Small cell lung cancer: Are we making progress?

Internal Medicine Grand Rounds
3/27/09

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In the late 1970's, there was great optimism that small cell lung cancer (SCLC) could be cured [1]. At that time, SCLC had been demonstrated to be sensitive to several chemotherapy agents, and much of the next decade was spent attempting to mix and match these drugs in order to identify the optimal chemotherapy combination, schedule and duration. Unfortunately, these trials failed to identify a regimen superior to the standard of platinum and etoposide. As a result, in 2009, the management of advanced (extensive stage) SCLC differs little from that of 25 years ago. Not surprisingly, the outcome for this group of patients has changed little as well (vide infra).

The following review discusses the epidemiology, clinical presentation, staging, and current management of this disease. The seminal discoveries that have moved the treatment of this disease forward, such as the benefit of chest irradiation in limited stage disease and the utility of prophylactic cranial irradiation in limited and extensive stage disease, are also highlighted. Lastly, a discussion is undertaken of the ever increasing understanding of the biology of this disease and how this will hopefully lead to improved therapies for SCLC patients.

EPIDEMIOLOGY

In 2009, an estimated 25 -30,000 patients will be diagnosed with SCLC in the United States [2]. Although SCLC is the 5th most common cause of cancer-related death in the U.S., many oncologists that treat this disease feel they see fewer of these patients than they did 10 or 20 years ago. Govindan et al. reviewed the Surveillance, Epidemiologic, and End Results (SEER) Cancer Incidence Public Use Database from 1973 – 2002 [3]. They found that the proportion of SCLC among all lung cancer histologies decreased from a high of 17.62% in 1986 to 12.95% in 2002 (Figure 1). Since 1989, the absolute incidence of SCLC has decreased at an annual rate of 2.4%. This downward trend is highly statistically significant ($P < .0001$), providing convincing evidence that the observation is not merely random statistical fluctuation. These investigators also noted that the male predominance for this disease has decreased markedly during the same time period. In 1973, 72% of small cell cases occurred in men, but by 2002, the proportion had decreased to 50% (Figure 2).

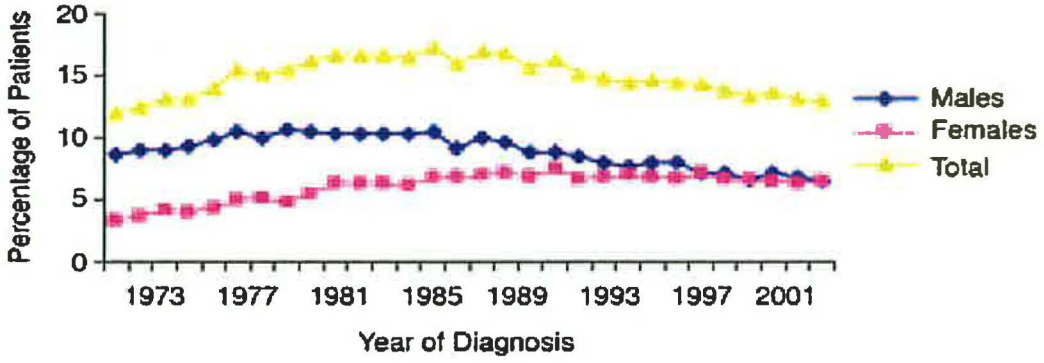

Figure 1. The diagnosis of SCLC as a percentage of all lung cancers over 30 years (from reference 3)

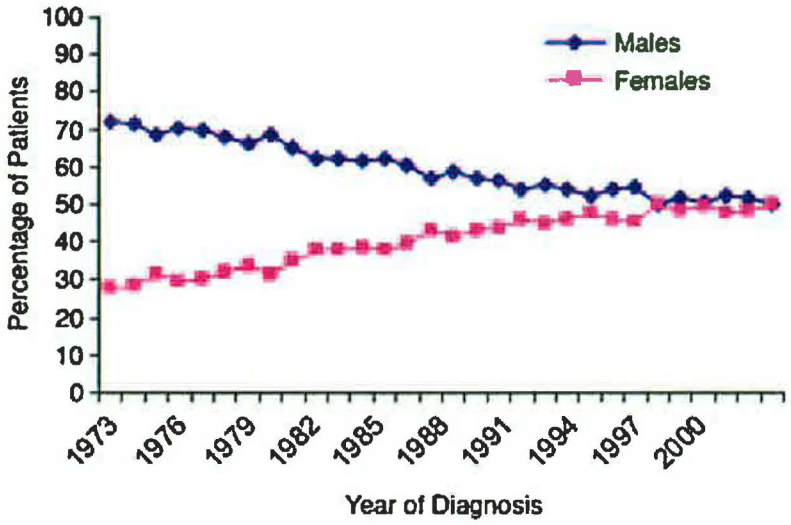

Figure 2. The diagnosis of SCLC by sex over 30 years (from reference 3)

The reasons behind these significant changes are not immediately apparent; though these authors and others have put forth several theories to explain the observations. The increased proportion of women with SCLC may be at least partially due to the overall increase in the number of women diagnosed with lung cancer during the period in question. It has long been known that SCLC is highly associated with the duration and intensity of cigarette smoking [4]. The peak prevalence of smoking in US women occurred later in the twentieth century than that of men. As a result, while the incidence of lung cancer cases in men began to decline around 1984, the number of cases in women only began to plateau around the mid-1990's [5]. Another hypothesis is that female smokers are more prone to develop SCLC than male smokers. However, at this point, that remains speculation.

One suggested explanation for the overall decrease in the incidence of SCLC is the increased use of filtered cigarettes. Studies have shown that those smoking filtered cigarettes inhale more deeply and deposit smoke particles in the smallest airways and alveoli [6, 7]. These are regions of the lung where adenocarcinomas typically arise whereas the central airways are typically the site of origin of SCLC. Another possible explanation is the change in pathologic classification of these tumors. In 1999, the World Health Organization and the International Association for the Study of Lung Cancer pathology committees published a new pathologic classification of lung cancer. In this classification, a variant of lung cancer called large cell neuroendocrine carcinoma is included under large cell carcinoma, a subtype of non-small cell carcinoma (NSCLC)[8]. Large cell neuroendocrine carcinoma shares many pathologic features with SCLC and distinguishing between the two, especially when making a diagnosis based on scant tissue from a fine needle aspirate, may be difficult. At this point, the exact impact of these possible explanations on the falling incidence of SCLC is not clear, though it is likely that they, along with other as of yet unrecognized factors, are contributing to this observed decrease.

CLINICAL PRESENTATION

As noted above, SCLC typically begins in the central airways, and metastasizes to regional lymph nodes and to distant organs early in the course of the disease. It is generally assumed that virtually all patients have microscopic metastatic disease at presentation, and > 60% present with radiographic evidence of metastases [3]. The typical sites of distant metastases include liver, bone, brain, and adrenal glands. Common initial symptoms include cough, dyspnea, chest discomfort, and hemoptysis [9]. In addition, SCLC is the most common cause of the superior vena cava syndrome. Given the typical systemic nature of the disease, as many as 50% of patients will also present with fatigue, malaise, anorexia and weight loss [10]. In addition, patients with spread of disease to the bone or brain may present with symptoms referral to those areas such as bone pain, seizures, and headaches. Of note, fewer than 10% of SCLC patients will be diagnosed prior to the development of symptoms [11, 12].

One unique feature of SCLC is its frequent association with paraneoplastic syndromes. As many as 50% of SCLC patients will develop a paraneoplastic syndrome during the course of their disease (if cancer cachexia is included) as opposed to < 10% with non-small cell lung cancer (NSCLC) [13]. Ectopic ACTH production (Cushing syndrome) frequently occurs in SCLC, with as many as half of patients demonstrated to have evidence of ectopic ACTH production on careful testing. However, fewer than 5% develop significant symptoms [11]. Another endocrinopathy frequently associated with SCLC is the syndrome of inappropriate diuretic hormone (SIADH) production. Anywhere from 15-40% of SCLC patients will develop the syndrome and life threatening hyponatremia may result [10, 11]. Clinically significant neurologic paraneoplastic syndromes occur in 1-3% of SCLC patients [10]. The prevailing pathogenetic theory behind their occurrence is the development of antibodies against "onconeural antigens" expressed by the cancer that cross-react with elements of the central and peripheral nervous system [14]. For example, the Lambert-Eaton myasthenic syndrome (LEMS), associated with the development of antibodies against the voltage dependent calcium channel affects 1-3% of SCLC patients [14, 15]. As many as 50% of LEMS patients will eventually be found to have SCLC, and therefore, the occurrence of LEMS in any smoker should prompt evaluation for underlying SCLC. In addition, a syndrome of sensory neuronopathy/multifocal encephalomyelitis occurs in SCLC and is associated with the development of anti – Hu antibodies. These antibodies are directed against RNA binding proteins in neuronal nuclei and can be identified in 15% of SCLC patients, though far fewer than this ever develop an associated neurologic syndrome. It is therefore unclear whether the antibodies are truly pathogenic. In this syndrome, patients develop asymmetric numbness and paresthesias involving the face, trunk, and proximal limbs that then typically progress distally. Motor power is generally intact, but patients eventually lose proprioception and vibratory sense and become unable to walk. The neurologic disease may remit or stabilize with effective treatment of the underlying SCLC. As with LEMS, this syndrome typically presents prior to the diagnosis of SCLC, and it is therefore critical that patients with symptoms suggestive of the syndrome be screened for the presence of anti-Hu antibodies (in the serum or CSF). In those in whom anti-Hu antibodies are found, a diagnostic evaluation for SCLC should be undertaken. Other less common neurologic syndromes seen in SCLC include cerebellar degeneration and limbic

encephalitis (both seen in association with anti – Hu antibodies), and cancer-associated retinopathy.

DIAGNOSIS

A pathologic diagnosis of SCLC is typically made using light microscopy. The cells are small (typically < 20 microns), have scant cytoplasm, absent or inconspicuous nuclei, and finely granular nuclei (so called "salt and pepper" chromatin). They frequently also display "nuclear molding," which is the tendency of the nuclei to become deformed by contact with adjacent cells or structures. The tumor is exceptionally proliferative so mitoses are frequently noted, and there are rarely fewer than 10 mitoses per ten high power fields. The cells are also fragile and therefore crush artifact is common [16].

Although the diagnosis can frequently be made based on histology alone, immunohistochemical studies can provide confirmation. Stains for keratin and epithelial membrane antigen are virtually always positive, and thyroid transcription factor – 1 is also detected in the vast majority of cases. In addition, at least one stain for neuroendocrine differentiation (e.g. neuron specific enolase, chromogranin – A, CD56, and synaptophysin) is detected in 75% of SCLC cases [16-18]. While the pathologic diagnosis of SCLC is generally not difficult, as noted above, distinguishing it from large cell neuroendocrine carcinoma (which is a variant of NSCLC) may be challenging especially when limited tissue is available from a fine needle aspiration [19].

STAGING

The most widely used staging system for SCLC is that introduced by the Veterans' Affairs Lung Study Group (VALSG) in the 1950's [20]. This system divides patients into two groups – limited stage (LS) and extensive stage (ES). LS patients have disease confined to one hemithorax that can be encompassed in a reasonable radiation port. The LS designation includes patients with mediastinal and ipsilateral supraclavicular lymph nodes. Any spread beyond this extent is ES.

Accurate staging in SCLC is critical given that both therapy and prognosis differ markedly for LS and ES patients (vide infra). Once a diagnosis of SCLC is established it is generally recommended that all patients have computed tomography of the chest and abdomen in order to image the lungs, liver and adrenal glands. Further staging should include MRI of the brain. Bone scan is generally reserved for those patients with LS disease based on computed tomography of the chest and abdomen and MRI of the brain in order to exclude occult bone metastases prior to initiation of curative intent treatment as well as those patients with bone pain at presentation. Small prospective series suggest that positron emission tomography (PET) scan may more accurately stage patients with SCLC, but further prospective studies are needed. In the U.S. reimbursement for PET scan for this diagnosis can be an issue.

NATURAL HISTORY AND PROGNOSIS

SCLC is a highly aggressive malignancy. The natural history of untreated SCLC was established in a VALSG study that compared single-agent cyclophosphamide treatment with placebo. The median survival in the untreated patients with LS and ES stage disease was 12 weeks and 6 weeks respectively [9]. Stage remains the only prognostic factor in SCLC that has been repeatedly validated in prospective studies. In more modern series, LS stage patients that receive appropriate therapy have a median survival of 18 – 20 months and 5 – year survival rates of 15 – 25% while treated ES patients have a median survival of approximately 10 months and fewer than 10% survive 2 years.

TREATMENT

Surgery

For many years, surgery has not been considered part of standard therapy for SCLC. This conclusion was largely based on a British Medical Research Council study published in 1973 that compared surgery and radiation as the primary management of SCLC. No difference in survival between the modalities was seen [21]. A subsequent trial of 340 patients with LS disease failed to demonstrate a benefit to surgery after induction chemotherapy [22]. A legitimate criticism of these studies is that many of the patients were inadequately staged when compared to current standards. Several more recent reports demonstrate excellent outcomes for very early stage SCLC patients that receive surgery as part of therapy. A retrospective review of 82 patients with stage I SCLC who all received surgery followed by standard chemotherapy reported a startling 86% 5-year survival rate [23]. In addition, another retrospective study reported a 47% 5-year survival rate for stage IA-IIB that received surgery followed by chemotherapy with or without thoracic radiation [24]. These reports have several limitations. Notably, they are retrospective and therefore patient selection may introduce significant bias. In addition, post-surgical therapy was not standardized. Nonetheless, these reports have renewed interest in the role of surgery in early stage SCLC, and prospective randomized trials are planned [10]. If there is benefit to surgery in SCLC, it is likely confined to those patients with what some have termed "very limited stage disease" (VLS) (i.e. small primary tumors with no lymphadenopathy). Given that < 5% of patients present with VLS, few will be candidates for this approach.

Limited stage disease

In 2009, the primary goals of treatment for LS SCLC are improved survival and cure. For many years, therapy of LS SCLC consisted of combination chemotherapy alone. However, intrathoracic failure rates of 75 – 90% were observed [25, 26]. Subsequent studies confirmed that a combination of chemotherapy and radiation significantly improved local control rates. However, not all of the trials demonstrated a significant survival advantage for the combination of radiation and chemotherapy. In 1992, two large meta-analyses were performed to answer this question. Pignon et al. analyzed 2410 patients on 13 randomized trials comparing chemotherapy alone with chemotherapy and radiation in LS disease. The relative risk of death in the chemotherapy

and radiation group was 0.86 (95% CI; .78 - .94; P = .0001) which corresponded to a 14% reduction in mortality and an absolute benefit in survival of 5.4% at 3 years (8.9% vs. 14.3%) [27]. The meta-analysis by Pignon also attempted to identify the ideal timing of radiation in relation to chemotherapy (sequential, concurrent or alternating), but found no statistically significant differences among these options. However, 3 out of 4 trials that demonstrated a significant survival advantage with combined chemotherapy and radiation utilized a concurrent or alternating scheme. In contrast, 7 of the 9 trials that did not identify an improvement in survival with the combination of chemotherapy and radiation employed a sequential treatment plan [28]. The second analysis by Warde and Payne reviewed 11 randomized trials and also reported a survival benefit favoring the addition of thoracic radiation to chemotherapy (OR – 1.53; 95% CI 1.30 – 1.76; $p < .001$). This resulted in an absolute improvement in survival of 5.4% at 2 years. Following the publication of these meta-analyses, standard therapy for LS disease was established to be a combination of chemotherapy and thoracic radiation. In the United States, the most frequently used regimen is etoposide and cisplatin (EP), due to the ease of administering these drugs with radiation. As noted above, even with optimal therapy for LS in 2009, only approximately 20% of patients can be expected to be cured and the median survival is approximately 20 months. Both local and distant control rates are disappointing, suggesting that our current chemotherapy and radiation need improvement [29]. Therefore, efforts are ongoing to identify more effective systemic treatment (vide infra). In addition, the optimal timing, fractionation, treatment volume, and dose of radiation are still debated and are the subject of ongoing study.

Given that patients with LS SCLC are treated with curative intent, continued health maintenance efforts in this group during and after treatment of their SCLC are critical. Undoubtedly the most important of these efforts is smoking cessation. Videtic and colleagues attempted to identify the impact of continued smoking on LS SCLC patients [30]. They performed a retrospective review of all 215 LS patients treated in a uniform way at their institution between 1989 and 1999. Patients were classified based on whether they had quit smoking prior to initiation of SCLC therapy. They found that those that continued to smoke during treatment had a statistically inferior survival to those that had stopped smoking They observed median survivals of 15.8 months vs. 13.6 months and 5 – year survival rates of 8.9% vs. 4% ($p = .0017$) favoring non-smokers (Figure 3). The authors initially believed that those that continued to smoke may tolerate therapy more poorly. However, they found no statistical difference between smokers and non-smokers in the number of patients that required a break in treatment due to toxicity (9.7% vs. 10.8%; $p = .49$). With respect to cause of death, 94.7% of deaths in smokers were cancer related as compared with 84.4% in non-smokers ($p = .034$). There are several hypotheses to explain theses results. Nicotine has been shown to be a growth factor for some SCLC cell lines [31]. Smokers often have lower oxygen saturation due to increased carboxyhemoglobin levels, and this may negatively impact the effects of radiation, which are at least partially oxygen dependent [32-34]. Also, it is well-known that SCLC patients who survive are at risk for a second smoking related malignancy (at rates as high as 1-2% per year). Patients that continue to smoke likely further increase that risk.

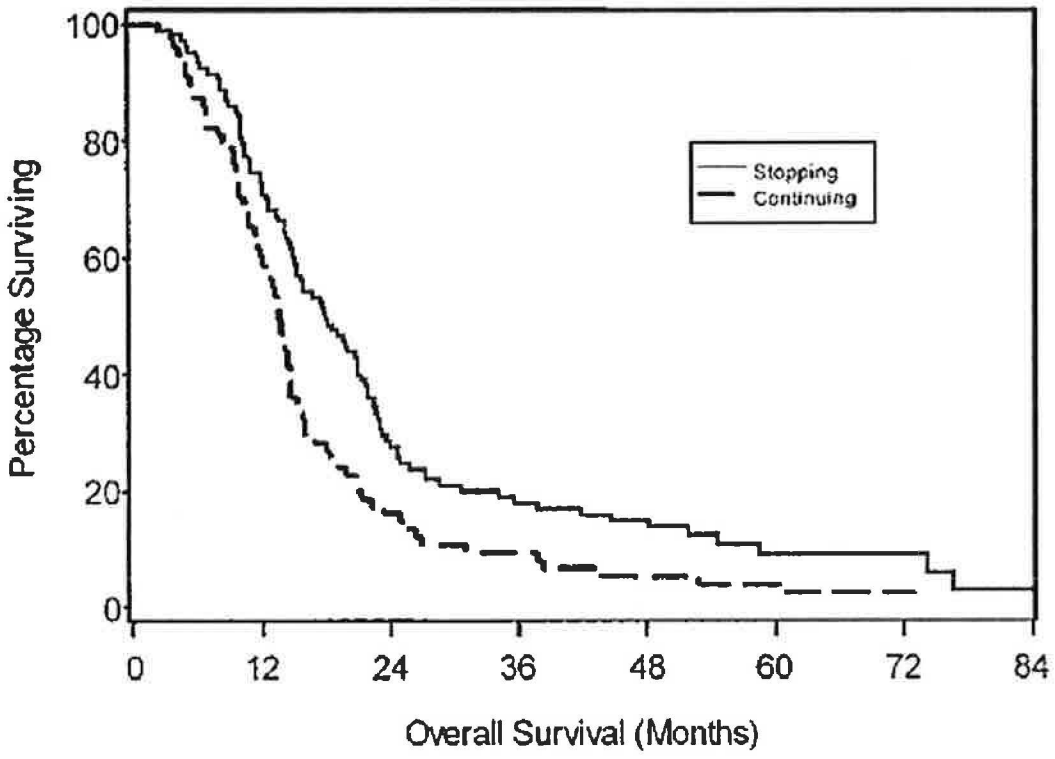

Figure 3. Actuarial survival according to smoking status during chemoradiotherapy (P = .0017)(From reference 29).

This study clearly has limitations. It is retrospective, they did not attempt to quantify amount of smoking prior to treatment, and they had no way to verify ongoing smoking status after the initiation of therapy. Nonetheless, it provides a compelling rationale for aggressive attempts at smoking cessation in this population.

Extensive stage disease

Approximately 70% of newly diagnosed SCLC patients present with ES disease. For more than 20 years, combination chemotherapy has been the standard treatment for this population and modestly improves survival over single-agent treatment and best supportive care [35]. Initial response rates to first-line therapy are high (50-70%), but unfortunately typically are short-lived and virtually all patients eventually relapse. The problem appears to be rapid development of chemoresistance (or the emergence of chemoresistant clones), and the subsequent inability of second-line treatment to greatly impact survival. With the realization almost 3 decades ago that SCLC was (at least initially) a chemosensitive disease, a number of approaches were evaluated over the ensuing thirty years to attempt to augment this response. These include protracted duration of therapy [36], maintenance therapy [36], alternating non-cross resistant chemotherapy [37], immediate second-line therapy [38], and increased dose-intensity

either with or without stem cell support [36]. All failed to demonstrate convincing improvements in survival. More recently newer chemotherapy agents (such as irinotecan [39, 40], topotecan [41, 42], and pemetrexed [43]) were evaluated in combination with platinum against the existing standard of PE. Again, no significant improvements in survival were observed.

The options are even bleaker for those with recurrent disease after initial treatment with PE. Those with progressive disease after first-line treatment with PE are classified as "chemosensitive" if it has been more than 90 days since they completed first-line therapy. Those that have progressed within 90 days from the completion of first-line therapy are considered "chemoresistant." Patients with chemosensitive relapse that progress more than 6 months from completion of initial therapy can be retreated with platinum and etoposide with response rates as high as 50 -67% [44-46]. For those that progress 3-6 months after initial therapy, the only FDA approved agent is topotecan. In this population treated with topotecan, response rates of 25% and median and 1 –year survivals of 6-7 months and 14% respectively are observed [47, 48]. For the group with chemoresistant relapse, outcomes with second-line therapy are poor (regardless of the agent chosen) with objective tumor response rates under 10% and fewer than 5% of patients surviving 1 year. A number of small phase II trials have evaluated numerous other agents (including docetaxel, paclitaxel, gemcitabine, ifosfamide) in the second-line setting, but none have shown enough activity to generate excitement about a randomized phase III comparison with the current standard of topotecan.

Amrubicin

Despite the grim discussion above, there is one new chemotherapy agent under evaluation in SCLC that is generating interest. Amrubicin is a fully synthetic 9-aminoanthracycline that is converted in the body to amrubicinol, which has a higher anti-tumor activity than the parent compound. Although classified as an anthracycline, it primarily exerts its anti-tumor effects through inhibition of the DNA topoisomerase-II enzyme rather than through DNA intercalation [49]. An initial Japanese phase II study of amrubicin in untreated ES SCLC patients reported a tumor response rate of 75.8% and an encouraging median survival of 11.8 months. A subsequent randomized phase II trial of amrubicin versus topotecan in previously treated patients with ES SCLC has recently been published. The 60 patient trial included those with both chemosensitive and chemoresistant relapse, and the treatment groups were well-matched regarding this and other prognostic variables. The overall response rate with amrubicin was 38% versus 13% for topotecan. Median progression-free survival also favored amrubicin (3.5 months versus 2.2 months), though this difference was not statistically significant. In addition, in the chemoresistant group (which is typically refractory to additional chemotherapy), the overall response rate was 17% [49]. A preliminary report of a second trial of amrubicin in 39 assessable patients with chemoresistant disease reported a response rate of 18% and a progression-free survival of 3 months [50]. Toxicity with amrubicin appears manageable with the primary side effects being neutropenia and asthenia. Importantly, given that this is an anthracycline, cardiac toxicity has not been reported. These admittedly preliminary results are at least modestly encouraging, and phase III trials of

amrubicin are underway in both the first and second-line setting in SCLC to better define its activity and role in this disease.

Prophylactic cranial irradiation (PCI)

The brain is a common site of metastatic disease in SCLC. Approximately 10-18% of patients have brain involvement on initial presentation [51, 52], and as many as 60 – 80% of those patients that survive 2 years will develop brain metastases during the course of their illness [51, 53]. This is an especially important issue in the LS population where a significant proportion of patients live greater than 2 years. The general assumption is that micrometastatic disease to the brain is relatively protected by the blood brain barrier, thereby making it unlikely to be eradicated with systemic chemotherapy. For these reasons, there was interest in evaluating PCI in LS patients that had a complete response to initial treatment with chemotherapy and chest irradiation. A number of randomized trials were done that clearly demonstrated significant decreases in the cumulative rate of brain metastases, but not all of the trials found an improvement in overall survival with PCI. In 1999, Auperin and colleagues published a meta-analysis of individual patient data on 987 patients that participated in 7 randomized trials of PCI. For the primary endpoint of overall survival, the relative risk in the PCI group was .84 (95% CI .73 - .97; p = .01). This corresponded to a 5.4% absolute increase in survival at 3 years (15.3% 3 –year survival in the control group vs. 20.7% in the PCI group). PCI also reduced the cumulative risk of brain metastases at 3 years from 58.6% to 33.3% [54].

Until recently, the conventional wisdom was that ES SCLC patients were not likely to benefit from PCI. The thought was that given the limited ability to control ES SCLC, patients would succumb to their systemic disease before occult micrometastases in the brain caused significant clinical impact. A recent European study has challenged that assumption. Slotman et al. published a randomized phase III trial of PCI versus observation in 286 ES patients that had responded to first-line chemotherapy. Of note, a complete response to treatment was not required; partial response was acceptable. For the primary endpoint of *symptomatic* brain metastases, the cumulative rate was reduced from 41.3% in the control arm to 16.8% in the PCI arm ($p < .001$). Quite unexpectedly, the secondary endpoint of overall survival was also significantly improved in the group that received PCI. Median survival in the control arm was 5.4 months versus 6.7 months in the PCI arm ($p = .003$). This translated into an improvement in 1 – year survival from 13.3% to 27.1% (Figure 4). On quality of life analyses, overall functioning scores were similar between the two groups. However, the PCI arm had more fatigue and hair loss [55].

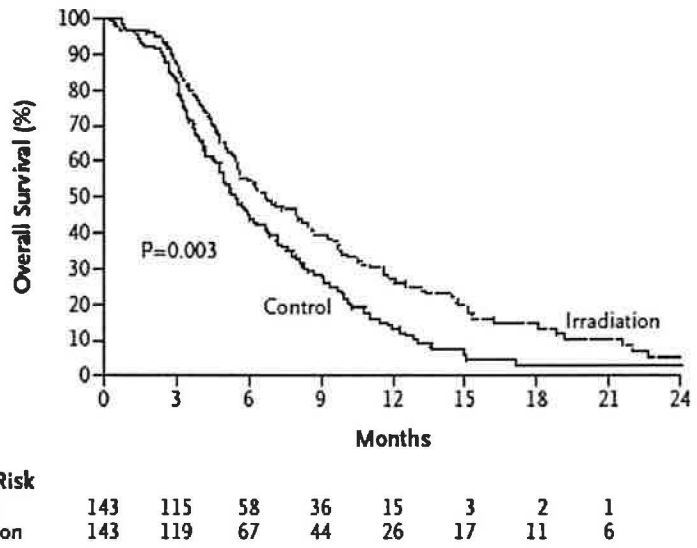

Figure 4. Overall survival for ES patients receiving PCI (P = 0.003; hazard ratio, 0.68; 95% CI, 0.52 to 0.88)(from reference 54).

This trial is one of very few in the past 2 decades to show a significant improvement in survival for a treatment intervention in ES SCLC, and based on these results, it is now recommended that PCI be offered to ES patients with a good response to initial chemotherapy. In addition, as has been standard for several years, LS patients with a complete or "near-complete" response to chemotherapy and chest irradiation should be referred for PCI. The major debate regarding the utility of PCI in SCLC centers on reports of long-term cognitive and neuropsychiatric effects. However, despite these concerns, there are no definitive studies that have clearly defined these risks. Ongoing studies are evaluating different doses and schedules of radiation for PCI in the hopes of improving efficacy as well as gaining a better understanding of the long-term sequelae.

FUTURE DIRECTIONS

The logical conclusion to draw from the above discussion is that significant improvements in survival in SCLC are unlikely to come from enhancements of traditional chemotherapy (with the possible exception of amrubicin) and that novel approaches are clearly needed. In the past decade, numerous biologic targets for anti-cancer therapy have been identified and are currently being exploited therapeutically in a variety of malignancies. Potential targets include growth factors and growth factor receptors, signal transduction pathways, extracellular matrix/angiogenic pathways, cell survival pathways, tumor associated antigens/markers, and the proteosome. Unfortunately, initial attempts to direct therapy against seemingly important molecular pathways in SCLC (VEGF, matrix metalloproteinase, c-kit, bcl-2) were unsuccessful. Despite these failures, several therapeutic targets currently under study appear to hold promise.

CD56 is a member of the neural cell adhesion molecule (NCAM) family and is expressed by neuroendocrine cancers such as SCLC [56], [57], [58]. BB-10901 is a humanized monoclonal antibody directed against CD56 that is linked to a cytotoxic compound DM-1. When BB-10901 binds to the target antigen CD56, it is internalized and releases DM-1, a potent anti-microtubule agent. In a phase I trial of BB-10901, the drug was well-tolerated at doses of 60 mg/m^2 given weekly for 4 weeks out of 6 [59]. A phase II study in patients with SCLC as well as other CD56 expressing neuroendocrine carcinomas is underway and 1 partial response and 2 minor responses were seen in the first 10 patients enrolled, prompting expansion to a larger cohort [60], [61]. Enrollment to this cohort continues.

Src kinase

Src kinase represents a family of non-receptor tyrosine kinases that modulate signals from a myriad of proteins, including cell-surface molecules, growth factors, integrins and G protein coupled receptors [57]. The majority of the Src family are located on hematopoietic cells. However, several members of the family, including c-Src, are found on epithelial tissues [62]. c-Src expression has been detected in both SCLC and NSCLC cell lines and tumors, but not in normal lung tissue [63]. Dasatinib is a tyrosine kinase inhibitor that blocks several kinases including c-Src. In preclinical models, dasatinib prevented migration and invasion of NSCLC cells as well as inducing G_1-S arrest in these cells [64]. Targeting c-Src in SCLC preclinical models also results in decreased proliferation [65]. Currently the Cancer and Leukemia Group B (CALGB) is conducting a phase II trial of dasatinib in SCLC patients with chemosensitive relapse. In addition, AZD0530, a dual specific c-Src and c-Abl inhibitor is being given following 4 cycles of standard chemotherapy for ES SCLC in a phase II trial underway through the North Central Cancer Treatment Group (NCCTG)[57].

Hedgehog pathway

The hedgehog pathway (Hh) is an embryonic signaling cascade that regulates stem-cell differentiation pathways. The Hh pathway is therefore critically important in organ development, including mammalian lung [66, 67]. Smoothened (Smo) is a transmembrane protein that is required for activating the Hh pathway. Patched, an inhibitory protein, constitutively downregulates Hh pathway activity by inhibiting Smo. There are 3 patched ligands (Sonic Hh, Indian Hh, Desert Hh) that can all bind to and inactivate Patched, thereby depressing Smo and activating the Hh pathway [57].

In the lung, the Hh pathway has been shown to be activated in airway epithelium in response to injury, and this is thought to lead to malignant change by repeatedly expanding the stem cell pool [68]. SCLC frequently displays constitutive activation of the Hh pathway and expresses high levels of the Sonic Hh ligand. The cells within SCLC tumors in vivo that are involved in Hh signaling are compartmentalized and appear to recapitulate the process seen in airway development and injury repair. It has therefore been speculated that these cells are maintained as tumor stem cells through ongoing Hh signaling [69, 70]. The plant-derived alkaloid cyclopamine is a potent Smo antagonist

that therefore downregulates the Hh pathway [71]. Treatment of SCLC cell lines and xenografts with cyclopamine produces growth arrest in both models [72]. Based on this preclinical data, there is great interest in the development and testing of Hh pathway inhibitors in SCLC. The first to reach clinical testing is GDC-0449, an orally bioavailable synthetic inhibitor of the Hh pathway. In early phase I testing, GDC-0449 was well-tolerated and the maximum tolerated dose was established [73]. Phase II studies in several tumor types, including SCLC are planned.

Table 1. Molecularly targeted agents previously studied or currently under evaluation in SCLC

Matrix metalloproteinase inhibitors	**Anti-angiogenesis agents**
marimostat	bevacizumab
tanomostat	cedarinib
C-kit inhibitors	vandetanib
imatinib	sorafenib
Vaccines	thalidomide
mitumomab	CC-4047
adenovirus p53 vaccine	**EGFR inhibitors**
Bcl-2 inhibitors	gefitinib
oblimersen	**Farnesyltransferase inhibitors**
AT-101	tipifarnib
obatoclax	**Multidrug resistance inhibitor**
MTOR inhibitors	biricodar
temsirolimus	**Anti-CD56 monoclonal antibody**
everolimus	BB-10901
Src inhibitors	**Hedgehog pathway inhibitors**
dasatinib	GDC-0449
AZD0530	

Bcl-2

Bcl-2 is central mediator of apoptosis that has been implicated in cell survival, tumorigenesis, and resistance to chemotherapy in many different malignancies [74, 75]. It is also expressed in > 80% of human SCLC [76, 77]. Preclinical studies demonstrated that inhibition of bcl-2 increased the sensitivity of SCLC cell lines and xenografts to chemotherapy [78]. In addition, small molecule inhibitors of bcl-2 had significant anti-tumor effects in SCLC preclinical models [79-81]. Initial attempts to target bcl-2 in human SCLC studies using antisense to bcl-2 mRNA failed to demonstrate improvement in tumor response or survival when that agent (oblimersen) was given with chemotherapy. In retrospect, however, there are questions as to whether the antisense compound was truly hitting the target and downregulating bcl-2. Currently, there are at least three small molecule inhibitors of bcl-2 and bcl-2 related proteins are in

development. All three (obatoclax, AT-101, ABT-263) are currently in phase I and II trials in advanced SCLC.

ARE WE MAKING PROGRESS?

In their 30-year review of the SEER database discussed earlier, Govindan and colleagues also examined changes in overall survival of SCLC patients during the same time period (1973 – 2002). They noted modest, but statistically significant, improvements in 2 – year and 5 - year survival for limited stage and extensive stage patients respectively. The 5-year survival rate for limited stage patients increased from 4.9% in 1973 to 10% in 2002. Similarly, the 2 – year survival rate for extensive stage patients improved from 1.32% to 3.57% over the same time period. Gaspar et al. reviewed the National Cancer Data Base from 1985 to 2000 and found similar results. They reported that the 5 – year survival rate for limited stage SCLC improved from 10.5% to 13.3% for those patients that received chemotherapy and radiation [82]. Given that the information from both of these reviews comes from large population databases, it is impossible to know how much of this modest increase in survival is attributable to improvements in therapy versus more accurate staging of patients and better supportive care. Regardless, it is fair to say that whatever advances in therapy have occurred in the past two or three decades, the overall results impact on survival has been minimal.

CONCLUSIONS

Despite a gradual decline in incidence over the past 30 years, SCLC remains a significant cause of cancer mortality in United States and across the world. With appropriate treatment, approximately 20% of patients that present with limited stage SCLC can be cured of their disease. Unfortunately, for those 80% with limited stage that are not cured and for all patients with extensive stage SCLC, outcomes remain poor. The only significant advance in extensive stage SCLC in the past two decades is the recent discovery that prophylactic cranial irradiation improves survival in those patients whose disease has responded to initial chemotherapy. Numerous attempts to enhance the anti-tumor effects of traditional chemotherapy for SCLC have not been successful. As the understanding of the biology of SCLC increases, numerous rational molecular targets for therapy are identified. Although initial attempts at "targeted therapy" in SCLC have not yet born fruit, several newly identified targets hold promise and give hope that significant improvements in therapy for this challenging disease are not far away.

ACKNOWLEDGEMENTS

Special thanks to Janice Box for her assistance in the preparation of this manuscript.

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