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Small cell lung cancer: Treatment review

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Abstract: Lung cancer was relatively uncommon at the turn of the 20th century, and has increased in prevalence at alarming rates, particularly because of the augmented trend in smoking, so that it is now the most common cause of cancer death in the world. As almost a quarter of these cancers are of small cell in origin, it seems only appropriate that small cell lung cancer receives ample attention, rather than seemingly to have been overlooked over the last 10–15 years. Despite its generally late presentation and high risk of dissemination, it is exceptionally sensitive to chemo-radiotherapy. This review looks at the diverse options of treatment that have been used over the last few years and tries to highlight the best available. As more than 50% of patients diagnosed with lung cancer are over 70 years of age and various studies have shown that older people respond just as well as their younger counterparts, with similar results in response rates, toxicity and outcomes, it is imperative that the older generation are not disregarded in terms of age being a contraindication to therapy.

Key words: lung cancer, small cell lung cancer, treatment.

PREVALENCE

Globally, lung cancer is the most common malignancy in men, and the leading cause of cancer death in both men and women, overtaking breast cancer as the commonest cause of death from cancer in women in many countries. In 2000, more than one million people died from lung cancer worldwide. Overall, women accounted for just more than one quarter of all lung cancer deaths.[1] Small cell carcinomas, account for approximately 20–25% of all lung cancers.[2] It is almost entirely related to smoking and is the most aggressive of all the lung cancer cell types, with a median survival time without treatment of 2–4 months.[3,4] In the mid-1970s small cell lung cancer (SCLC) seemed treatable and even curable as new chemotherapy regimens were developed, and single-agent therapy became double or triple drug therapy combinations. The median survival increased from 6 months to 18 months for limited disease presentations and to 9 months for those with extensive disease. However, since the mid-1980s there has been almost no progress in survivorship of this cell type. This review will detail the past, but there is too little to say for the last 15 years as interest has switched to the much less chemo-sensitive non-small cell lung cancers (NSCLC), which although four times more common than SCLC, still seems a less attractive tumour when one considers the potential for cure. Nevertheless, the overall 5-year survival for 100 new cases of either cell type remains at approximately 5% overall, with surgery being the only curative treatment for NSCLC, and chemotherapy for SCLC.

SYMPTOMS AND SIGNS

Small cell lung cancer presents late with obviously abnormal chest radiographs and with bulky, usually mediastinal, involvement. The length of symptoms is short, approximately 8–12 weeks prior to presentation. The symptoms can result from local intrapulmonary tumour growth (cough, wheeze, dyspnoea, haemoptysis), extrapulmonary intrathoracic spread (mediastinal syndromes including superior vena caval obstruction, dysphagia, etc.), distant spread and/or paraneoplastic syndromes. It is associated more than the other cell types with mediastinal presentations and with paraneoplastic syndromes.

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Table 1 Summary of factors that predict improved survival

	Good prognosis	Poor prognosis
Performance status (Karnofsky index)	>70	<70
Hb (g/dL)	Normal	<11
WCC	Normal	High
Platelets ($\times 10^9$/L)	Normal	<150
Na (mmol/L)	>136	<135
Albumin (g/L)	>36	<36
Alk phosphatase (ULN)	<1.5	>1.5
LDH	Low	High
CEA	Normal	High
D28 NSE	Normal	
Weight	<10 lb	>10 lb in preceding 6 months
Sex	Female	Male
Disease state	Minimal	Extensive
	Extra-abdominal	Intra-abdominal
	Single organ	Multiple comorbidities

CEA, Carcinoembryonic antigen; NSE, neurone-specific enolase; ULN, upper limit of normal.

STAGING AND PROGNOSTIC FACTORS

The tumour nodes metastasis (TNM) system does not effectively apply in SCLC except for those few patients (<5%) who may benefit from very detailed staging because they appear resectable.

The Veterans Administration Lung Group developed a much simpler two-stage system based on suitability for radiotherapy. Patients with disease confined to one hemithorax, with or without mediastinal, contralateral hilar, or ipsilateral supraclavicular or scalene lymph nodes were considered to have limited-stage disease, whereas those with disease involvement at any other location were considered to have extensive-stage disease. The staging determines the prognosis and management of SCLC.[3,5] However, there are subsets within each group that do better: minimal disease versus bulky disease in limited stage, extra-abdominal versus intra-abdominal in extensive disease and single organ versus multi-organ involvement.[6] Generally, approximately 30% of patients have limited disease stage.

In terms of prognosis there are several factors that predict for improved survival; one of the most relevant is initial performance status greater than or equal to 70 (Karnofsky index). Others include Hb level, total WCC, neurone-specific enolase and LDH level specifically relevant in limited disease and in extensive disease minimal weight loss (less than 10 pounds over the 6-month period prior to therapy) and a normal platelet count. More commonly used factors are an albumin >36 g/L, serum sodium >136 mmol/L and an alkaline phosphatase <1.5 upper limit of normal.[7–13] Table 1 summarises these.

TREATMENT

Small cell lung cancer is extremely sensitive to chemotherapy and radiotherapy. However, despite initial responses, including 50% of limited-stage disease patients achieving a complete response with modern chemotherapy, relapse is common and most patients eventually succumb to the disease.[14] Nevertheless, patients are cured and the 2-year survival rate in one study with limited disease is 8.5% and extensive disease 2.2%,[15] and in another study, at 5 years the overall survival rate was 3.5% (limited disease 4.8% and extensive disease 2.3%), in fact in the same study their survival rate for 10 years was 1.8% overall (limited disease 2.5% and extensive disease 1.2%).[16] Sadly, of those alive and disease-free at 2 years, half will ultimately die of NSCLC.

CHEMOTHERAPY

Small cell lung cancer is likely to be disseminated or at least locally advanced at diagnosis, making the possibility of resection immediately unlikely. Chemotherapy is, therefore, the cornerstone of therapy. Many studies looking at cytotoxic agents in varying combinations and dose schedules have shown that most regimens have similar response rates as long as at least two active drugs are given for at least four cycles.[17] There have been significant improvements to minimize side-effects of the therapy, so that the majority of treatment is given as an outpatient.

The choice of regimen may depend on the patient's comorbidities, for example inadequate renal function or a significant pre-existing peripheral neuropathy may be a contraindication for cisplatin. Because of the need for over-hydration for platinum-based therapy, heart disease may complicate this drug choice. Vinca alkaloids should be avoided if there is pre-existing neuropathy. Also doxorubicin should be avoided after thoracic radiotherapy as it augments post-radiation pneumonitis.

First-line chemotherapy

The current first-choice regimen is four to six courses of etoposide and cisplatin.[14,18–25] When carboplatin is

given with etoposide it appears to be as effective as cisplatin and etoposide, with less toxicity (apart from increased myelosuppression).[26] The Hellenic Oncology Group conducted a Phase III randomised controlled trial (RCT) comparing carboplatin-etoposide and cisplatin-etoposide in both limited- and extensive-stage patients. The median survivals were similar in both arms at approximately 12 months.[27] More recently, there have been some promising results with irinotecan (a topoisomerase I inhibitor) and cisplatin, in patients with extensive disease, showing that there is a tendency for a better outcome over etoposide and cisplatin, with an improved median survival from 9.4 months to 12.8 months and 2-year survival of 5.2% increasing to 19.5% with irinotecan and cisplatin.[28–31] In the Japanese group the study was stopped early because of a survival advantage to the irinotecan group. However, that study when repeated has not confirmed this improvement.[28]

The problem with treatment is that the tumour becomes resistant to the chemotherapy, or a resistant clone is left to grow. Ways around this problem have been evaluated with dose intensification[32] using different schedules including weekly administration,[33] bone marrow protection using GM-CSF[34] and also very-high-dose therapy with re-infusion of pretreatment-harvested bone marrow.[35,36] None of these trials have shown any significant survival benefit for the intensification arm, and, in fact there was huge difficulty in getting the planned treatments delivered due to haematological side-effects, and therefore intended dose intensities were seldom achieved in this often elderly population.[33,37–40] Moreover, patients with extensive disease tolerated dose intensification much less well.[41,42] However, one study of patients with limited disease, randomized to a conventional dose of cisplatin, cyclophosphamide, etoposide and doxorubicin alternating with thoracic irradiation, versus the same regimen but where the doses of cyclophosphamide and cisplatin were increased by 20% for the first treatment cycle only, did show a 2-year survival that was significantly higher in the so-called intensive group (43% vs. 26%).[43] Overall, however, this has been a disappointing line of pursuit.

Maintenance chemotherapy

Maintenance chemotherapy after induction therapy, again has been thoroughly assessed. A review of the literature shows that there is little benefit from extending treatment,[24,44] although some studies did find an advantage.[45,46] The optimal duration of treatment is six to eight cycles of the second-generation drugs[47,48] but is probably six courses of the modern doublets such as cisplatin and etoposide. A Cancer Research Campaign trial showed that giving only four courses of second-generation chemotherapy agents was associated with an inferior survival compared with eight cycles, which improved median survival from 30 weeks to 39 weeks, and the responding population was particularly disadvantaged by just four courses. A similar UK Medical Research Council study showed no difference in survival between six and 12 courses, although relapse occurred earlier with shorter course treatment, but there was greater toxicity and poorer quality of life measured with the prolonged treatment.[49] Maintenance chemotherapy does not appear to offer a better chance of cure than short-course chemotherapy and does not prolong survival. Short-course, combination chemotherapy appears to be a reasonable choice for standard treatment.[50]

Interestingly, the Hoosier Oncology Group performed a phase III RCT by randomizing patients to receive additional 3 months oral etoposide in non-progressing patients with extensive-stage disease following four cycles of etoposide, ifosfamide and cisplatin. Out of 144 patients randomized there was a significant improvement in the progression-free survival (8.2 months vs. 6.5 months) and a trend towards improved survival overall.[51]

Second-line chemotherapy

When relapse or progression occurs, second-line chemotherapy is, in general, much less effective than initial treatment. The outcome is influenced by: the first-line drugs used, the tumour's initial response and the length of the progression-free interval, which ideally should be at least 3 months.[3,52] However, second-line treatment did improve survival compared with best supportive care in one study with a median survival of 5.3 months versus 2.2 months.[53] Aggressive re-treatment could be considered in patients whose disease has relapsed after a remission of at least 6 months, as some may achieve a second complete response, which in turn has an improved survival benefit.[54,55] Topotecan has had good reviews in recurrent disease;[56,57] like irinotecan, topotecan is a novel topoisomerase I inhibitor, with established antitumour activity in recurrent SCLC and has a predictable, non-cumulative toxicity profile. Furthermore, topotecan has been shown to improve symptom control in this mainly palliative setting.[58] The results from a phase II trial of weekly bolus topotecan in patients with recurrent SCLC have been reported, and shown that this regimen was generally well tolerated.[59] Topotecan combined with paclitaxel, given on day 1 on a weekly basis, produced a response rate of 26.8% in pretreated patients with SCLC. Myelotoxicity, particularly neutropenia, was the main adverse reaction, but only in a small group of patients.[60] However, as with all treatments, there have been some negative trials, for example a paclitaxel–carboplatin–etoposide combination produced a superior overall response rate and time to progression interval in patients with extensive-stage SCLC compared with paclitaxel and topotecan.[61]

Granulocyte colony stimulating factor

The incidence of grade IV toxicities, in particular neutropenia, is relatively common even with conventional chemotherapy, so various studies have looked at whether there is any benefit in giving granulocyte colony stimulating factor to speed up the return of

neutrophils. It does not seem to have any effect on reducing the incidence of myelosuppression or have any effect on survival, as mentioned above.[62–65] However, recovery rate can be improved and therefore there is the potential to increase dose intensity, that is, doses in milligrams per metre squared per week.[17]

Oral versus i.v. chemotherapy

Etoposide is the one active agent in SCLC that can be delivered orally and was widely prescribed as a first-line treatment 10 years ago, either as an alternative to the i.v. form, or as an oral substitute to make 3-day treatments with etoposide feasible, by just giving the first dose intravenously. It also has been considered for maintenance treatment.[51] However, oral etoposide varies in its absorption characteristics both within and between subjects. Two studies evaluated oral etoposide with i.v. chemotherapy, and both were stopped prematurely because of poorer quality of life and shorter progression-free intervals in the etoposide arms.[66,67]

RADIOTHERAPY

Several RCTs in the 1980s attempted to establish the role of thoracic radiotherapy as an adjunct to chemotherapy. Most showed an advantage for local control and fewer relapses at the primary site, but survival was not clearly prolonged as patients died from distant metastatic disease, basically because chemotherapy failed to eradicate disseminated metastases. The addition of radiotherapy to chemotherapy, did, in some trials show a survival benefit, but two meta-analyses were required to demonstrate a survival advantage of approximately 4% at 2 years. Following these, radiotherapy became an established adjunct to chemotherapy, but only in those who showed a complete response or a good partial response to chemotherapy.[68,69]

Dose

The optimal dose of radiotherapy is still open to debate. Some studies showed benefit with up to 70 Gy once daily for limited-stage disease, with a median overall survival of 22.4 months,[70] whereas others have given 45 Gy with good results.[30,71] One way to increase the effectiveness of radiotherapy was to use hyperfractionated accelerated radiotherapy, although the total dose given may be more important than the fractionation schedule. Twice daily radiation may have the advantage shown *in vitro* data that SCLC cells lack the ability to rapidly repair sublethal damage. Therefore, this allows multiple small doses of radiation for an increased tumour kill.[69]

Timing

When irradiation followed chemotherapy, there was no survival benefit, even when the irradiated field was reduced to that of the postchemotherapy tumour volume; the 2-year survival being less than 20%.[72–74] There is a consensus that radiotherapy should be given concurrently with the chemotherapy.[75–78] This has been examined by seven randomized trials comparing the effect on survival of giving the radiotherapy early, that is, within 6 weeks of starting chemotherapy, or late, that is, with the last course of chemotherapy. Although only three of these trials have shown a significant survival advantage for the early radiotherapy arm,[79–81] a meta-analysis of all these trials suggested a modest improvement in 2- and 3-year survival among patients given early radiotherapy.[76] There is also an indication that benefit of early treatment is associated with the use of hyperfractionated accelerated radiotherapy or platinum-based chemotherapy. However, the trials that failed to show an advantage for early radiotherapy failed to reach their planned dose intensity of chemotherapy, which may be the over-riding factor here.

Prophylactic cranial irradiation

Approximately 10% of patients present with cerebral metastases at the time of initial diagnosis, and an additional 40–50% will develop cerebral metastases at some point during the course of their disease. However, prophylactic cranial irradiation in patients who achieve complete remission delays or reduces the incidence of central nervous system disease.[23,68,82–84] Its cost-effectiveness and positive impact on patient quality of life have also been shown.[85] Prophylactic cranial irradiation in a meta-analysis prolonged survival with 5% more likely to be alive at 3 years and also an overall reduction in brain metastases of 45%.[86]

SURGERY

Consideration of surgery for patients with SCLC should only be entertained in patients with stage I or perhaps IIA tumours and seeing as there are very few patients who are detected that early, this applies to only a handful of patients. Nevertheless, this is an important subgroup and if careful staging, including mediastinoscopy, and, possibly, PET scanning, is favourable, they should go to thoracotomy. Another important caveat is that diagnosis, usually by fibreoptic bronchoscopy or fine-needle aspiration produces small samples and it is possible to misdiagnose a carcinoid tumour. These are chemo-insensitive and should always be resected if peripheral. There is little data on resected SCLC to suggest an advantage for adjuvant chemotherapy, and in the absence of trail data, it is still recommended.[87]

QUALITY OF LIFE

As patients have limited survival expectations, symptom palliation, quality of life and convenience of treatment schedules are particularly important endpoints.[88] There have been a few studies looking at how

quality of life can be assessed, namely involving the use of diary cards or questionnaires such as the Lung Cancer Symptom Scale or the European Organization for Research and Treatment of Cancer Lung Cancer Questionnaire.[89–91] Quality of life end-points are being increasingly incorporated into clinical trials to further establish meaningful response. Generally, responses to chemotherapy show dramatic improvement in tumour-related symptoms and hence improve quality of life. However, when patients undergo second-line chemotherapy there is a poor response in quality of life. Quality of life measurements may also be helpful in choosing between treatment alternatives where little difference in outcome is observed.[89]

ELDERLY

There is a general trend worldwide of an increasing elderly (over 70 years of age) population. The results from the 2001 UK Census show that 11.4% of the total population are over 70 years old[92] and by 2051 the percentage of elderly patients will rise to 22.9%.[93] Age is the greatest risk factor for cancer,[94] so this demographic shift has important implications in how people approach the treatment of this disease.[95] Lung cancer is the commonest cancer of adults worldwide, and 53% of lung cancer cases between 1991 and 1994 were over 70 years old,[96] so it seems only appropriate that these people are exposed to the same degree of investigation and treatment as those of a younger age. In clinical trials elderly patients are poorly represented ranging between 13% and 29% of patients aged over 70 years,[97–100] yet various studies have shown that older people respond just as well as their younger counterparts, with similar results in response rates, toxicity and outcomes.[98,100]

There may be a bias against treating the elderly, with doctors sometimes assuming that life-prolonging therapy is more important to younger patients, and symptom relief is more important to elderly patients.[101] Furthermore, physicians may shy away from treating the elderly for fear of toxicity. However, it is vital to consider the patient's medical history balanced with their current health and functional status and the presence or absence of comorbid conditions, nutritional status and cognitive functions, not just their age. Elderly patients with poor performance status and comorbid disease are at considerable risk of ineffective treatment and are also at greater risk for potentially fatal toxicity.[102] The patient's age alone is not a contraindication to treatment.[95]

SUMMARY

Small cell lung cancer remains an enormous challenge to respiratory physicians and oncologists. It is so much more sensitive to therapy than NSCLC and deserves a resurgence of research interest. It has, in many ways suffered another blow by the cell type apparently not being responsive to the new class of agents under investigation, the epidermal growth factor receptor antagonists. Chemotherapy remains the treatment of choice, with radiotherapy to those who have responded well. The elderly should get the same approach to treatment, if fit, as their younger counterparts. Surgery is still a factor to consider whenever suitable, a fact often overlooked by oncologists.

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