Small Cell Lung Cancer: An Update on Therapeutic Aspects

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ABSTRACT

Small cell lung cancer comprises approximately 20% of all lung cancers and continues to be a difficult management issue. More than two-thirds of cases present with extensive disease, which has spread beyond the hemithorax and regional ipsilateral nodes. While response rates to chemotherapy are relatively high, durable responses are rare, and long-term survival rates are anecdotal. Although many attempts have been made to develop new therapies, a combination of etoposide with either cisplatin or carboplatin remains the most widely used first-line therapy for extensive disease. For those with limited disease, chemotherapy with concomitant radiotherapy (given with the first or second cycles of chemotherapy) is considered the standard of care. Over the last decade, several new drugs and targeted agents have been identified with the aim to improve outcome of this malignancy. In this review we highlight recent developments in the management of this tumour. [Indian J Chest Dis Allied Sci 2006; 48: 49-57]

Key words: SCLC, Treatment, Chemotherapy, Radiotherapy.

INTRODUCTION

Lung cancer is the commonest cancer worldwide, accounting for 18% of all cancers in men1. It is also the most common cause of mortality, with more than 800000 deaths per year around the world2. Small cell lung cancer (SCLC) accounts for about 20% of newly diagnosed lung cancer cases and it has the most aggressive clinical course3. Untreated, the median survival after diagnosis is only two to four months. Despite being sensitive to chemotherapy and radiotherapy (RT), most patients do not get cured since they present with extensive disease. As many as 60-70% of patients with extensive stage-(ES-) SCLC will have a major response to systemic chemotherapy, and 15-20% of patients will achieve a clinical complete response; nevertheless, the median survival is only 8-11 months with 2-year survival rates less than 5 to 7 percent4. The major problem is that SCLC develops rapid resistance to therapy, and response to second-line therapy is limited.

Tobacco exposure is the primary risk factor, association being the strongest with SCLC than with any other type of lung cancer. It has been estimated that more than 98% of patients have a history of cigarette smoking. Smoking cessation, however, has been associated with a reduction in the risk. A meta-analysis by Khuder5 including 28 studies published between 1970 to 1999 showed that the risk reduction was the highest in SCLC with the benefit being greater for males than for females. The reduction in lung cancer risk continued for more than 10 years but did not approach that of the non-smokers, reinforcing the importance of continued abstinence from smoking. Discontinuation of smoking even at diagnosis may be beneficial, as patients who continue to smoke during treatment appear to have a decreased survival6.

The staging of SCLC is different from other solid cancers. A two-tiered staging system divides the patients as having either limited stage (LS) or extensive stage (ES) disease. Patients with LS disease are often treated for potential cure with combined chemotherapy and radiotherapy (CT-RT), whereas those with ES disease receive chemotherapy with or without RT in a palliative manner. According to the Veteran Affairs Lung Cancer Study Group (VALG), LS is defined as disease within one hemithorax, including ipsilateral supraclavicular nodes, which can be safely encompassed in a single RT portal7. This definition excludes pleural effusion and the involvement of any contralateral nodes. All other patients are classified as having ES disease. The International Association for the Study of Lung Cancer modified this definition, according to which, LS disease is not restricted to one hemithorax with regional ipsilateral suprachlavicular nodes, which can be safely encompassed in a single RT portal8. This definition excludes pleural effusion and the involvement of any contralateral nodes. All other patients are classified as having ES disease. The International Association for the Study of Lung Cancer modified this definition, according to which, LS disease is not restricted to one hemithorax with regional ipsilateral nodal metastasis, but also includes the involvement of contralateral mediastinal nodes, as well as any ipsilateral pleural effusion9. However, the
traditional VALG criteria are more widely used in practice and in clinical trials.

The diagnostic evaluation includes a biopsy or cytology of the primary or the metastatic site in a patient with suspected SCLC. The staging work up includes history, physical examination, pathology review, chest radiography, complete blood counts, liver and renal function tests, serum electrolytes, calcium / phosphates, lactate dehydrogenase (LDH), and, chest and upper abdominal computed tomography (CT) scans. Additional tests to define limited disease in patients with symptoms or abnormal physical examination suggesting metastases are: bone scintigraphy, and CT scan or magnetic resonance imaging (MRI) of the brain. Bone-marrow aspiration or biopsy is indicated if LDH is elevated, and pleural aspiration for malignant cytology is recommended if pleural effusion is present; positive cytology predicts a poorer outcome. When any of these tests is positive, extensive disease is confirmed and there is no need for further investigations. Consistently, the strongest clinical prognostic factors in patients with SCLC include extent of the disease, performance status, and weight loss. For reasons that are not clear, the prognosis of women is slightly better than men. Laboratory factors, which have implications for prognosis, include LDH, neuron-specific enolase, hemoglobin, total white cell count, serum sodium and alkaline phosphatase.

**TREATMENT**

**Extensive Stage Disease**

In 1969, an important randomised trial by the VALG documented that three courses of cyclophosphamide more than doubled median survival compared with the best supportive care (BSC) in ES-SCLC. Several trials thereafter and a recent review from Cochrane database have established the value of chemotherapy in the management of ES-SCLC.

**Cisplatin-based chemotherapy: cisplatin/ Etoposide or cisplatin/irinotecan**

In 1970s, the most commonly used regimen for SCLC incorporated cyclophosphamide, doxorubicin and vincristine (CAV). Etoposide, which has significant activity in SCLC, was added subsequently to CAV (CAVE). This resulted in some improvement (few weeks) in response duration albeit at the cost of greater toxicity. With the arrival of cisplatin, etoposide/ cisplatin (EP) regimen was introduced in late 1980s. In uncontrolled trials it was demonstrated that SCLC patients treated with EP denovo had 86% response rates and more importantly about 55% of those patients also responded, who had been previously treated with CAV.

Thereafter, in early 1990s based on randomised controlled studies, EP was established as the superior frontline therapy for ES-SCLC. In one of these studies, Fukuoka et al compared EP with CAV. Patients treated with EP had a higher response rate than those treated with CAV (78% vs 55%). Following progression patients were allowed to cross over to the other arm; those initially treated with CAV responded to second-line therapy with EP 23% of the time, but those initially treated with EP responded to second-line CAV therapy only 8% of the time. Three important meta-analyses have subsequently confirmed the value of cisplatin and EP in ES-SCLC.

Based on these analyses, which provide ample, clear, and definitive evidence, cisplatin-based therapy, in particular EP, has become the standard frontline therapy for ES-SCLC. Most regimens include 80-100 mg/M² cisplatin on days 1 or 2, and 100-mg/M² etoposide on days 1-3 (both given intravenously), every 3-4 weeks. In general, major toxicities include nausea, vomiting, bone marrow suppression and neuropathies.

Until recently, no novel regimens had shown superiority to EP. However, the Japanese Cooperative Oncology Group (JCOG) published a randomised trial in 2002 that may ultimately change the management of patients with ES-SCLC. This study demonstrated therapeutic superiority for irinotecan (a novel topoisomerase II inhibitor) in combination with cisplatin (IP) vs standard EP. Response rates (84% vs 67%), progression free survival (6.9 vs 4.8 months) median survival (12.8 vs 9.4 months), and 1-year (58% vs 38%) and 2-year (20% vs 5%) survival rates were all significantly higher in the IP arm. As expected, IP resulted in significantly more grade 3 diarrhea and nausea and vomiting, while EP produced significantly more neutropenia and thrombocytopenia. Some of the important regimens used for SCLC are shown in the table.

Based on the above study although IP has become the new standard of comparison in Japan in ES-SCLC, a certain degree of skepticism still persists in the rest of the world and confirmatory phase III studies are ongoing. One trial, conducted through the Southwest Oncology Group (SWOG), has replicated the doses and schedules employed in the Japanese trial and has begun enrollment. A North American-based study completed accrual in June of 2003 with more than 330 patients enrolled; patients in the standard arm received EP while those on the experimental arm IP. This study used a lower dose of irinotecan (65 mg/m²) given intravenously on day 1 and 8 as compared to JCOG study and excluded patients with performance status of 2 or more. An interim safety analysis concluded that this regimen was well tolerated and delivered a higher relative dose-intensity (actual/planned dose) than the JCOG regimen (89% vs 80%).
Carboplatin as a substitute for cisplatin

Carboplatin as compared to cisplatin is less emetogenic, less neurotoxic and less ototoxic. For most malignancies, with few exceptions however (e.g., germ cell tumours), the two agents are equivalent in terms of efficacy. The Hellenic Oncology Group conducted a phase III trial in which patients were randomised to either EP or etoposide and carboplatin (EC)\(^22\). There was no statistically significant difference in median survival (EC vs EP, 11.8 vs 12.5 months), and overall response rate (58% vs 57%), in patients with SCLC. Brahmer and Ettinger\(^{23}\) reviewed all recent phase II and phase III data regarding the use of EC in SCLC, and concluded that EC is as effective and has less overall toxicity. Thus, both agents can be used interchangeably in ES-SCLC, and tailored toward individual toxicity.

Role of maintenance therapy and total treatment duration

In 1970s, patients with SCLC were often treated with uninterrupted therapy until either the disease progressed or death occurred. Considering that SCLC was a tumour with rapid proliferation index and a high rate of response to chemotherapy, the concept of ‘maintenance therapy’ was applied with the intention of at least prolonging the duration of remission, if not actually improving the overall cure rates. Subsequently, there have been several randomised trials that have tried to evaluate this practice\(^24-27\). Most of the studies have evaluated patients with both LS and ES disease and have compared 4 to 6 courses of chemotherapy with or without the addition of maintenance therapy for patients responding to induction therapy. Two studies have shown a survival advantage for the maintenance chemotherapy arm\(^{26-27}\). However, most studies have been negative on the benefits of maintenance therapy, and one major study even demonstrated that maintenance therapy was detrimental\(^{28}\). Given the variable results, Sculier\(^{29}\) et al recently reviewed 13 major randomised trials evaluating the role of maintenance chemotherapy. Only one trial showed a statistically significant advantage for maintenance therapy overall. Given the lack of clear and convincing evidence of benefit, maintenance therapy has no role outside the clinical trial in the management of ES-SCLC.

The optimal duration of chemotherapy is not clearly defined, but there is no obvious improvement in survival when the duration of chemotherapy exceeds six months. Most oncologists treat ES-SCLC patients with four cycles of induction with EP or EC, and consider two additional cycles of same drugs for those who respond.

Alternating regimens

Based on the Goldie and Coldman\(^{30}\) mathematical model, which predicts that the best possibility of cure would be achieved by early administration and rapid alternation of active multiple chemotherapeutic drugs; such strategy has been evaluated in at least three randomised studies in SCLC. The first trial by Evans\(^{31}\) et al demonstrated the superiority of this method when they randomised 289 ES-SCLC patients to either six

Table. Commonly used chemotherapeutic regimens and their results in SCLC\(^1\)

<table>
<thead>
<tr>
<th>Regimen* (Author)</th>
<th>Drugs</th>
<th>Schedule</th>
<th>Major Toxicities</th>
<th>Response Rates (%)(CR+PR)</th>
<th>Median Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jackson (Jr) et al(^14) CAVE</td>
<td>Cyclophosphamide 800 mg/m(^2) IV d 1, Doxorubicin 50 mg/m(^2) IV d 1, Vincristine 1.4 mg/m(^2) IV d 1, Etoposide 60 mg/m(^2) IV d 1-5</td>
<td>Nausea/vomiting, hemotologic</td>
<td>70</td>
<td>9.6 months</td>
<td></td>
</tr>
<tr>
<td>Fukuoka et al(^16) CAV</td>
<td>Cyclophosphamide 800 mg/m(^2) IV d 1, Doxorubicin 50 mg/m(^2) IV d 1, Vincristine 1.4 mg/m(^2) IV d 1</td>
<td>Nausea/vomiting, heamatologic</td>
<td>55</td>
<td>9.9 months</td>
<td></td>
</tr>
<tr>
<td>Noda et al(^20) EP</td>
<td>Etoposide 100 mg/m(^2) IV d 1-3, Cisplatin 80 mg/m(^2) IV d 1</td>
<td>Nausea/vomiting hemotologic</td>
<td>67</td>
<td>9.4 months</td>
<td></td>
</tr>
<tr>
<td>Noda et al(^20) IP</td>
<td>Irinotecan 60 mg/m(^2) IV d 1, 8, 15, Cisplatin 60 mg/m(^2) IV d 1</td>
<td>Diarrhea, nausea/vomiting, hematologic</td>
<td>84</td>
<td>12.8 months</td>
<td></td>
</tr>
<tr>
<td>Skalros et al(^22) EC</td>
<td>Etoposide 100 mg/m(^2) IV d 1-3, Carboplatin 300 mg/m(^2) IV d 1</td>
<td>Hematologic, nausea/vomiting</td>
<td>58</td>
<td>11.8 months</td>
<td></td>
</tr>
<tr>
<td>von Pawel et al(^23) Topotecan#</td>
<td>Topotecan 1.5 mg/m(^2) IV d 1-5</td>
<td>Hematologic</td>
<td>24</td>
<td>25 weeks</td>
<td></td>
</tr>
</tbody>
</table>

\(^1\): Most trials have included patients with extensive and limited stage both.
\(^2\): Regimens are repeated q 21-q 28 days depending upon the toxicity and count recovery.
\(^3\): Given as second-line therapy in chemosensitive recurrent SCLC. Therefore, response-rates and survival are inferior compared to other combinations shown in the table, which have been used as first-line therapy.
cycles CAV or CAV alternating with EP (3 cycles each). Response rates (80% vs 63%), and survival times (9.6 vs 8 months) were superior with alternating therapy. Subsequently, two confirmatory studies have however, not found beneficial results for alternating therapy. Given the lack of benefit, alternating non-cross-resistant regimens cannot be recommended for ES-SCLC.

**Dose-intense/dose-dense/high-dose therapy**

Numerous methods have been devised to deliver higher doses of chemotherapy for SCLC in order to overcome resistance. These include: dose-intensification to maximal toxicity, dose intensification with autologous stem cell rescue, and time compression of chemotherapy. Growth factors are often used along with these approaches.

One of the approaches is rapid sequencing of several active agents over a short time period. A regimen CODE, consisting of weekly treatments of cisplatin, vincristine, doxorubicin and etoposide (alternating myelosuppressive with non myelosuppressive agents) was designed to double the dose intensity of these agents in comparison with the more traditional regimen of CAV alternating with EP. While the results utilising this strategy were promising in the pilot study, subsequent phase III trials failed to confirm the survival advantage with CODE regimen.

Another approach is to concentrate chemotherapy to an overall shorter time (dose-dense approach) by decreasing the time interval between cycles. In a randomised trial, 233 ES-SCLC patients were allocated to one of the following: (i) a regimen of epirubicin, vindesine, and ifosfamide for six cycles given every three weeks, (ii) the same regimen given every two weeks with GM-CSF and (iii) the same regimen as given in (ii), but with oral cotrimoxazole. Response rates were higher in arm (ii) compared to arm (i) (76% vs 99%) but there was no difference in median (264 vs 286 days) or 2-year (6% vs 5%) survival rates. Toxicity was grater with more frequent thrombocytopenia (without bleeding) in arms (ii) and (iii), and there were more infectious complications in arm (ii) but not in arm (iii).

Further dose escalations of chemotherapy may be performed with high-dose chemotherapy with autologous stem cell transplantation (ASCT). Most current trials are in phase II setting, that demonstrate modest results compared with historical data; however, there has been no randomised study for such an approach. Humblet et al. evaluated 101 patients who received standard-dose therapy for several cycles. Those who responded, received a late intensification with ASCT. Most of the patients in this study had LS disease; for those with ES-SCLC, overall complete response rates were 15% to 20%, and survival did not appear to be improved as compared to historical controls. A review of all data from 1989-1997 from the Autologous Blood and Marrow Transplant Registry did not demonstrate a benefit from the use of ASCT.

Thus, at present there is no convincing data to favour higher-dose chemotherapy over standard chemotherapy in ES-SCLC.

**Double vs triple therapy**

Many ongoing studies are investigating novel cytotoxic agents, such as irinotecan, gemcitabine, docetaxel, ifosfamide, paclitaxel-topotecan and vinorelbine. As single agents, the response rate vary from 24 percent to 57 percent. Most of these agents have been evaluated in combination with standard drugs in phase II trials, and a few in phase III trials. The Hoosier Oncology Group evaluated the benefit of adding ifosfamide to EP in a phase III randomised trial of 171 patients with ES-SCLC. The 2-year survival rate increased from 5% to 13%, at the expense of more toxicity. Mavroudis et al. evaluated the addition of paclitaxel to EP (TEP vs EP), with G-CSF support on the TEP arm. The planned accrual was for 480 patients but the study was terminated early due to more deaths in the TEP arm (8 vs zero with EP). There was a statistically significant benefit in the time-to-tumour progression in the TEP arm, but no benefit in overall survival. In another intergroup trial comparing TEP with EP, 587 patients were randomised. There was no improvement in overall survival; however, incidence of grade 3 and 4 neutropenia (63% vs 21%), thrombocytopenia (44% vs 11%), and neurologic toxicities (25% vs 10%) were higher with TEP compared with EP. Thus, there is no convincing data to support the addition of a third cytotoxic agent to the standard 2-drug combination therapy.

**Newer agents**

Since cytotoxic therapy, as discussed above, has failed, newer approaches are being tried. An ECOG trial used retinoic acid, a differentiation agent, in conjunction with EP; but no additional benefit over EP was demonstrable. Since anti-angiogenesis agents had significant activity when combined with EC, a phase III study is currently being planned. Others have looked at targeted therapy with imatinib, results though are limited. Matrix metalloproteinase inhibitors, which affect the extracellular matrix, are currently being tested in phase III trials.

**Role of radiotherapy (RT)**

In ES disease RT plays an extremely important role in palliation of symptoms of the primary tumour and metastatic disease, particularly brain, epidural, and bone metastases. Chest RT is sometimes given for superior vena cava syndrome, but chemotherapy alone (with irradiation reserved for non responding patients) is the appropriate initial treatment. Brain metastases are appropriately treated with whole-brain radiation therapy. Radiotherapy combined with chemotherapy
does not improve survival compared with chemotherapy alone in patients with ES-SCLC. Prophylactic cranial irradiation (PCI), as discussed later, should be considered for patients who have achieved complete response to chemotherapy.

**Limited Stage Disease**

Patients with LS-SCLC are best treated with a multimodality approach. Usually a platinum-based chemotherapy is given along with RT. Surgery was discarded as a treatment option about 30 years ago, when a randomised study by Medical Research Council demonstrated that RT produced better results\(^4^4\). In this study, 70 patients with LS-SCLC were randomised to undergo surgery and 73 to be treated with radical RT. The results showed that only one percent of patients treated with surgery vs 4% of those treated with RT were alive at five years. Median survival was 199 days for surgery as against 303 days for RT.

Two meta-analyses published in 1992, using different methods, documented the survival benefit for the addition of thoracic RT to chemotherapy in LS-SCLC\(^4^5,4^6\). Pignon et al\(^4^5\) collected data on 2140 patients from 16 randomised trials comparing chemotherapy alone versus chemotherapy plus thoracic RT, and found an improvement in absolute survival of 5.4% at three years. A study by Warde and Payne\(^4^6\), based on results from 11 prospective randomised trials of chemotherapy with or without thoracic RT, showed that RT improved overall survival by 5.4% at two years and local control by 25 percent.

Most studies in the above meta-analyses were initiated before 1981 and included cyclophosphamide or doxorubicin-based chemotherapy. RT was frequently incorporated sequentially due to excessive mucosal toxicity and myelosuppression with concurrent administration. However, it was only a few trials with concurrent chemoradiation that showed a survival benefit. None of the trials in which RT was given as “consolidation” after completion of chemotherapy showed an impact on survival. The meta-analyses did not show concurrent radiation to be superior to sequential.

**Timing of chemotherapy and radiotherapy: whether to be given sequentially or concurrently?**

The potential advantages of using chemotherapy and RT concurrently rather than sequentially are: (1) early use of both modalities eliminates cancer cells over a shorter time period, thus decreasing the possibility of accelerated repopulation, metastatic events, and emergence of resistance to treatment; (2) ability to plan RT more accurately; and (3) shorter overall treatment time. The disadvantages are: (1) it is more complex, and requires early multidisciplinary involvement; and (2) enhanced normal tissue toxicity, which could result in dose modifications and treatment breaks.

The sequencing and timing of chemotherapy and thoracic RT are still controversial. This issue has been addressed in several randomised trials. The JCOG reported a prospective randomised study for LS-SCLC patients treated by sequential or concurrent thoracic RT, given in a dose of 45 Gy over three weeks (1.5 Gy twice daily)\(^4^7\). All patients received four cycles of EP every three weeks (sequential arm) or four weeks (concurrent arm). Thoracic RT was started on day 2 of the first cycle of chemotherapy in the concurrent arm and after the fourth cycle in the sequential arm. Concurrent RT yielded better survival than sequential RT. The median survival time was 19.7 months in the sequential arm versus 27.2 months in the concurrent arm. The 2-, 3-, and 5-year survival rates for patients who received sequential RT were 35.1%, 20.2% and 18.3%, respectively, as opposed to 54.4%, 29.8% and 23.7%, respectively, for the patients who received concurrent RT. Hematologic toxicity was more severe in the concurrent arm. However, severe esophagitis was frequent in both arms, occurring in 9% of the patients in the concurrent arm and 4% in the sequential arm. This study suggested that EP and concurrent RT are more effective than EP and sequential RT.

The National Cancer Institute of Canada Clinical Trials Group studied early versus late concurrent thoracic RT in a randomised trial\(^4^8\). All the 308 eligible patients received CAV alternating with EP every three weeks for three cycles each. Patients randomised to early thoracic RT received 40 Gy in 15 fractions over three weeks to the primary site concurrent with the first cycle of EP (week 3), and late thoracic RT patients received the same radiation concurrent with the last cycle of EP (week 15). After completion of all chemotherapy and thoracic RT, patients without progressive disease received PCI (25 Gy in 10 fractions over two weeks). The complete remission rates were not significantly different between the two groups; however, progression-free survival and overall survival were superior in the early thoracic RT group. Patients in the late thoracic RT group had a higher risk of brain metastases. This study indicated that early administration of thoracic RT with concurrent chemotherapy is superior to late or consolidation thoracic RT.

The EP is the most frequently used combination given concurrently with RT. Compared with trials incorporating cyclophosphamide or doxorubicin, EP is relatively less myelosuppressive and has less mucosal toxicity, and is thus better tolerated combined with concurrent thoracic RT. More recent chemotherapy, which includes paclitaxel or ifosfamide in addition to EP, has not shown long-term benefits for patients with LS-SCLC. The concurrent administration of IP with radiotherapy has been evaluated in a dose-finding study in non-small cell lung cancer and found to have
excess toxicity. The main dose limiting toxicity was leucopenia, therefore a large proportion of patients were unable to tolerate both the dose levels of irinotecan. There are also concerns about the potential for increased pulmonary toxicity and esophagitis, due to the radiosensitising properties of irinotecan.

**Radiotherapy dose, fractionation and volume**

Despite the use of concurrent chemoradiation, the local relapse rate in LS-SCLC remains high, with approximately 30% of patients experiencing an isolated in-field relapse and 20% both in field and distant relapse. In view of this, a few studies have looked at the feasibility of escalation of the radiation dose. A randomised trial compared high dose (37.5 Gy in 15 fractions) versus low dose RT (25 Gy in 10 fractions) in patients with LS-SCLC. Radiotherapy was given in a consolidative manner after completion of induction chemotherapy.

Although no difference was seen in the overall survival, a significant difference was found in the local control between the two groups of patients. Choi and Carey, in a retrospective analysis of 154 patients with LS-SCLC, demonstrated a reduction in local recurrence rate from 79% with 30 Gy to 37% with 50 Gy. Arriagada et al reviewed the combined data of four phase II studies performed by the French Cancer Center’s Lung Group. These delivered increasing doses of radiotherapy as an alternating treatment with chemotherapy. Despite an increase in the dose from 45 Gy to 65 Gy, no improvement was observed in the local control. Thus RT doses above 50 Gy have not been shown to unequivocally improve outcome.

As SCLC is biologically very sensitive to small doses of RT, delivery of more frequent, small fractions (hyperfractionation) of radiation may be preferable to larger daily doses. This strategy is thought to decrease the toxicity to normal tissues while preserving the antitumour effect. Theoretically, hyperfractionation should counter the problem of accelerated repopulation. In a randomised trial, the delivery of 45 Gy in twice daily fractions over five weeks concurrently with EP beginning with the first cycle resulted in a survival advantage compared with the same dose given in once daily fractions over five weeks. After eight years median follow-up, the median survival (23 vs 18 months), 2-year survival (47% vs 41%), and 5-year survival (26% vs 16%) were significantly better in the twice-daily RT as compared to once-daily RT arm. The toxicities in the two arms were identical with the exception of grade 3 esophagitis, which was more frequent in the daily fraction group. Additionally, a trial of 54 Gy in once daily fractions showed survival advantage when this cycle was commenced with the first cycle of chemotherapy compared to delaying until the sixth week.

In the older studies of chemoradiation, for instance South West Oncology Group (SWOG) trial 7628, the volume irradiated included the gross tumour volume, ipsilateral hilum, bilateral mediastinum, and both supraclavicular fossae. In contrast, in some of the most recently published data using more intensive chemotherapy agents, this volume has been reduced to just the gross tumour volume (primary and involved nodes) with a margin of 2 cm. Increasing the size of RT field to pre-treatment tumour volume, as opposed to the post treatment mass, does not appear to increase local control. The risk of pneumonitis and severe esophagitis are volume-dependent. To minimise the dose to the lungs and esophagus, a two-phase technique has been employed, using anterior-posterior fields to treat until the spinal cord tolerance dose has been reached and then oblique fields to complete the treatment.

The evidence thus suggests that concurrent chemoradiotherapy and thoracic RT is the current standard of care for management of LS-SCLC, but one has to expect and manage frequent toxicities in the form of myelosuppression, esophagitis and pneumonitis. Ideally, thoracic RT should be given early either with the first or the second course of chemotherapy. Standard thoracic RT dose is 45 Gy given as 1.5 Gy twice-daily fractions with concurrent EP. If the patient is planned for once-daily thoracic RT, a higher dose may be indicated. After completion of chemotherapy (4 cycles) the patient should be re-evaluated for response.

**Role of prophylactic cranial irradiation (PCI)**

Those patients with LS-SCLC who are treated with chemotherapy and thoracic RT, and have achieved a complete remission, should be considered for PCI. The risk of developing central nervous system metastases can be reduced by more than 50% by the administration of PCI in doses of 2400 cGy. It has a small survival advantage (about 5%), as determined in a large meta-analysis. This meta-analysis included all patients with SCLC in complete remission, majority being in LS and only 20% with ES disease. With appropriate dosing of PCI, there is usually minimal neurotoxicity, and the potential for a significant quality-of-life benefit. Patients who complete treatment have to be followed carefully to detect any recurrence or a second malignancy.

**Relapsed SCLC**

While SCLC is usually initially sensitive to chemotherapy and radiotherapy, responses are rarely long lasting. Overall, the majority of patients die in less than two years, and the 5-year survival rate is 4.8% for LS-SCLC and 2.3% for ES-SCLC. Frustratingly, most patients ultimately relapse, often with increasingly treatment resistant disease and thus become candidates for second-line chemotherapy. After failing first-line
therapy, survival with best supportive care only is short. The positive impact of second-line therapy has been defined. Response to second-line therapy is influenced by time to progression after first-line therapy. Patients with sensitive disease are defined as those who relapse ≥ 3 months after completion of the first-line therapy. Patients with refractory disease are those who progress while on, or relapse within three months after completing the first-line therapy. Second-line therapy should be given to only those with adequate performance status.

Currently there is no well-established standard second-line therapy for patients with refractory disease and the response rates are <10 percent. For patients with sensitive SCLC, researchers have studied several active agents-cyclophosphamide, doxorubicin, vincristine, topotecan, irinotecan, taxanes, gemcitabine, and vinorelbine, among others-in phase II trials. Until better data are obtained, treatment with topotecan is probably the best option. Patients relapsing more than three months after the first-line therapy, retreatment with the same first-line therapy has been demonstrated to be effective.

Indian Scenario

There is not much data published on SCLC from India. In the largest series of 1009 patients of primary lung cancer, from 1977 through 1986 at the Postgraduate Institute, Chandigarh, SCLC comprised 20.3% of all histologically or cytologically confirmed cases. Most of the cases had extensive stage at presentation. Behera et al. reported their experience of treating ES-SCLC patients with a chemotherapy regimen of vincristine, etoposide and ifosfamide. A total of 98 patients were enrolled during January 1990-June 1999, of which 35 (35.7%) did not return after the first cycle of chemotherapy and were excluded from the analysis. Evaluable patients received between two and eight chemotherapy cycles. Additional palliative RT was given to 21 (33.3%) patients. The response rate was 47.6%; median survival was 22 weeks, and one year survival was 12.7 percent. The poor median survival was attributed to poor treatment compliance and follow-up; lack of affordability being one of the major factors for dropouts.

At our hospital, we treat ES-SCLC patients with EP regimen. For patients who can afford, IP is offered. If a patient continues to respond between cycles two and four, an additional two cycles are given, up to a maximum of six cycles. LS-SCLC patients receive four cycles of EP followed by thoracic RT. The possibility of concurrent thoracic RT with chemotherapy is being explored in the context of a clinical trial. Routine use of concurrent chemoradiation is avoided because of excessive toxicities faced by our patients who have poor performance and nutritional status. For SCLC patients who go into complete remission, PCI is considered.

CONCLUSIONS

Chemosensitive nature of SCLC is not in doubt. For patients with limited-stage disease, EP with concurrent thoracic RT, usually given during first or second cycle is the standard. Prophylactic cranial irradiation following a complete response also adds to benefits in terms of prevention of central nervous system disease and overall survival. In patients with extensive-stage disease, 4-6 cycles of EP or EC offer survival advantage compared to supportive therapy. There is a possibility that IP regimen may prolong survival time. Other approaches, including dose intensification with or without stem cell rescue, alternating non-cross resistant regimens, use of three or more drugs as against two drugs, and use of growth factors have failed to come up to the desired expectations. Search for methods to have better outcome in SCLC continues in the form of targeted therapies, including differentiation agents, anti-angiogenic agents, signal-transduction inhibitors, farnesyl-transferase inhibitors, and matrix metalloproteinase inhibitors.

REFERENCES


