attempts to summarize the progress made toward that goal since then. Clinical trials have provided landmarks in the therapy of limited-stage small cell lung cancer (LS-SCLC). These are: (a) the proof that thoracic radiation therapy adds to systemic chemotherapy, (b) the superiority of twice-daily radiation therapy over daily fractionation, and (c) the need for prophylactic central nervous system radiation (prophylactic cranial irradiation). Each of these innovations adds about 5%–10% to the overall survival rate.

In extensive-stage disease, irinotecan plus cisplatin may be a possible alternative to the "standard" etoposide–cisplatin chemotherapy doublet, but there has been little progress otherwise. It is imperative that, whenever possible, patients be given the opportunity to participate in future clinical trials so that the survival for these patients can continue to improve. ***The Oncologist*** 2007;12:1096–1104

INTRODUCTION

Twenty-five years ago we were poised to cure small cell lung cancer (SCLC). We had devised a unique staging system, established the effectiveness of several chemotherapeutic agents and radiation therapy, and even discovered the central nervous system sanctuary, which would require distinct treatment. SCLC was being added to some lists of "curable cancers" [1]. A quarter of a century later, patients with this disease do not have a significantly better outlook [2]. SCLC is distinguished from the other forms of lung

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cancer by its aggressive clinical course, with widespread metastases at diagnosis, the frequent occurrence of paraneoplastic syndromes, and its sensitivity to both chemotherapy and radiation therapy. Because of its unique behavior it has a separate staging system, with tumors divided into limited-stage (LS-SCLC) or extensive-stage (ES-SCLC), rather than the customary tumor–node–metastasis (TNM) classification.

LS-SCLC is defined as tumor confined to the hemithorax of origin, the mediastinum, and supraclavicular lymph nodes, which can be encompassed within a tolerable radiation therapy port. Patients not considered to have LS-SCLC are instead felt to have ES-SCLC. In 2007, it is estimated that there will be approximately 28,000 cases in the U.S. [3], about 12% of all lung cancers [2]. The etiology is invariably cigarette smoking.

Over the last 25 years, landmarks in therapy have been provided by clinical trials of LS-SCLC. These are: (a) the proof that thoracic radiation therapy adds to systemic chemotherapy, (b) the superiority of twice-daily radiation therapy over daily fractionation, and (c) the need for prophylactic central nervous system radiation (prophylactic cranial irradiation [PCI]). Each of these innovations has contributed to the improvement in the 5-year survival rate. For ES-SCLC, progress has been minimal until recently.

Prognostic Factors

From the time of diagnosis, the median ranges of survival for LS-SCLC and ES-SCLC are 15–20 months and 8–13 months, respectively. Approximately 20%–40% of LS-SCLC and <5% of ES-SCLC patients survive 2 years [4, 5]. The respective values for the 5-year survival rate are 10%–13% and 1%–2% [6–8]. The most important tumor-related prognostic factor is the extent of disease, either LS-SCLC or ES-SCLC. In LS-SCLC, early-stage disease (TNM stage I) carries a favorable prognosis, while an elevated lactate dehydrogenase is considered unfavorable [7, 9]. In ES-SCLC, the number of organ sites involved is inversely related to prognosis [6]. Furthermore, metastatic involvement of the central nervous system, the marrow, or the liver is unfavorable compared with other sites, although these variables are confounded by the number of sites of involvement.

SCLC frequently is associated with paraneoplastic syndromes either via ectopic hormone production or antibody-mediated tissue destruction. Ectopic hormone production has been associated with ES-SCLC and a poorer outcome; the antibody-mediated neurologic paraneoplastic syndromes are associated with more favorable outcomes [10]. The correlation of paraneoplastic neurological symptoms with better outcomes indicates that immune-mediated therapy should be further explored. Patient-related factors predicting a poor outcome include both poor performance status and weight loss [11]. As in other malignancies, women fare better than men.

Thoracic Radiation

A breakthrough occurred in the late 1960s with the recognition that SCLC patients were relatively more responsive to available chemotherapeutic agents when compared with an inert compound [12]. While encouraging results were achieved with chemoradiotherapy, the standard of care for LS-SCLC was chemotherapy alone for the better part of two decades [13]. As a result, the 1980s saw a flurry of clinical trials investigating chemoradiotherapy versus chemotherapy alone in LS-SCLC. The defining report, Cancer and Leukemia Group B (CALGB) 8083 [14], published in the *New England Journal of Medicine*, showed, for patients with LS-SCLC, a local control, failure-free survival, and overall survival benefit with the addition of thoracic radiation to chemotherapy using a cyclophosphamide and doxorubicin–based regimen. At 2 years, only 13% of patients who received chemotherapy alone maintained local control, compared with 54% of patients receiving chest radiotherapy. Overall, the 2-year survival rate was 27%, and there was significantly longer survival among patients receiving radiotherapy ($p = .01$).

Two meta-analyses [15, 16] published in the early 1990s, comprising a total of 14 trials, established a survival benefit of 5% at 2 and 3 years for thoracic radiotherapy in the treatment of LS-SCLC. In addition, a recent overview of prospective research in LS-SCLC included 26 randomized clinical trials initiated by cooperative groups in North America between 1972 and 1992, and only five studies showed a statistically significant longer survival in the experimental arm compared with the control arm [17]. All five positive trials studied some aspect of thoracic radiotherapy. Although several important questions remain unanswered regarding the optimal integration of thoracic radiotherapy and chemotherapy in LS-SCLC treatment, no patient has been enrolled into a U.S. Intergroup phase III study addressing LS-SCLC in >15 years.

Although there is relatively uniform agreement on the need for thoracic radiation therapy, controversy remains. How large should the ports be? What fields should be used? Most important, to what dose should the radiotherapy be given and how frequently—once daily or twice daily? Against this background, the issue of the timing of thoracic radiation simmers on. The two positions are, simply put, to give thoracic radiotherapy concurrently with the first or second cycle of chemotherapy ("early") or to wait and give

it concurrently with the third cycle of chemotherapy ("delayed").

Radiation Treatment Volume

Several reports [18–22] have demonstrated that the use of postchemotherapy volumes, with an associated smaller port size, does not increase the recurrence rate. However, these fields still, in general, encompassed the primary tumor, ipsilateral hilum, mediastinum, and frequently the supraclavicular region. Elective regions were still commonly treated. While the use of elective nodal irradiation has not been adequately studied, the Intergroup 0096 trial [23] limited elective radiation by not allowing treatment with radiation to the contralateral hilum or to supraclavicular nodes, unless there was bulky superior mediastinal adenopathy. The use of even larger fields otherwise may only increase the toxicity. Bulky SCLC tumors often require large ports that can be reduced after effective chemotherapy shrinks the tumor, reducing toxicity to the lungs and esophagus, and enhancing the therapeutic ratio.

Benefit can be gained with positron emission tomography (PET) in designing radiation treatment volumes. It is known that a feature of malignant tissue is its high rate of glycolysis, and this feature is exploited for oncologic imaging by PET with the glucose analogue [^{18}F]fluoro-2-deoxy-D-glucose (FDG). In a prospective evaluation, the principal value of PET in LS-SCLC was the detection of additional sites of disease within the thorax. PET identified unsuspected regional nodal metastasis in six (25%) of 24 patients, and the radiation therapy plan was significantly altered to include the PET-positive/computed tomography (CT)-negative nodes within the high-dose region in each of these patients [24]. Thus, selective enlargement of radiotherapy fields may also enhance the therapeutic ratio.

Early Versus Delayed Radiotherapy

Takada et al. [25] reported on 231 patients randomized to either early concurrent or delayed sequential thoracic radiotherapy. Using current staging and four cycles of etoposide–cisplatin chemotherapy, patients were randomized to receive 4,500 cGy of thoracic radiation over 3 weeks (1.5 Gy per fraction given twice daily), starting concurrently with cycle 1 or after completion of cycle 4 of the chemotherapy. The patients receiving concurrent radiotherapy had a higher overall survival (OS) rate than those receiving sequential treatment (3-year OS, 29.8% versus 20.2%; $p = .097$). Meta-analyses investigating the timing of radiotherapy [26–28] have demonstrated that a short time between the initiation of chemotherapy and the subsequent completion of radiotherapy is prognostic for survival. In a subgroup analysis by Fried et al. [27], the benefit to early radiotherapy was seen only in patients receiving hyperfractionated radiation and/or platinum versus nonplatinum-based chemotherapy. Regression analysis showed an 18% absolute benefit associated with twice-daily radiotherapy and platinum-based chemotherapy when comparing early versus late radiotherapy. It is debatable whether hyperfractionated radiotherapy is a surrogate for a higher biologically effective dose (BED), compared with once daily to the same dose, or if the shortened total treatment duration of the hyperfractionated scheme is the reason for the importance of radiation timing.

Delayed radiotherapy avoids the significant myelosuppression seen with full-dose chemotherapy and large-volume radiotherapy. The experience with growth factors in this setting has clearly been negative, with unexpected thrombocytopenia [29]. In the CALGB experience, early radiotherapy resulted in a dose reduction that continued throughout the rest of the chemotherapy [14]. As mentioned, effective chemotherapy shrinks the tumor, reducing toxicity to the lungs and esophagus, and enhancing the therapeutic gain [30, 31] of delayed radiotherapy. Furthermore, delaying radiotherapy also helps select out those patients whose disease is resistant to chemotherapy or those patients who have been understaged and actually have ES-SCLC and are unlikely to benefit from thoracic radiotherapy. Those who advocate early radiotherapy commonly cite the Intergroup trial [23] (where chemotherapy and radiotherapy started on day 1), which demonstrated the best prospective survival data to date. For patients with a good performance status and nonbulky disease, intensive therapy with early radiotherapy is appropriate. For patients with either a poor performance status or very bulky disease, delaying the initiation of radiotherapy until the third cycle of chemotherapy to increase the therapeutic result would seem prudent. As the elderly comprise increasing portions of patients with SCLC, determining which patients will benefit from intensive therapy and which will benefit from delayed radiotherapy becomes critical. Available evidence does suggest that abbreviated therapy may still be of benefit to elderly and infirm patients [32].

Radiation Treatment Dose

Typically, modest doses of radiation, in the range of 45–50 Gy, were tested because of the observed responsiveness of SCLC to radiotherapy [33]. In the Intergroup 0096 trial [23], 45 Gy given in a once-daily fraction resulted in a 75% intrathoracic failure rate. A single-institution review of 54 patients treated to doses >50 Gy once daily, building on earlier experience from the same institution, suggested a dose–response relationship for doses of 30–50 Gy [34, 35]. The local control rate for doses ≥50 Gy at 3 years was 78%.

The maximum-tolerated dose (MTD) of once-daily radiotherapy has been found to be at least 70 Gy [36]. CALGB 39808 explored this further in the phase II setting [37]; 57 patients were treated with 70 Gy in 35 fractions concurrent with carboplatin plus etoposide after two induction cycles of paclitaxel and topotecan. The 2-year overall survival rate was 48%, while 16% (5%) of patients reported grade 3 (4) dysphagia. The CALGB has completed further studies (CALGB 30002 and 30202) of 70 Gy of thoracic radiotherapy with different chemotherapy combinations in >140 additional patients. Still, the experience with 70 Gy of radiotherapy to the chest in SCLC is limited. A recent Patterns of Care study showed that the median radiotherapy dose used in the community was 50.4 Gy [38]. The current National Comprehensive Cancer Network guidelines suggest a dose of at least 50 Gy be administered; we do recognize that stronger evidence supporting a dose–response relationship in SCLC is needed.

Altered Fractionation Radiotherapy

Phase I data have shown the MTD for hyperfractionated (treatment twice per day) thoracic radiotherapy concurrent with cisplatin–cyclophosphamide–etoposide chemotherapy to be 45 Gy in 30 fractions [36]. Esophagitis of grade ≥4 was the dose-limiting toxicity. The Intergroup 0096 trial randomized 417 patients to receive 45 Gy of concurrent thoracic radiotherapy given either twice daily over 3 weeks or once daily over 5 weeks. All of the patients were to receive four 21-day cycles of cisplatin plus etoposide. Radiation was scheduled to begin with the start of chemotherapy. At 5 years, the OS rate favored twice-daily radiation, 26% versus 16% ($p = .04$). The rate of local failure was lower with twice-daily radiation 52% versus 36% ($p = .06$). However, toxicity was greater with twice-daily radiation, particularly esophagitis. The rate of grade 3 espohagitis was 27% with twice-daily radiotherapy compared with 11% with once-daily radiotherapy. It is important to note that the incidence of grade 4 esophagitis did not differ, nor was the overall pattern of toxicity otherwise different. It should be noted that, among 572 patients treated in three different phase III trials using hyperfractionation, no permanent esophageal strictures have been reported [21, 23, 25].

In the treatment of other malignancies, for example, head and neck cancer, grade 3 toxicities are not felt to be dose limiting. However, despite the Intergroup trial data and the fact that no randomized trial has compared accelerated hyperfractionated radiotherapy with modern dose-escalated once-daily radiotherapy, there is a common perception that continuous-course twice-daily radiotherapy has significantly greater toxicity than once-daily radiotherapy, which must be mitigated. This perception has contributed to the common clinical practice of only using twice-daily fractionation in good performance status patients with favorable radiation field sizes. Others might argue that the benefit seen with twice-daily radiotherapy was not simply related to hyperfractionation, but instead the result of greater treatment intensity. Such would not only be consistent with the meta-analysis previously mentioned regarding treatment length but also a negative trial comparing different fractionation schemes of the same radiotherapy intensity [21]. A recent survey of nearly 700 radiation oncologists showed that only 23% of them used the hyperfractionated technique in their practice (S. Fong, University of Michigan, personal communication).

Other altered fractionation schemes have been examined as well. Komaki et al. [39] recently reported the phase I Radiation Therapy Oncology Group (RTOG) 9712 trial, which used a concomitant boost technique to escalate dose while keeping the total treatment duration at 5 weeks. In the concomitant boost technique, thoracic radiotherapy was initially given as 1.8 Gy daily for 3–4 weeks, followed by 1–2 weeks of twice-daily thoracic radiotherapy. The MTD was found to be 61.2 Gy using this technique with concurrent cisplatin–etoposide chemotherapy. A subsequent phase II study also run by the RTOG, the RTOG 0239 trial, investigated 61.2 Gy of thoracic radiotherapy with four cycles of cisplatin–etoposide chemotherapy. The survival analysis for that study is not yet mature. In Table 1, we present a comparison of outcomes and toxicity of selected phase II trials reported with the superior arm of the Intergroup 0096 trial.

The efficacy of radiotherapy fractionation schemes can potentially be predicted by calculating the BED [40]. The BED reflects the tumor type (doubling time), dose per fraction, and nominal total dose, and may also take into account the time to complete therapy. In comparison with the accelerated 45-Gy via twice-daily treatment regimen studied in the Intergroup 0096 trial, as shown in Table 2, both the CALGB thoracic radiotherapy regimen of 70 Gy once daily and the RTOG concomitant-boost approach yield substantially higher BEDs. Given the impact of intensified local therapy seen in the Intergroup 0096 trial, evaluation of thoracic radiotherapy regimens that have the potential to further enhance local tumor control and survival is warranted. Importantly, the CALGB 70-Gy once-daily treatment regimen and the RTOG 61.2-Gy concomitant-boost regimen may be better tolerated and more practical to deliver than the 45-Gy twice-daily treatment regimen.

Table 1. Comparison of selected phase II trials for LS-SCLC with the superior arm of INT 0096

	Induction chemotherapy	Radiation therapy	Concurrent chemotherapy	Median survival (months)	2-Year OS	Grade ≥3 esophagitis
INT 0096	None	45 Gy b.i.d	Cis + E	23	47%	33%
CALGB 39808	P + T × 2	70 Gy q.d.	Carb + E	22.4	48%	19%
CALGB 30002	E + P + T × 2	70 Gy q.d.	Carb + E	20	35%	30%
RTOG 0239	None	61.2 Gy CB	Cis + E	Not yet mature		17%

Abbreviations: b.i.d., twice daily; CALGB, Cancer and Leukemia Group B; Carb, carboplatin; CB, concomitant boost; Cis, cisplatin; E, etoposide; LS-SCLC, limited-stage small cell lung cancer; NT, Intergroup; OS, overall survival; P, paclitaxel; q.d., once daily; RTOG, Radiation Therapy Oncology Group; T, topotecan.

Table 2. Predicted biological equivalent dose (BED) for thoracic radiotherapy

	Total dose	Fraction size	Treatment frequency	Treatment length	BED	BED-time	Relative BED
INT 0096	45 Gy	1.5 Gy	b.i.d.	3 wks	52 Gy	43 Gy	1.0
CALGB	70 Gy	2.0 Gy	q.d.	7 wks	84 Gy	63 Gy	1.4–1.6
RTOG	61.2 Gy	1.8 Gy	CB	5 wks	72 Gy	57 Gy	1.3–1.4

Abbreviations: CALGB, Cancer and Leukemia Group B; CB, concomitant boost; INT, Intergroup; q.d., once daily; RTOG, Radiation Therapy Oncology Group.

PCI

The recognition of the central nervous system as a sanctuary for SCLC cells led to the use of radiation therapy, initially for the treatment of established metastases, then prophylactically. All the phase III trials and most of the other studies mentioned in this review have incorporated PCI into the treatment plan. A meta-analysis of 987 patients has shown a 5.4% OS benefit at 3 years with the use of PCI, as well as a higher rate of disease-free survival and a lower cumulative incidence of brain metastasis [41]. It is the concern for potential late effects on the brain following PCI that has steered some clinicians away from recommending its routine delivery [42]. As a result, the optimal dose of PCI and full extent of neuropsychological sequelae are being explored further in the International Cranial Irradiation Trial, PCI 01-EULINT1. That trial has completed accrual and hopefully will be presented soon.

Solid evidence demonstrating the importance of PCI comes from patients with ES-SCLC. A recently reported European Organization for Research and Treatment of Cancer trial randomized ES-SCLC patients with any response to chemotherapy to PCI or no PCI. The 1-year survival rate was 27.1% for PCI and 13.3% for the control arm [43]. PCI also significantly reduced the risk for symptomatic brain metastasis and significantly improved both disease-free survival and OS. Therefore, PCI should be offered to all patients, both ES-SCLC and LS-SCLC, who show any response to initial chemotherapy.

A contemporary view of radiation-induced brain injury [44], as can occur with PCI, suggests that it can be partially prevented and/or treated by the application of therapies similar to those used in Alzheimer's disease. In a prospective phase II trial, donepezil, an acetyl cholinesterase inhibitor, significantly improved the cognitive functioning, mood, and health-related quality of life for patients with low-grade gliomas receiving radiotherapy [45]. A phase III trial investigating donepezil as a radiation modulator has been planned for patients with primary brain tumors. If donepezil is found to be beneficial, such therapy may similarly be beneficial for patients requiring PCI for LS-SCLC.

Chemotherapy for ES-SCLC

With improvements in staging through the use of CT and magnetic resonance imaging, more patients are found to have ES-SCLC. The ratio of LS-SCLC to ES-SCLC was formerly 1:1 and is now 1:3 as more subtle lesions, such as silent adrenal and brain metastases, are identified. Several therapeutic agents and strategies have been tested during the last three decades in ES-SCLC. Response rates of 70%–85%, with complete response rates of 20%–30%, are encouraging, but virtually every patient relapses. The standard of care chemotherapy program in the U.S. has been the combination of cisplatin and etoposide since the 1980s [46]. Carboplatin may be substituted for cisplatin without an apparent loss of effect and is preferred in older patients or those with renal insufficiency [47].

Newer agents do not appear to be more active than older agents. For example, epirubicin, ifosfamide, vinorelbine, carboplatin, gemcitabine, the taxanes, and the topoisomerase I inhibitors tested in the 1990s and 2000s are not more active than doxorubicin, cyclophosphamide, vincristine, cisplatin, and the topoisomerase II inhibitors tested in the 1970s and 1980s. Still, some promising results have been reported. Noda et al. [48] demonstrated the superiority of cisplatin plus irinotecan compared with cisplatin plus etoposide in a Japanese Clinical Oncology Group (JCOG) trial. Unfortunately, when Hanna et al. [49] tried to replicate a comparative trial in the U.S., both treatments were equally effective. Part of the failure by Hanna et al. [49] may have been secondary to clinical trial design and the use of a different schedule and dose of cisplatin plus irinotecan when compared with that used in the JCOG trial. A Southwest Oncology Group trial further addressing this question has not been completed or reported. Still, two-drug regimens have been demonstrated to be more effective than single-agent regimens, even in elderly patients with a poor performance status [50–52]. The addition of a third agent has produced higher response rates but at the cost of greater toxicity, without improving the median survival duration over that seen with cisplatin plus etoposide alone [53–56]. Treatment beyond four to six cycles of any chemotherapy regimen is not beneficial. After four cycles of standard cisplatin plus etoposide, treatment with either maintenance therapy or four cycles of topotecan failed to improve survival [57, 58].

The issue is not that of sensitivity to only a few chemotherapy drugs, as is the case in melanoma, for example. Rather, the problem is the rapid development of drug resistance and the failure of second-line therapy to produce meaningful response rates and longer survival times, especially if the tumor fails to respond to primary treatment or there is rapid progression, within 3 months. The only U.S. Food and Drug Administration-approved second-line therapy, topotecan, produces response rates of 10%–40% and a median survival time of 6.0 months [59, 60]. Topotecan can be used orally or via i.v. infusion with the same result [61]. For ES-SCLC, therefore, we need either much better cell kill initially or alternative, non–cross-resistant therapies for second-line therapy.

Chemotherapy for LS-SCLC

As already mentioned, the initial breakthrough in SCLC treatment occurred in late 1960s with the recognition that SCLC patients were more responsive to available chemotherapeutic agents than to an inert compound [12]. Innovations in chemotherapy for LS-SCLC are first proven in patients with ES-SCLC. Thus, cisplatin plus etoposide was originally shown to be equivalent to doxorubicin-based chemotherapy in patients with ES-SCLC [62]. The results were extrapolated for use in LS-SCLC without confirmation because of the compatibility with radiotherapy and a significantly better toxicity profile. Subsequent clinical trials did confirm the superiority of the cisplatin–etoposide–radiotherapy regimen [63].

Based on the experience of the JCOG in ES-SCLC, Saito et al. [64] explored cisplatin plus irinotecan in combination with thoracic radiotherapy for LS-SCLC patients and found it to be an active regimen warranting further testing in phase III clinical trials. However, it should be noted that, in the phase II trial, only 53% of the patients were able to complete the entire therapy. Brain metastasis as an initial site of relapse was observed in 26% of the patients. A distant site was the initial site of failure in 77% of the patients. These rates appear slightly higher than those in the studies evaluating etoposide and a platinum with concurrent twice-daily thoracic radiotherapy [25, 65]. Insufficient administration of cisplatin plus irinotecan as consolidation may explain, in part, this finding.

Other novel attempts have been made at integrating new cytotoxic agents into the treatment of patients with LS-SCLC. CALGB 30002 assessed two cycles of a three-drug induction chemotherapy regimen (etoposide, paclitaxel, and topotecan) followed by 70 Gy of thoracic radiotherapy concurrent with carboplatin and etoposide [66]. Greater hematologic toxicity was observed during induction chemotherapy in comparison with a prior study, and 16% of patients entered into the study did not proceed to the planned protocol radiotherapy. The potential adverse effect of combining three drugs in SCLC has also been noted in other trials. An induction chemotherapy regimen of cisplatin and irinotecan was evaluated in the CALGB 30206 trial, which again included consolidation with 70 Gy of thoracic radiotherapy plus carboplatin and etoposide. Follow-up data are not mature enough to analyze outcomes at this time. A recently completed phase I study conducted by the RTOG/CALGB, the 0241/30202 trial, included an evaluation of 70-Gy once-daily thoracic radiotherapy concurrent with the first two cycles of chemotherapy. The main objective of that trial was to determine the MTD of irinotecan in combination with cisplatin and thoracic radiotherapy, and the study was designed to include both 45-Gy twice-daily treatment and 70-Gy once-daily treatment thoracic radiotherapy.

At this time, there is not an obvious hypothesis regarding the integration of novel systemic therapy that would merit testing in the phase III setting for LS-SCLC. Importantly, it is necessary to define an optimal thoracic radiotherapy regimen for the design of future studies that may

test the merit of novel cytotoxic agents and molecular-targeted therapies.

Future Clinical Trials

Defining an optimal thoracic radiotherapy regimen in LS-SCLC remains critical and will have a major impact on clinical practice. The results of the Intergroup 0096 trial [23] are still clearly the best in terms of long-term outcome and clearly established that improving the efficacy of thoracic radiotherapy can significantly impact survival in patients with LS-SCLC. Given the reluctance for practitioners to adopt the results of the superior treatment arm from the Intergroup 0096 trial, the validity of this regimen needs to be assessed in the context of thoracic radiotherapy regimens that have higher predicted biologic efficacy and may have better tolerability and acceptance. Superior outcomes in an experimental arm would lead to establishing a change in the standard of care for patients with LS-SCLC. Conversely, if the best outcomes were observed with accelerated 45-Gy twice-daily treatment with thoracic radiotherapy, then the results of this study would provide convincing and definitive evidence for practitioners to adopt this regimen.

Currently, CALGB 30610 (Table 3) is a phase III trial for LS-SCLC that will address a pure radiotherapy question. This two-stage trial has also been approved by the RTOG, but is waiting approval by the Cancer Therapy Evaluation Program. Initially, the trial will consist of three arms: arm A, 45 Gy (1.5 Gy twice daily over 3 weeks); arm B, 70 Gy (2 Gy once daily over 7 weeks); arm C, 61.2 Gy (1.8 Gy once daily for 16 days followed by 1.8 Gy twice daily for 9 days). Patients will be randomized in a 1:2:2 fashion. After a planned early interim assessment of toxicity, only one of the two experimental arms (arm B or arm C) will be selected to continue accrual. Thus, the final study design will include a phase III comparison of one experimental arm with standard therapy (arm A). Etoposide plus cisplatin for four cycles will be the chemotherapy in all arms to start day 1 with radiotherapy. Those patients who achieve a complete response or good partial response to initial therapy will be offered PCI. It is extremely important that all eligible patients be offered participation in this trial.

Current clinical trials for ES-SCLC are focusing on the addition of targeted agents to the etoposide–cisplatin chemotherapy "backbone." In non-small cell lung cancer, the tyrosine kinase inhibitors did not add to standard combination chemotherapy, but the antiangiogenic agent bevacizumab clearly added benefit to the paclitaxel–carboplatin combination. Newer agents will thus be integrated into chemotherapy, looking first for tolerability, then effectiveness.

Table 3. Schema for CALGB 30610 trial

CALGB 30610 trial schema
Stage I
Arm A: 45 Gy b.i.d. (1.5 Gy/fx in 3 wks), P + E × 4
Arm B: 70 Gy q.d. (2.0 Gy/fx in 7 wks), P + E × 4
Arm C: 61.2 Gy CB (1.8 Gy/fx in 5 wks), P + E × 4
Randomize 1:2:2
Stage II
Arm A: 45 Gy b.i.d. (1.5 Gy/fx in 3 wks), P + E × 4
Arm B or arm C, depending on which arm is less toxic.
Randomize 1:1

Abbreviations: b.i.d., twice daily; CALGB, Cancer and Leukemia Group B; CB, concomitant boost; E, etoposide; fx, fraction; P, paclitaxel; q.d., once daily.

Summary

While progress has been made in the treatment of LS-SCLC, significant work is still needed before SCLC can be considered a curable cancer. Clinical trials have been instrumental in developing the treatment paradigm of chemoradiotherapy. Studies have been completed investigating the optimal delivery of PCI and are similarly under way investigating the optimal delivery of thoracic radiotherapy. In ES-SCLC, irinotecan plus cisplatin may be a possible alternative to the standard etoposide–cisplatin chemotherapy doublet. All patients with both LS-SCLC and ES-SCLC who respond to chemotherapy should be offered PCI. It is imperative that patients be given the opportunity to participate in future trials so that the survival for these patients can continue to improve.

Acknowledgments

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