Small Cell Lung Cancer

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Abstract

Small cell lung cancer (SCLC) is an aggressive cancer of neuroendocrine origin, which is strongly associated with cigarette smoking. Patients typically present with a short duration of symptoms and frequently (60–65 %) with metastatic disease. SCLC is a heterogeneous disease including extremely chemosensitive and chemoresistant clones. For this reason, a high percentage of patients respond to first-line chemotherapy but rapidly succumb to the disease. SCLC is generally divided into two stages, limited and extensive. Standard treatment of limited stage disease includes combination chemotherapy with cisplatin and etoposide for four cycles, thoracic radiation initiated early with the first cycle of chemotherapy, and consideration of prophylactic cranial irradiation (PCI) in the subset of patients with good response. Surgery may play a role in TNM stages I and II. In extensive disease, platinum agents and etoposide, used in combination, are again the first-line standard of care in the USA. However, thoracic radiation therapy is used predominately in patients where local control is important and PCI is of uncertain benefit. Despite these treatments, prognosis remains poor and novel therapies are needed to improve survival in this disease.

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Contents

1 Introduction

1.1 Epidemiology and Risk Factors

Small cell lung cancer (SCLC) comprises 13 % of all lung cancers and leads to approximately 30,000 deaths annually in the USA [1]. It is strongly associated with cigarette smoking with 95 % of all patients having a history of heavy tobacco exposure. This strong association is further highlighted by the decreasing incidence of SCLC with the decline of smoking rates, changes in smoking habits, and increased use of filtered cigarettes in the USA [2]. The decline in rate could also be related to changes in the World Health Organization classification of lung tumors which made the diagnosis of SCLC more restrictive. Other risk factors for the development of SCLC include exposures to radon, halogenated ethers, arsenic, asbestos, chromium, polyaromatic hydrocarbons, and vinyl chloride. Women smokers are more likely to develop SCLC when compared to their male counterparts due to factors that are not clearly defined [2].

1.2 Presentation

Patients typically presented with a short duration of symptoms, on average three months. Endobronchial tumors may manifest with symptoms of cough, wheezing, dyspnea, or post-obstructive pneumonia. Patients with regional extension of disease may experience vocal hoarseness, chest or throat pain, dysphagia, or superior vena cava syndrome due to the central nature of these tumors. Patients with metastatic disease may present with abdominal pain, bone pain, nausea, vomiting, anorexia, weight loss, or focal neurologic deficits. Patients of any stage may present with paraneoplastic syndromes. The majority of SCLC cells are extremely sensitive to chemotherapy. In fact, patients with a large tumor burden may develop tumor lysis syndrome when exposed to potent chemotherapy. Unfortunately, these tumor cells are heterogeneous with chemoresistant clones ultimately surviving, proliferating, and causing disease recurrence and death.

1.3 Histology

SCLC histology reveals dense sheets of cells with neuroendocrine differentiation that are small, round, and blue (Fig. 1) [3]. Light microscopy shows monotonous undifferentiated morphology with finely granular nuclear chromatin, faint or absent nucleoli, a high nuclear to cytoplasmic ratio and frequent mitoses [3]. These cells divide quickly are highly metastatic, invasive, and angiogenic. In fact, 60–65 % of patients present with extensive metastatic disease [2]. Occasionally, SCLC may occur in conjunction with non-small cell lung cancer (NSCLC) [3]. When assessed using the immunoperoxidase antibody panel, cells are typically keratin positive and

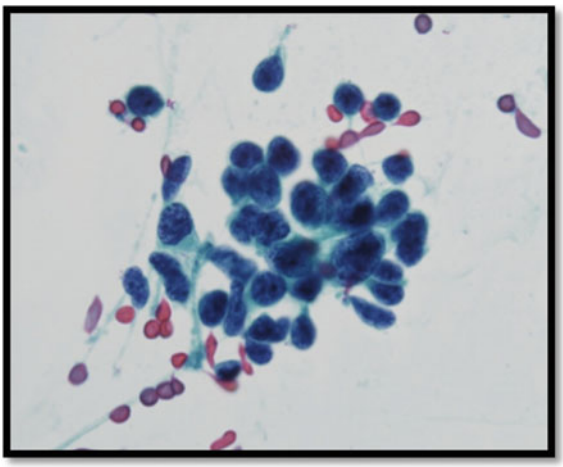

Fig. 1 Papanicolaou-stained cytology smear, at 400x magnification, demonstrating malignant epithelium tumor consisting of small cells with scan cytoplasm and ill-defined boarders classic for small cell lung cancer. Photograph provided courtesy of Dr. Chen Zhang, Indiana University School of Medicine Department of Pathology

CD45/leukocyte common antigen (LCA) negative. Neuroendocrine markers such as synaptophysin and chromogranin, and thyroid transcription factor are usually positive [4].

2 Paraneoplastic Syndromes

2.1 Endocrine Paraneoplastic Syndromes

Given its ability to produce multiple hormones, SCLC is associated with several paraneoplastic syndromes. These include hyponatremia associated with syndrome of inappropriate antidiuretic hormone secretion (SIADH), Cushing's syndrome associated with adrenocorticotropic hormone secretion, and acromegaly associated with growth hormone secretion by tumor cells [5]. In fact, symptoms of paraneoplastic syndromes may precede the discovery of the underlying cancer. Likewise, they may be the first sign of relapse after a remission has been achieved. Therefore, typical signs of paraneoplastic disorder should prompt a swift search for the underlying cancer. In fact, the only definitive treatment for these disorders is chemotherapy (± radiation if limited stage) to target the cancer itself.

2.2 Neurologic Paraneoplastic Syndromes

More rarely, SCLC is associated with neurologic paraneoplastic disorders that include sensory, sensorimotor, and autoimmune neuropathies as well as encephalomyelitis. These syndromes are thought to occur through autoimmune mechanisms when antibodies bind to both the SCLC and the central nervous system. In patients with SCLC, the most common neurologic paraneoplastic disorders are subacute sensory neuropathy and/or paraneoplastic encephalomyelitis [5]. These disorders are associated with anti-Hu antibodies and are sometimes referred to as "anti-Hu syndromes." Anti-Hu-associated subacute sensory neuropathy usually presents with numbness in the distal extremities including hands and feet. Anti-Hu-associated encephalomyelitis may present with an array of central neurologic symptoms including but not limited to memory loss, confusion, seizure, muscle weakness, aphasia, dysarthria, facial numbness, or neuropsychiatric disturbance including anxiety or depression. Serum and cerebral spine fluid (CSF) are tested for paraneoplastic antibodies and, when elevated, are diagnostic of this condition. Lambert–Eaton syndrome is less commonly associated with SCLC and is caused by autoantibody impairment of voltage-gated calcium channels on the muscle cell membrane [5]. Patients presented with proximal leg weakness that improves with repetition. Electromyography is used for definitive diagnosis. Rare neurologic disorders seen in SCLC include cerebellar degeneration, opsoclonus, retinal blindness, and Stiff Person Syndrome [5].

2.3 Treatment and Prognosis of Paraneoplastic Syndromes

Treatment of the underlying cancer will improve symptoms and often times reverse the course of associated paraneoplastic syndromes. This is especially true to SIADH, Cushing's syndrome, and acromegaly, as the associated hormone secretion is dramatically reduced along with the decreased tumor burden. However, neurologic paraneoplastic disorders typically involve irreversible destruction of neurons secondary to inflammation and immune activation of autoantibodies. Therefore, manifestations of neurologic disease may persist even after treating the underlying malignancy [5].

3 Staging

Given the rapid doubling time of SCLC, prompt workup and treatment is essential. In fact, given the highly metastatic potential of SCLC cells, workup should not delay definitive treatment with chemoradiation. Given its correlation with multiple

paraneoplastic syndromes, a thorough history, physical examination, and laboratory investigation should be completed. We also recommend computed tomography (CT) of the chest, abdomen, and pelvis along with magnetic resonance imaging (MRI) of the head for standard staging. If the patient is suspected to have limited disease by preliminary imaging, then position emission tomography (PET) and possible endobronchial ultrasound with biopsy may be indicated to exclude or confirm mediastinal disease. In a study on the use of PET in clinical staging, 11 % of patients classified as limited stage by CT were upgraded to extensive disease while 18 % of patients originally thought to have extensive disease were downgraded to limited disease after scanning [6]. Therefore, when staging by CT and MRI is in question, PET may be of utility in establishing a definitive stage.

3.1 Limited Versus Extensive Disease

Limited disease (LD) is defined as tumor that is confined to one hemithorax and associated regional lymph nodes. This constitutes approximately 35–40 % of patients and includes tumor node metastasis (TNM) stages I through III [2]. Tumor must be encompassed by a tolerable radiation port and exclude pleural or pericardial involvement with malignant effusion. Extensive disease (ED) is defined as tumor outside the confines of limited stage disease including patients with malignant pericardial and pleural effusion. ED includes patients of TNM IV.

3.2 Tumor, Node, Metastasis Staging

TNM staging has gained popularity in recent years, particularly since the International Association for the Study of Lung Cancer (IASLC) lung cancer staging project revealed significant variability in survival based on stage [7]. TNM staging system seems more accurate than the Veterans Administration Lung Study Group staging of limited versus extensive stage in determining prognosis. This is especially true in the earlier stages of the disease [7]. T1 is defined as tumor less than or equal to 3 cm in greatest dimension, surrounded by lung or visceral pleura, without bronchoscopic evidence of invasion, more proximal than the lobar bronchus; or superficial spreading of tumor in the central airways confined to the bronchial wall [8]. T1 is then further subdivided into stage T1a (tumor less than 2 cm in greatest dimension) and stage T1b (tumor greater than 2 cm but less than 3 cm in greatest dimension). T2 is generally defined as tumor greater than 3 cm but less than or equal to 7 cm [8]. However, smaller tumors that are 3 cm or less may be upstaged to T2 if they involve the main bronchus but are greater than 2 cm distal to the carina, involve atelectasis or obstructive pneumonitis extending into the hilar region but not the entire lung, and/or invade the visceral pleura of the lung. Additionally, T2 is also subdivided by size. Tumors greater than 3 cm and less than or equal to 5 cm are classified as T2a. Tumors that are greater than 5 cm but are lesser than or equal to 7 cm are classified as T2b. T3 is defined as any tumor greater than 7 cm in

size or one that directly invades any of the following: chest wall, parietal pleural, diaphragm, phrenic nerve, mediastinal pleura, or parietal pericardium [8]. Additionally, if the tumor is less than 7 cm but involves the main bronchus and is less than 2 cm distal to the carina but without involvement of the carina, it is also upstaged to a T3 lesion. If the tumor is less than 7 cm in size but is associated with atelectasis or obstructive pneumonitis of the entire lung, it is upstaged to a T3 lesion. Finally, if the primary lesion is less than 7 cm but there is at least one separate tumor nodule in the same lobe, then the patient is upstaged to T3. T4 is defined as a tumor of any size that invades any of the following: heart, mediastinum, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, carina, or a separate tumor lesion(s) in the ipsilateral lobe [8]. N0 is defined as no regional lymph node metastasis. N1 is defined as metastasis to the ipsilateral peribronchial, hilar, or intrapulmonary nodes. N2 is defined as metastasis to the ipsilateral mediastinal or subcarinal nodes. N3 is defined as metastasis to the contralateral mediastinal, or hilar nodes, and/or any scalene or supraclavicular lymph nodes. Metastasis is defined as absent (M0) or present (M1). Staging and prognosis is then completed using the following chart (Table 1) [8].

Table 1 Staging as established by the TNM system and associated median survival with optimal chemoradiation or chemotherapy

Stage	Tumor	Node	Metastasis	Median survival
(Limited)				
Ia	T1a	N0	M0	60 months
	T1b	N0	M0	
Ib	T2a	N0	M0	43 months
IIa	T1a	N1	M0	34 months
	T1b	N1	M0	
	T2a	N1	M0	
	T2b	N0	M0	
IIb	T2b	N1	M0	18 months
	T3	N0	M0	
IIIa	T1	N2	M0	14 months
	T2	N2	M0	
	T3	N1	M0	
	T3	N2	M0	
	T4	N0	M0	
	T4	N1	M0	
IIIb	T4	N2	M0	10 months
	T1	N3	M0	
	T2	N3	M0	
	T3	N3	M0	
	T4	N3	M0	
IV (*Extensive*)	T Any	N Any	M1	6 months

3.3 Pleural Effusions

Of the patients in the IASLC database, 68 had pleural effusion with associated cytologic examination. Interestingly, in patients with LD, the presence of cytologically negative pleural effusion conferred an intermediate prognosis, which was worse than LD but better than ED [7]. Also, the survival of patients with positive effusions and otherwise LD was superior to that of patients with ED [7]. Other poor prognostic factors associated with ED include multiple metastatic sites, performance score (PS) 3–4, cachexia, older age, and increased levels lactate dehydrogenase (LDH) in the serum [9]. Favorable prognostic factors include a single metastatic site, PS 0–2, younger age, and a normal serum LDH [9]. Though the initial response rate to chemotherapy is as high as 70 %, the disease universally recurs in patients with ED and the majority of patients with LD, leading to the poor prognosis associated with SCLC.

4 Treatment of Limited Stage Disease

4.1 Surgery

A prospective randomized trial was conducted and published in 1994 to assess the role of surgical resection in limited stage disease [10]. Patients first received chemotherapy with cyclophosphamide, doxorubicin, and vincristine for a total of five cycles. Patients that achieved at least partial response and were fit for surgery were randomized to thoracotomy versus no surgery. There was no difference in survival between the arms of the study. This was the only phase III trial evaluating the role of surgical resection of residual disease after chemotherapy in limited stage SCLC. In 2009, the IASLC published their lung cancer study project [7]. Of the 8000 cases of SCLC in the IASLC database, 349 cases included SCLC that had been resected and pathologically staged. The data revealed a statistically significant survival advantage for stage I and stage II patients when surgically staged and resected: stage IA, 60 months versus 119 months; stage IB, 43 versus 81 months; stage IIA, 34 versus 49 months; and stage IIB, 18 versus 34 months. Surgery alone is not the treatment of choice in SCLC as it is a disease characterized by rapid early hematogenous spread. We believe surgery might have a role in a small group of patients with peripheral T1N0 SCLC tumors. Given the IASLC data, resection followed by adjuvant chemotherapy is reasonable in these patients.

4.2 Evolution of Chemotherapy Regimens

Given the early metastatic potential of SCLC, most patients with LD are initially treated with concurrent chemoradiation. This includes four cycles of etoposide and cisplatin (EP) combined with chest radiotherapy. Though EP is the current standard,

cyclophosphamide was the first drug to show activity against SCLC. Anthracyclines and vincristine were later combined with cyclophosphamide resulting in the CAV regimen. Until the late 1980s, CAV was the standard chemotherapy for limited stage SCLC. At that time, data began to suggest that EP may be superior in the treatment LD SCLC. A study published in 1988 by Einhorn et al. [11] revealed that patients who were treated with EP consolidation, after response to CAV initial therapy, remained in remission and ultimately survived longer. This led to a 1993 phase III study by Johnson, et al. [12] which compared response rates and survival in patients treated with CAV versus CAV plus radiation therapy who, after response, were then again randomized to either observation or consolidation chemotherapy with EP. The study did not show a statistically significant response rate or survival advantage in the chemotherapy alone versus chemoradiation groups; however, patients who received consolidation chemotherapy did have superior median and two-year survival when compared to the observation group [12]. A larger 1999 study by Turrisi et al. [13] did find superior survival when combining EP with chest radiotherapy. A 2002 phase III trial also confirmed that EP was superior to carboplatin, epirubicin, and vincristine (CEV) in LD SCLC. This study followed patients for five years and revealed that the two- and five-year survival rates were significantly increased in the EP versus CEV groups (14 and 5 % vs. 6 and 2 %, $P = 0.0004$) [14]. However, for the group of ED SCLC patients, there was no significant survival advantage for EP over CEV. Finally, two meta-analyses revealed a small but significant survival benefit with regimens including cisplatin and etoposide [15, 16]. These data led to cisplatin and etoposide becoming the preferred chemotherapy regimen to be administered concurrently with chest radiation in patients with LD SCLC. Although the study by Einhorn et al. suggested benefit of EP in the context of consolidation, later studies failed to show benefit with induction or consolidation chemotherapy in the context of standard treatment with EP and radiation therapy (XRT) (Table 2).

Table 2 Studies evaluating induction and consolidation chemotherapy

Author	Induction	Standard	Consolidation	Number of patients	Median survival (months)	*P* value
Thomas [54]	None	Cis, etop, vincris + XRT	Etoposide	114	24.2	NS
Edelman [55]	None	EP + XRT	Carbo, paclitax	87	17	NS
Maranzano [56]	CAV	EP + XRT	Vincris, MTX, etop, doxorub, cyclophos	55	17	NS
Bogart [57]	Topotecan, paclitaxel	EP + XRT	None	63	22.4	NS

Legend: *XRT,* radiation therapy; *NS,* not significant *p* value

4.3 Chemotherapy Versus Chemoradiation

In the early 1980s, investigators began to study the possible synergetic effects of chemoradiation. SCLC was found to be both a chemosensitive and a radiosensitive disease. Theories suggested that radiotherapy controlled bulky chest disease while also conferring increased chemosensitivity of the primary tumor. During this period, smaller studies investigating the addition of XRT to chemotherapeutic regimens revealed mixed results. Finally, two meta-analyses explored the benefit of radiation therapy in conjunction with chemotherapy for limited stage SCLC. The first, published by Pignon in the New England Journal of Medicine in 1992, pooled data from 13 trials including 2140 patients with limited disease and 433 patients with extensive disease [17]. The results revealed a 14 % reduction in mortality and a 5.4 % increase in survival at three years when patients were treated with combination chemoradiation. A second study by Warde and Payne [18], during the same year, confirmed a small but significant increase in two-year survival of 5.4 % in patients treated with concurrent chemoradiation.

4.4 Concurrent Versus Sequential Chemoradiation

The timing of chest radiation therapy has also been evaluated. A phase III study in Japan randomized 231 patients with limited stage SCLC to either sequential or concurrent thoracic radiotherapy [19]. The results revealed a significant survival advantage with concurrent chemoradiation. Patients in the sequential group were treated with four cycles of chemotherapy with EP every three weeks. Chemotherapy was followed by 45 Gray of radiation therapy over three weeks. The concurrent arm was treated with four cycles of EP every three weeks with radiation starting on day two of the first chemotherapy cycle. The median survival time was 19.7 months in the sequential group versus 27.2 months in the concurrent group although not statistically significant. The question of concurrent versus sequential radiation therapy was also evaluated by a randomized trial published in the New England Journal of Medicine in 1987 [20]. This study revealed a slight survival advantage when radiation therapy was given sequentially but this was not statistically significant (Table 3). Concurrent chemoradiotherapy is currently the standard of care

Table 3 Summary of studies exploring benefits of concurrent versus sequential chemoradiation

Author	Regimen	Number of patients	Median survival (months)	*P* value
Perry [20]	CAV + concurrent XRT	125	13.1	NS
	CAV + sequential XRT	145	14.6	
Takada [19]	EP + concurrent XRT	114	27.2	0.097
	EP + sequential XRT	114	19.7	

Legend: *XRT,* radiation therapy; *NS,* not significant *p* value

in patients with LD SCLC who are healthy enough for the combination. The benefit in survival is modest at 5 % improvement in five-year survival and many confounding patient variables can enhance or eliminate this benefit.

4.5 Early Versus Late Chemoradiation

The benefits of early versus late radiation therapy have been explored in three landmark studies: Murray et al. [21], Work et al. [22], and Jeremic et al. [23]. Two of these studies favored survival benefit when radiation therapy was given early with the first two cycles of chemotherapy (Table 4). The benefits of early versus late radiation therapy were then verified by systematic review solidifying early chemoradiation as the standard of care [24].

4.6 Standard Versus Hyperfractionated Radiation

Standard versus hyperfractionated radiotherapy has been the subject of multiple studies in SCLC. Two phase III trials compared standard to hyperfractionated chest radiotherapy in combination with chemotherapy in patients with LD SCLC. The first by Bonner et al. in 1999 enrolled 311 patients to receive late chemoradiation therapy [25]. All patients received three cycles of EP up-front. Patients who did not progress on this regimen were then randomized to receive either twice-daily thoracic radiation or once-daily thoracic radiation with two additional cycles of EP. There was no difference in progression rates or overall survival; however, the twice-daily group did experience a greater rate of grade ≥3 or higher esophagitis [25]. In the Turrisi et al.'s trial, 417 patients with limited stage disease were randomized to receive 45 Gy of early radiation therapy (concurrently with EP chemotherapy) either twice-daily over a three-week period or once-daily over a

Table 4 Summary of studies exploring benefits of early versus late chemoradiation

Author	Regimen	Number of patients	Median survival (months)	*P* value
Murray [21]	CAV + EP with early XRT	155	21.2	0.008
	CAV + EP with late XRT	153	16	
Work [22]	EP followed by early CAV +XRT	99	10.5	NS
	EP followed by later CAV + XRT	100	12	
Jeremic [23]	EP + early hyperfractionated XRT	52	34	0.027
	EP + late hyperfractionated XRT	51	26	

Legend: *XRT,* radiation therapy; *NS,* not significant *p* value

Table 5 Summary of studies evaluating standard versus hyperfractionated radiotherapy

Author	Regimen	Number of patients	Median survival	*P* value
Bonner [25]	EP (3 cycles) followed by EP (2 cycles) + daily XRT	132	24.6 months	NS
	EP (3 cycles) followed by EP (2 cycles) + twice-daily XRT	130	23 months	
Turrisi [13]	EP + daily XRT (over 5 weeks)	185	19	0.04
	EP + twice-daily XRT (over 3 weeks)	196	23	

Legend: *XRT,* radiation therapy; *NS,* not significant *p* value

period of five weeks. Hyperfractionated radiotherapy was associated with a small but significantly increased survival (23 vs. 19 months, $P = 0.04$) [13]. However, twice-daily treatment was again associated with increased rates of radiation-induced side effects including an increased incidence of grade 3 esophagitis. The toxicity and the inconvenience of twice-daily radiation for patients have precluded hyperfractionated radiation from being considered standard of care in the USA (Table 5).

4.7 Prophylactic Cranial Irradiation (PCI)

After remission is achieved, the brain unfortunately remains an area of frequent recurrence for SCLC and is a sanctuary site. Although no single trial showed a statistically significant survival benefit with PCI, when examined by meta-analysis the results were practice changing. This meta-analysis, by Auperin et al. [26], published in the New England Journal of medicine in 1999, reviewed seven trials and included a total of 987 patients. The results revealed a 5.4 % increased rate of survival at three years when patients with limited disease who were in complete remission were prophylactically irradiated. Unfortunately, whole brain radiation is not without risk. Patients may experience acute or delayed neurotoxicity including ataxia, confusion, memory loss, and dementia associated with the reduced quality of life [27].

4.8 Summary

To summarize, the standard of care in limited stage SCLC continues to be cisplatin and etoposide for four cycles concurrently with chest radiation. Surgical resection can be considered with adjuvant chemotherapy in a small group of patients with peripheral T1N0 disease. PCI should be considered in patients who achieve a good response to chemoradiotherapy.

5 Treatment of Extensive Stage Disease

5.1 Choice of Chemotherapeutic Regimen

In the USA, platinum combined with etoposide is the standard first-line chemotherapy for extensive stage SCLC [28]. However, as discussed under the treatment of LD, CAV was the regimen of choice until the late 1980s. A 1991 study comparing CAV with EP for initial therapy revealed improved response rates as well as reduced toxicity with EP [28]. The study treated 288 patients who were randomized into three groups: CAV, EP, and a third group alternating CAV and EP (CAV/EP). The response rates for EP were significantly higher (78 %) while the CAV/PE and CAV response rates were 76 and 55 %, respectively. Complete response rates were similar among all three groups (EP 14 %, CAV/EP 16 %, and CAV 15 %). Interestingly, 23 % of the patients who failed to respond to the initial CAV treatment responded to EP at the time of crossover. Conversely, 8 % of patients who failed to respond to EP responded to CAV suggesting the two regimens were non-cross-resistant. CAV is still considered occasionally as a second-line chemotherapy in a small group of patients that are highly fit after progressing on EP. A year later, a similar study was completed by Roth et al. comparing 12 weeks of EP with 18 weeks of CAV, and 18 weeks of alternating treatment with CAV and EP. Results revealed no significant difference in response rate (61, 51, and 59 %), complete response rates (10, 7, and 7 %), or median survival (8.6, 8.3, and 8.1 months, respectively). The Norwegian Lung Cancer Study Group compared CEV with EP and showed no survival difference in the ED setting [14]. Therefore, EP for a total of four cycles became the standard of care for both LD and ED SCLC. Studies from Japan indicate that platinum combined with Irinotecan is more effective than EP in that population [29]. These data, however, could not be replicated in the USA [30].

5.2 Substitution of Carboplatin for Cisplatin

In 1994, a randomized study from the Hellenic Co-operative Oncology Group revealed that carboplatin can be effectively substituted for cisplatin [31]. This study enrolled 143 patients randomized to receive either EP or etoposide and carboplatin (EC) in combination with chest radiation. The results revealed similar response rates and median survival, 12.5 months for EP and 11.8 months for EC, respectively [31]. In addition, the study also reported decreased adverse events such as neutropenia, nausea, vomiting, and neurotoxicity in the EC group. A randomized phase III study from Japan confirmed these results in a group of elderly or poor-risk patients exclusively with ED [32]. Again, similar response rates (73 % to 73 %) and survival (median 10.6 months versus 9.9 months) with less toxicity were observed in patients treated with EC [32]. Therefore, carboplatin is often substituted for cisplatin in older patients or those who may not tolerate standard cisplatin therapy.

5.3 Strategies for Improving Current Chemotherapy

Multiple other strategies have been studied in ED SCLC with hopes of improving outcomes in this chemosensitive disease. These included increased dose intensity, three drug combinations rather than two, and maintenance chemotherapy. These studies showed higher response rates with no improvement in overall survival at the consequence of increased toxicity [33, 34]. With regard to maintenance chemotherapy, one meta-analysis suggested a small overall survival advantage; however, many randomized trials have given negative results [35–37]. In particular, most studies revealed an increased time to progression at the consequence of increased toxicity and no overall improvement in survival [35, 36].

5.4 Radiation Therapy for Extensive Disease

Recent data have suggested thoracic radiation might have a role not only in LD, but also in ED. Thoracic radiation therapy has been shown to increase overall survival in select patients with ED SCLC. A European multicenter trial assessed overall survival and progression-free survival in patients treated with chest radiation therapy versus observation after at least a partial response to systemic chemotherapy [38]. As a caveat, all patients were treated with PCI as initial PCI studies suggested improved OS in ED setting. The overall survival at one year was only minimally increased; however, two-year survival and progression-free survival were significantly increased, 13 % versus 3 % ($p = 0.004$) and 24 % versus 7 % ($p = 0.001$), respectively. Another study assessed radiation therapy versus further chemotherapy [39]. To be included in the study, ED SCLC patients were required to show complete response at distant sites of metastasis with at least a partial response in the original lung lesion. When compared to additional cycles of chemotherapy, thoracic radiation increased the overall survival and the five-year survival rate, 11 months versus 17 months and 4 % versus 9 %, respectively. We believe thoracic radiation might have a place in a subset of patients with ED SCLC, particularly those with bulky mediastinal disease where local control is important.

5.5 Prophylactic Cranial Irradiation for Extensive Disease

PCI was previously thought to reduce the risk of brain metastases and prolong survival in patients with extensive stage SCLC [40]. However, this study was not associated with the standard of care platinum-based chemotherapy nor did it require baseline MRI to rule out the presence of brain metastasis prior to study enrollment. Recently, a 2014 randomized phase III trial from Japan revealed that while PCI did reduce brain metastases (32.4 % vs. 58 % at 12 months) it reduced overall survival when compared to observation (10.1 months vs. 15.1 months) [41]. This study included 330 SCLC patients with extensive disease who were randomized to PCI versus observation after any response to first-line platinum-based chemotherapy.

Patients were only allowed on the study after baseline MRI revealed the absence of brain metastases. Given this conflicting evidence, more studies are needed to determine the role of PCI in ED SCLC and we do not routinely recommend that to patients with ED SCLC

5.6 Summary

To summarize, standard of care first-line chemotherapy for ED SCLC includes combination chemotherapy with etoposide and a platinum agent (cisplatin or carboplatin). Similarly to LD SCLC, four cycles are considered optimal while increased dose intensity and maintenance therapies have not proven beneficial. For elderly or debilitated patients, chemotherapeutic modifications with attenuated EP or oral etoposide alone can be considered. Thoracic radiation may help a select group of patients while the role of PCI is undetermined. Enrollment in clinical trials remains a valuable option in patients with ED SCLC.

6 Second-Line Chemotherapy

Most patients will respond to first-line chemotherapy with EP but the majority will relapse with the emergence of chemoresistant clones. Unfortunately, response to second-line chemotherapy is poor. A patient's response to second-line chemotherapy can be predicted based on the interval from the completion of initial therapy to relapse. If this interval is less than three months, then the patient is thought to have chemoresistant disease. In these individuals, response to second-line agents is typically poor and is estimated to be less than 10 % [9]. If the interval is greater than three months since completion of initial chemotherapy, then the patient is deemed chemosensitive. These patients have a predicted response rate of approximately 25 % [9]. Regardless, relapsed disease is difficult to treat as evidenced by a reduced median survival of 4–5 months even with second-line chemotherapy [9].

Multiple agents have shown activity in relapsed SCLC including: platinum agents (cisplatin and carboplatin), podophyllotoxins (etoposide and teniposide), camptothecins (irinotecan and topotecan), alkylating agents (cyclophosphamide and ifosfamide), anthracycline (amrubicin, doxorubicin, epirubicin), taxanes (docetaxel and paclitaxel), vinca alkaloids (vincristine and vinorelbine), the folate antimetabolite methotrexate, and the pyrimidine analog gemcitabine [9]. Unfortunately, topotecan is the only FDA approved agent for the treatment of relapsed disease. This was based on a British study in 2006, which randomly assigned relapsed SCLC patients to oral Topotecan as compared to best supportive care alone (BSC) [42]. Survival was increased from 13.9 weeks in the BSC group to 25.9 weeks in the topotecan group. Partial response rate to topotecan was 7 % while 44 % of patients exhibited stable disease. The most common toxicities

included grade 4 neutropenia (33 %), grade 3–4 anemia (25 %), and grade 4 thrombocytopenia (7 %).

A German study in 1999 studied the efficacy of intravenous (IV) topotecan versus CAV in relapsed SCLC patients [43]. Patients were eligible for the study if they had relapsed at least 60 days after the completion of first-line chemotherapy and displayed adequate marrow, liver, and renal function with an ECOG performance status of 2 or less. Response rates and median time to progression were both improved with topotecan over CAV, 24.3 % versus 18.3 % and 13.3 weeks versus 12.3 weeks, respectively. For these reasons, topotecan IV or oral is typically used first in relapsed disease.

7 Targeted Therapy

Multiple genetic abnormalities have been discovered in the tumors of patients with SCLC. In 2010, a SCLC cell line (NCI-H209) was sequenced for genomic mutations. The results revealed 22,910 mutations associated with the carcinogens present in tobacco smoke [44]. By dividing the number of mutations by the average smoking history in SCLC patients, this paper estimated that on average one new mutation is acquired for every 15 cigarettes consumed. Over a lifetime of heavy smoking, these mutations lead to an aggressive and highly complex cancer. The most notable mutations involve inactivation of tumor suppressor genes including P53 (80–90 %), RB1 (60–90 %), and PTEN loss of heterozygosity (13 % of all tumors) [41]. Chromosomal deletions have been reported in the regions of 3p, 4p, 5q, 16q, 13q, and 17p though the significance of these is not well understood. Infrequently, tumor cells carry activating mutations of proto-oncogenes including *KRAS*, *EGFR*, *C-myc*, and *C-KIT* [41]. These mutations have led to experimentation with several targeted therapies such as sorafenib, gefitinib, imatinib, and others (Table 6). Unfortunately, the vast majority of these targeted agents have failed to increase survival. SCLC tumors also exhibit increased levels of vascular endothelial growth factor, which likely enables their invasive and angiogenic potential; however, treatment with bevacizumab has not been shown to increase survival. Despite the multiple failures of many targeted agents, early in vitro studies suggest that poly (ADP-ribose) polymerase (PARP) inhibitors may show some activity against SCLC [45, 46]. More clinical trials are needed to support these positive preliminary findings. Finally, a study recently published in 2015 revealed a statistically significant increase in progression-free survival from 2.1 months to 3.7 months when sunitinib (a multiple receptor tyrosine kinase inhibitor) was used as maintenance therapy for extensive stage SCLC [47]. SCLC research has clearly demonstrated that SCLC has distinct biology from NSCLC and targeted agents that have activity in NSCLC do not show similar results in SCLC.

Cigarette smoking is the strongest risk factor for the development of SCLC and continued smoking after diagnosis is also associated with a poorer prognosis. Research has shown that nicotine enhances tumor growth, angiogenesis, metastatic

Table 6 Targeted agents that have been studied in the treatment of SCLC

Agent	Mechanism of action	Result
Sorafenib	Inhibits intracellular Raf kinases, most notably BRAF, and cell surface kinase receptors most notably, vascular endothelial growth factor (VEGFR)	No benefit
Thalidomide	Immunomodulatory and antiangiogenic effects vary given targeted cancer	No benefit
Bevacizumab	Monoclonal antibody which binds VEGFR	No benefit
Marimastat	Matrix metalloproteinase inhibitor	No benefit
Vandetanib	Tyrosine kinase inhibitor (TKI) of epidermal growth factor reception (EGFR) and VEGF	No benefit
Gefitinib	TKI inhibits multiple cell surface receptors including EGFR	No benefit
Imatinib	Inhibits Bcr-Able tyrosine kinase produced by the Philadelphia chromosome	No benefit
Bortezomib	Proteasome inhibitor	No benefit
Oblimersen	Antisense oligodeoxyribonucleotide directed at blocking production of Bcl-2	No benefit
Temsirolimus	Mechanistic target of rapamycin (mTOR) inhibitor	No benefit
AT 101	Inhibitor of the anti-apoptotic Bcl proteins (Bcl-2, Bcl-XL, Bcl-W, and Mcl-1) and an inducer of the pro-apoptotic proteins noxa and puma	No benefit
Romidepsin	Histone deacetylase inhibitor	No benefit
Dasatinib	Second generation BCR-ABL TKI	No benefit
Cediranib	TKI targeting VEGFR-1, 2, and 3, PDGFR-alpha/beta, FGFR-1, and c-kit	No benefit
Sunitinib	TKI targeting PDGFR, VEGFR1-3, FLT3, CSF-R1, and RET	Benefit [47]

potential, and chemoresistance [48]. Tumor growth and increased metastatic potential are thought to occur by nicotine-induced increased migration of malignant cells through collagen matrices. Nicotine also protects cells from apoptosis, thereby conferring chemoresistance. Interestingly, these effects are reversible with the withdrawal of nicotine during in vitro studies [48]. These data highlight the importance of smoking cessation even after the diagnosis of SCLC is made.

8 Immune Therapy

As discussed in treatment of ED SCLC, chest radiotherapy to the original small cell tumor confers a survival benefit in the face of metastatic disease [38]. Similar benefit has been shown in other solid organ malignancies, most notably renal cell carcinoma where resection of the primary tumor leads to improvement in survival [49]. The mechanism behind this observation has not been well defined. One theory suggests that the primary tumor may act as an immunologic sink, thereby diverting circulating antibodies and lymphocytes away from the sites of distant metastasis [50]. Another theory suggests that the bulk of the primary tumor may suppress the body's natural antitumor response through potentiating tolerance to the mass [49].

These observations along with others have led to testing a variety of immune therapies in SCLC. In a 2013 phase II study, SCLC patients were randomized to receive chemotherapy alone versus chemotherapy combined with interferon alpha. A small but statistically significant survival benefit was found in patients with LD [51]. Furthermore, improvement in immune markers accompanied clinical improvement, whereas decline in the same markers was associated with disease progression. Tumor vaccines have also been studied in the treatment of SCLC. Up to 90 % of patients have accumulation of altered p53 in their cancer cells, and targeting p53 by vaccine has been evaluated by phase II clinical trials. The overall immune response rate was low with anti-p53 immunity developing in only 41.8 % of patients in one study and 51.1 % in the second [4]. However, within the subset of patients developing immunity, response rates were significantly higher. Also of note, the ganglioside antigen N-glycolyl-GM3 is highly expressed in SCLC cells. This has led to phase I, II, and III studies to evaluate benefit from the vaccination of its anti-idiotypic antibody, 1E10 [4]. Unfortunately, the phase III trial did not improve survival, possibly because only a third of patients developed a detectable antibody response after vaccination.

More recently, ipilimumab (an anti-CTLA4 monoclonal antibody) has been studied in combination with carboplatin and paclitaxel in first-line ED SCLC [52]. The study yielded some useful hints at possible successful strategies harnessing the immune system including the importance of timing of immune therapies. Phased ipilimumab (ipilimumab given after chemotherapy) improved immune-related progression-free survival while concurrent ipilimumab (ipilimumab given with chemotherapy) did not [52]. However, there was no improvement in overall survival while immune-related adverse events were significant [52]. Pembrolizumab has shown some single agent activity in PD L1 positive SCLC patients and the activity of nivolumab in combination with ipilimumab seems promising. Further studies are needed to demonstrate whether immune therapies will have a place in treatment of SCLC.

9 Conclusion

In 2012, Congress passed the Recalcitrant Cancer Act, thereby requiring the National Cancer Institute (NCI) to develop scientific frameworks that will promote scientific and therapeutic progress against recalcitrant or deadly cancers [53]. SCLC was identified as one of these cancers given a five-year survival rate of less than 7 % with the loss of approximately 30,000 lives per year. The scientific framework put forth included building better research tools for the study of SCLC by increasing the collection of tumor tissue specimens, developing new tumor models including genetically engineered mouse models, expanding genomic profiling in hopes of developing new targeted therapies, and examining the underlying mechanisms contributing to the high rate of initial chemotherapeutic response yet rapid resistance following primary treatment. Given the lack of progress in the treatment of SCLC over the last 30 years, the hope is that this new scientific framework will lead to better treatment options for this deadly cancer.

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