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The treatment of limited small cell lung cancer: a report of the progress made and future prospects

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Abstract

The improvements in the treatment of small cell lung cancer over the last 30 years have been realised by understanding that it is a systemic disease, but that areas of bulk and sanctuary require a complementary therapy. Despite successful strategies using combinations and thoracic radiotherapy, there remains uncertainty about what the best regimens are, their timing and their intensity. However, earlier concurrent therapy and rather brief intense chemotherapy and radiotherapy seem to produce the best results in moderately fit patients of all ages. How to select the fit patients and what to do about the less fit ones remains controversial and have economic consequences for governments and payers. Despite a meta-analysis demonstrating the success of prophylactic cranial irradiation (PCI), doubts linger about its safety, despite nothing more than anecdotal evidence from a previous era. The role of surgery continues to be explored, more in Europe than North America or Asia. Strategies for treatment of minimum residual disease seem a focus. New drugs, molecular targeted therapy, immunotherapy and other molecular therapies offer promise and theory, but there is little evidence about their place in the treatment protocols of today.

Keywords: Chemoradiotherapy; SCLC; Treatment; Safety

1. Introduction

The past 30 years have demonstrated a steadfast improvement in the management of small-cell carcinoma of the lung. Prior to the 1970s, patients diagnosed with small cell were commonly managed like any other cell type of bronchogenic carcinoma, with surgery or radiation therapy. In 1969, the British Medical Research Council reported 5-year survival rates of 1% with surgery and 4% with radiotherapy [1]. In the early 1970s, the behaviour of small cell, characterised by early and wide dissemination, led to the division of obvious widespread disease, called *extensive disease* and less obvious or occult systemic disease that we call *limited disease*. The focus of clinical trials has emphasised systemic management with chemotherapy [2]. The initial results with chemotherapy produced a 4- to 5-fold increase in median survival, which generated great enthusiasm and the hope that small cell would be the next disease like leukaemia, conquerable with chemotherapy alone [3]. Unfortunately, more than 30 years later, patients continue to experience high rates of local and distant failure.

Improvements have occurred when we realised that areas of initial bulk required local therapy and sanctuary sites required the addition of radiotherapy, which was not denied access by the blood–brain barrier. Chemotherapy has often been selected because of its response rate in relapsed or extensive disease. For limited disease management, it is crucial for the systemic regimen to be highly active; however, it must also work well with local radiotherapy, and not produce enhanced toxicity to intrathoracic organs. Radiotherapy techniques, such as hyperfractionated, accelerated thoracic radiotherapy, and prophylactic cranial irradiation (PCI) have each produced improvements in survival for patients with limited disease [4,5]. New chemotherapeutic agents with high response rates in small cell lung carcinoma are emerging. While extensive disease and relapsed patients have been the crucible for mixing active single agents into effective combinations to test in the limited disease patients, cure remains elusive in the

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extensive disease population. This article will review the current approach to limited small-cell carcinoma of the lung, and will explore future directions and unanswered questions.

2. Staging and definition of limited disease

In the United States of America, because small cell carcinoma disseminates early and widely, a simple two-category staging has been in operation for years. Much to the chagrin of the American Joint Committee and many individuals, the Tumour, Nodes, Metastases (TNM) classification, has been used infrequently and without enthusiasm. It has not clearly influenced therapy or prognosis. The simplified staging system of 'limited disease' and 'extensive disease' has worked for prognosis and defining a group that has clear benefit from the addition of thoracic radiotherapy and a group where local therapy seems irrelevant or possibly reserved for a subset. The limited disease category includes patients whose disease can be encompassed within a 'reasonable radiation portal'. Size of the primary tumour, atelectasis, pleural-based nodules and supraclavicular nodal disease pose problems for even reasonable people to disagree about, and drawing objective guidelines to follow can be hard. Many nations have sought surrogate prognostic categories rather than expend resources on imaging studies.

For research purposes, the presence of an ipsilateral pleural effusion excludes patients from limited disease protocols. Minimal pleural effusions not large enough for cytological diagnosis [6] may be exceptions and commonly are included as limited disease in studies and clinical practice. However, many investigators [7–9] exclude all patients who are demonstrated to have pleural effusions by any study, including chest computed tomography (CT).

Similar variability in the definition of limited disease occurs with reference to the extent of nodal disease. Unlike the TNM system, there is no distinction for mediastinal laterality. When surgeons approach the mediastinum, the right or left thoracotomy precludes systematic dissection of the contralateral nodes, so the staging system classified these as N-3 nodes and this placed them in the usually inoperable category (stage IIIb). This is less important for small cell usually treated with external beam radiotherapy and rarely approached with surgery, especially if there are mediastinal nodes. The nodes above the clavicle provide another controversy. Some studies include patients with bilateral supraclavicular adenopathy [10], others [4,6] only ipsilateral. This issue may be due to concerns about radiotherapy portals and concern for spinal cord tolerance—it is hard to include both supraclavicular fossae in a reasonably sized radiotherapeutic treatment plan. Some policies include patients with contralateral hilar adenopathy in the limited disease category [9] others exclude them [4]. The TNM system does not deal with this controversy, but it is sensible enough to propose it as an M-1 category in non-small cell lung cancer, why not in small cell too? Let us agree that some of these issues are important in defining staging systems and doing clinical research, but are of little daily concern to the practising physician.

In addition to the variability in the definition of limited stage disease, one must also consider our increasing ability to detect extra-thoracic disease with more sensitive imaging modalities. In the older studies reported well into the 1990s, thoracic imaging consisted of simple chest radiographs [7,11,12]. Current staging requires CT of the chest, abdomen (assessing liver and adrenals) and brain. Some want Magnetic Resonance Imaging (MRI) to replace brain CTs and bone scans because they are more sensitive. A radionuclide bone scan has been part of staging for decades, but now is considered elective. Bone marrow involvement as the sole manifestation of extensive disease is quite rare, occurring in only 1.7% of patients [13]. Positron emission tomography (PET), while not presently a routine staging evaluation of small cell carcinoma patients, is a highly sensitive imaging modality, and may allow a quicker distinction between localised or systemic disease. It has the potential to become a very useful staging procedure for small-cell patients, and may additionally prove beneficial in terms of monitoring their response to therapy [14].

As imaging modalities continue to improve in sensitivity and specificity, the ability to detect disease outside of what might be 'encompassed within a reasonable radiation portal' will increase. Patients, previously classified as limited stage disease, will be migrated to the extensive disease category. This stage migration will appear to improve the outcome of both limited and extensive disease patients, another example of the Will Rogers phenomenon [15].

3. Chemotherapy

In the early 1970s, chemotherapy regimens were based on alkylating agents, commonly cyclophosphamide. One of the most commonly prescribed regimens, CAV, consisted of cyclophosphamide, doxorubicin and vincristine. While this regimen produced excellent response rates, most patients relapsed. The use of doxorubicin precludes combination with thoracic radiotherapy because of excessive oesophagitis, stricture, pulmonary, cardiac and cutaneous toxicity. Despite this awareness, the reliance on this agent and the CAV combination endures in many quarters. Despite its historical role, the use of doxorubicin and cyclophosphamide needs to be relegated to palliative cases. Its continued use is hard to

justify, and its incompatibility with radiotherapy and toxicity make its use anachronistic.

In the late 1970s, the regimen of cisplatin and etoposide was developed as front-line therapy [16]. Preclinical studies suggested marked synergy with this combination [17], and it was subsequently studied as salvage therapy for patients with recurrent or refractory small cell carcinoma, where it produced response rates as high as 52% [18]. Cisplatin/etoposide was then studied as first-line therapy, and was found to be active and amenable to combination with *concurrent* thoracic irradiation. This regimen proved to be at least equivalent or superior to all previous combinations and, during the 1980s, it became the treatment of choice in most of the world for limited small-cell carcinoma [19]. The exact doses and particularly higher doses of either or both drugs has never been shown to be critical. A prospective randomised comparison of standard-dose cisplatin/etoposide (cisplatin 80 mg/m^2 intravenously (i.v.) on day 1 and etoposide 80 mg/m^2 i.v. on days 1–3, repeated every 3 weeks) compared with high-dose cisplatin/etoposide (cisplatin 27 mg/m^2 i.v. on days 1–5 and etoposide 80 mg/m^2 i.v. on days 1–5, repeated every 3 weeks) showed no improvement in efficacy, but substantially increased toxicity with the high-dose arm [20]. Cisplatin regimens, however, produce significant toxicity, most notably nausea, vomiting, nephrotoxicity and neuropathy; however, these are dose related, and doses as low as 60 mg/m^2 are effective in small-cell lung cancer. Table 1 displays our bias.

Carboplatin induces little to no nephrotoxicity, nausea and vomiting, but primarily has myelosuppression as its dose-limiting toxicity. The carboplatin/etoposide combination demonstrates what appears to be comparable activity and survival in small cell-lung cancer. In a prospective randomised phase III trial from Greece, carboplatin/etoposide was reported to be equally effective and better tolerated than cisplatin/etoposide [21]. The limited disease patients in this study were eligible to receive concurrent thoracic irradiation with cycle 4 of the chemotherapy, and this conveyed a survival benefit. Based on the equivalent efficacy, more favourable toxicity profile and ease of outpatient administration, carboplatin/etoposide has preference with many clinicians. The combination of a platinum compound with etoposide remains the standard therapy for small-cell carcinoma. Over the past few years, however, several new cytotoxic agents with substantial activity in this disease have been developed. None has found its their way to front-line regimens, but response rates have motivated attempts to incorporate them.

Paclitaxel (Taxol) was introduced in 1993, and phase II studies demonstrated considerable single agent activity in previously untreated small-cell lung cancer patients [22,23]. The Sarah Cannon group of Nashville, TN, USA added paclitaxel as a 1-h infusion to a commonly used combination of carboplatin/etoposide [24]. In this study, etoposide was initially administered i.v., but when oral etoposide became routinely reimbursable, the regimen was changed to include 50 mg etoposide alternating with 100 mg orally on days 1–10 of a 3-week cycle [24]. While these investigators started with fairly low doses of paclitaxel (135 mg/m^2) and carboplatin (area under the concentration–time curve (AUC) = 5.0), myelosuppression was modest, and they subsequently treated a larger number of patients at increased doses of paclitaxel (200 mg/m^2) and carboplatin (AUC = 6.0) [25]. This study included previously untreated small-cell carcinoma patients with limited or extensive disease. The limited-disease patients received thoracic irradiation 1.8 Gray/day to a total dose of 45 Gray over 5 weeks, beginning concurrently with cycle 3 of chemotherapy. Using the higher dose regimen, the response rate in the entire group ($n = 79$) was 91%; amongst limited-disease patients ($n = 41$), 98%. This regimen was well tolerated; myelosuppression was the predominant toxicity.

Paclitaxel has also been combined with the cisplatin/etoposide regimen. This combination has produced a response rate of 94% in extensive disease patients [26]. Recently, a multi-institutional phase I/II study of this regimen administered with concurrent thoracic irradiation to limited disease small-cell patients was published [27]. In this trial, four 21-day cycles of chemotherapy were administered, and thoracic irradiation consisting of 45 Gray total dose over 5 weeks was given concurrently beginning on day 1 of cycle 1. 60 mg/m^2 cisplatin was given on day 2 for all cycles. Etoposide was given at a lower dose. 60 mg/m^2/day on days 1–3 during cycles 1 and 2 (with concurrent radiation); at a higher dose, 80 mg/m^2/day on days 1–3, during cycles 3 and 4. Granulocyte-colony stimulating factor (G-CSF) was given during cycles 3 and 4 as well. During the phase I portion of the trial, the paclitaxel dose given during cycles 1 and 2 was escalated to determine the maximum tolerated dose with concurrent radiation. This was

Table 1
Standard chemotherapy

- Cisplatin Etoposide!
  - Carboplatin may substitute for 60 mg/m^2 Cisplatin
  - 100–120 mg/m^2 Etoposide are the stand-fasts now for nearly 20 years. No evidence that higher dose platinum is better!
- Role of 'new' or third drug speculative and more toxic in limited disease.

found to be 135 mg/m^2, given over 3 h i.v. on day 1; grade 4 neutropenia was the dose-limiting toxicity. During cycles 3 and 4, paclitaxel was given at 170 mg/m^2. The overall response rate for this regimen was 96%, with 39% complete responses.

The topoisomerase-I inhibitors, topotecan and irinotecan, show significant activity against small-cell carcinoma. Topotecan has been studied in the salvage setting where it yielded a 38% response rate in patients with sensitive disease, defined as patients who responded to first-line chemotherapy and then subsequently relapsed at least 3 months after their chemotherapy was discontinued [28]. Topotecan was noted to be less effective in treating patients with refractory small-cell carcinoma (non-responders to initial therapy or brief interval from response to recurrence), where response rates have been only 6% [27] to 11% [29]. In previously untreated extensive disease patients, a response rate of 39% has been reported [30].

An ongoing phase I trial is being conducted to determine the maximum tolerated systemic exposure of topotecan when combined with carboplatin/etoposide in extensive disease patients [31]. Preliminary results show an 81% response rate. Jett and colleagues studied the combination of topotecan and paclitaxel as first-line therapy for patients with extensive disease; preliminary results yielded a 92% response rate [32]. The Cancer and Leukemia Group B has completed a study in limited disease patients. In this protocol, patients initially undergo two cycles of induction paclitaxel-topotecan with G-CSF support. Subsequently, they receive carboplatin/etoposide for three cycles. Thoracic irradiation is given starting with the third cycle, the first cycle of carboplatin/etoposide. The initial 10 patients received 60 Gy thoracic radiotherapy total dose, the subsequent 60 patients a total dose of 70 Gy. The study is completed, and awaits follow-up. While feasible, it is unlikely that this regimen will move treatment forward.

Irinotecan has also been demonstrated to have significant activity against small cell carcinoma. A phase II study, including both limited disease and extensive disease patients, evaluated the combination of 60 mg/m^2 irinotecan on days 1, 8 and 15, with 60 mg/m^2 cisplatin on day 1, every 28 days [33]. Patients with limited disease received four cycles of chemotherapy followed by thoracic irradiation to 50 Gy. The response rate in limited disease patients was 83% with 30% complete remissions; median survival was 14.3 months. The major toxicities were myelosuppression and diarrhoea. This chemotherapy regimen has also been explored with concurrent thoracic irradiation in limited disease small cell patients [34]. In this setting, the dose-limiting toxicity was found to be fatigue and the recommended dose for future study is 40 mg/m^2 irinotecan on days 1, 8 and 15 with 60 mg/m^2 cisplatin on day 1, every 28 days. Whether this combination will prove to be superior to standard therapy for limited disease patients awaits further study. Recently, however, a randomised phase III study in extensive-disease patients compared cisplatin/irinotecan with the standard regimen of cisplatin/etoposide [35]. The response rate was 89% with cisplatin/irinotecan; 67% with cisplatin/etoposide. Median survival and 1-year survival rate were 420 days and 60% with cisplatin/irinotecan; 300 days and 40% with cisplatin/etoposide. The survival benefit was statistically significant ($P = 0.0047$; log-rank test).

Irinotecan has also been combined with etoposide in the salvage setting. Masuda and colleagues [36] treated 25 patients with relapsed or refractory small-cell carcinoma (all patients had received prior platinum-based combination chemotherapy). Treatment was administered with G-CSF support; the major toxicities were myelosuppression and diarrhoea. The regimen was highly active with a 71% response rate, and the median survival was 271 days.

Thus, over the last few years many new chemotherapeutic agents with novel mechanisms of action have been tested in small-cell lung cancer. Encouraging response rates and encouraging single institutional survival found in the salvage setting and in extensive disease setting have pointed towards incorporating these new agents in the treatment of limited disease. The results of ongoing trials exploring the various ways of combining or sequencing these agents with each other, with the older, standard regimens, and with thoracic irradiation are anxiously awaited. Table 2 gives an overview of the response rates to the new agents. However, to date, none of these has been successfully engineered into a phase III study.

4. High-dose chemotherapy

A few continue to believe that there may be a role for very high-dose alkylating agent therapy with stem cell rescue. On the heels of the bone marrow transplant enthusiasm in other perhaps more fit and responsive tumours, and no credible evidence from controlled trials showing benefit, this may seem ill advised or stubborn to a large majority of solid tumour oncologists. Humb-

Table 2
Compilation response rates to 'new' agents

● Gemcitabine	26%
● Taxanes	
○ Docetaxel	28%
○ Paclitaxel	34–41%
● Topo-I inhibitors	
○ Topotecan	39%
○ Irinotecan	47%
● Amrubicin	79%
● Vinorelbine	13%

let and colleagues [37] tried high-dose therapy after induction chemotherapy with three cycles of cyclophosphamide, doxorubicin, vincristine and methotrexate, followed by two cycles of cisplatin/etoposide. This series included 101 patients with small-cell lung cancer. 45 responding patients (45%) were then randomised to either one cycle of high-dose therapy, consisting of high-dose etoposide, cyclophosphamide, and carmustine (BCNU) with marrow support, or one additional cycle of conventional-dose therapy. Thoracic irradiation *was not* performed for either group in this study. There was clear-cut evidence of a dose response, in that conversion from partial remission to complete remission occurred in 77% of the patients who received high-dose therapy versus 0% of the patients who received additional conventional-dose therapy. There was, however, an 18% toxic death rate on the autologous marrow transplant arm. While disease-free survival was improved with high-dose therapy, there was no benefit in terms of overall survival. In those who relapsed, there was a very high incidence of chest recurrence, likely related to the omission of thoracic irradiation in this trial.

Elias and colleagues [38] reported on the results of high-dose therapy in limited-disease patients, aged 60 years or younger, who had achieved complete or partial remission with conventional induction chemotherapy. 36 patients subsequently received high-dose cyclophosphamide, cisplatin and carmustine with haematological stem cell support. Patients, who had not received thoracic irradiation during induction therapy, were treated sequentially and late with thoracic irradiation after recovery from the acute toxicity of the high-dose therapy. Prophylactic cranial irradiation was also performed. In this study with selected patients, the 5-year survival rate after high-dose therapy was 41%. For the 29 patients in this trial who had achieved complete remission or near complete remission with conventional induction chemotherapy, prior to high-dose therapy, the actuarial 5-year progression-free survival rate was 53%. It is not obvious that an unselected limited-disease patient population with small-cell can replicate this seemingly favourable experience.

5. Thoracic radiation and its variables

Combination chemotherapy alone unfortunately results in an exceedingly high local failure rate, as high as 90% at 3 years [39]. Randomised trials, conducted in the 1980s, compared chemotherapy by itself to chemotherapy with thoracic irradiation. The majority of these studies demonstrated a substantial improvement in local control with the addition of radiation. The individual studies failed to demonstrate a convincing or significant survival advantage for the addition of thoracic radiotherapy. Subsequently, two meta-analyses, published nearly a decade ago, provided evidence for a significant survival benefit for the addition of thoracic radiotherapy [40,41]. However, the details about what kind of radiotherapy and how it was blended with systemic therapy were not finalised. None of these trials used early cisplatin/etoposide chemotherapy. The trials comprising the meta-analyses utilised chemotherapy regimens that were cyclophosphamide and/or doxorubicin-based, at least for induction. No conclusions can be drawn from the meta-analyses regarding the optimal timing and sequencing of chemotherapy and radiation.

The notable variables of radiotherapy include total dose, volume or area of the target, dose per time and frequency (fractionation) and timing with the other modalities. When concurrent therapy is used, there also is disagreement about whether it must be used early (during the first or second cycle) or later. A study by the National Cancer Institute of Canada Clinical Trials Group treated patients with cyclophosphamide, doxorubicin and vincristine alternating with cisplatin/etoposide every 3 weeks for six cycles [7]. Patients were randomised to receive 40 Gy of thoracic irradiation beginning concurrently with either the first or the last cycle of cisplatin/etoposide. Progression-free survival and overall survival were superior in the arm that used the *earlier* irradiation. In another, earlier prospective randomised trial, Perry and co-workers compared three arms: chemotherapy alone (a cyclophosphamide-based regimen), chemotherapy with early radiotherapy (beginning concurrently with cycle one), and chemotherapy with delayed radiotherapy (beginning concurrently with cycle four) [39]. The arms which included thoracic irradiation were superior to chemotherapy alone in terms of survival and complete response rates. Although not statistically significant, in this trial there was a trend towards improved 2-year survival with delayed radiotherapy compared with early radiotherapy. Importantly, the excessive myelosuppression encountered during concurrent therapy in this study mandated dose reductions of chemotherapy, particularly in the early-radiotherapy group. This variation in chemotherapy intensity may have influenced the modest survival differences more than the timing of the thoracic radiotherapy. The absolute survival figures were also very modest in this trial that used the dated cyclophosphamide and doxorubicin combinations, which were so markedly attenuated because of the observed toxicity.

Two later trials used current staging and platinum-based therapies. Takada and colleagues [42] compared concurrent versus sequential thoracic irradiation administered with cisplatin/etoposide chemotherapy. Early concurrent therapy was found to be superior to sequential treatment in which the radiation was given after the completion of four cycles of chemotherapy. Work and colleagues [9] reported a series allegedly comparing early with late radiotherapy. In fact, the trial

used sequential radiotherapy *before* or *after* nine cycles of chemotherapy, only three of which were platinum etoposide. Either of these sequential strategies resulted in greater than 70% local failure. The greatest value of this work is to point out that either of these methods is inadequate. While there is room for debate and further investigation of these topics, the preponderance of evidence points toward better survival with early and concurrent thoracic radiotherapy, as opposed to delayed or sequential radiotherapy.

Based on the available data, firm conclusions regarding the precise optimal timing of thoracic irradiation cannot be drawn. The platinum-based regimens have made the administration of relatively full-dose concurrent radiotherapy possible. The administration of one or two cycles of chemotherapy prior to starting concurrent therapy would allow the efficacy of the chosen chemotherapy regimen to be assessed. The volume reduction achieved with this approach allows the ensuing radiotherapy target to be smaller, which provides more sparing or protection to more normal tissue. As early as the beginning of the 1980s, we found a report from the Southwest Oncology Group (SWOG). For partial-responders to induction chemotherapy, this study randomised patients either to receive wide-field radiotherapy (directed at the pre-induction tumour volume) or reduced-field radiotherapy (directed at the post-induction tumour volume). The extent of chest irradiation *did not* affect survival or relapse patterns [12]. With these facts in mind, one could make a case for delaying the administration of concurrent thoracic irradiation briefly, allowing one or two cycles of induction chemotherapy to be administered. Whether even minimal delays are beneficial or detrimental the best results currently reported [4,7,42], which all use cycle one or two concurrent therapy, shall require prospective randomised trials. A theoretical disadvantage of delay is the emergence of resistant or metastasising clones that earlier radiotherapy prevents and eliminates.

6. Fractionation and dose

Small-cell lung cancer cell lines are exquisitely sensitive to radiation, even at very small doses [43]. These cell lines lack a radiobiological shoulder, the initial region of the radiation survival curve plots. This infers that exponential cell-killing occurs even at low doses per fraction. At these low doses, radiation spares cell populations with a shoulder on the curve, such as normal tissue. Based on this information, the clinical administration of multiple small fractions of irradiation would be expected to effectively kill small-cell carcinoma cells, while reducing the permanent damage or late toxicity to normal tissues.

Early clinical pilot studies of twice-daily thoracic irradiation combined with cisplatin/etoposide led to an intergroup phase III trial comparing this approach with conventional once-daily irradiation with the same chemotherapy [4]. 417 patients were randomised to receive 45 Gy of concurrent thoracic radiotherapy given either twice daily over 3 weeks (30 fractions), or once daily over 5 weeks (25 fractions). All of the patients received four 21-day cycles of cisplatin/etoposide, and irradiation began concurrently with cycle 1. The twice-daily radiation was superior, producing a 5-year survival rate of 26% compared with 16% with the once-daily radiation. Despite grade 3 oesophagitis occurring with a significantly greater frequency with the twice-daily treatment, there was no permanent oesophageal toxicity or stricture. Complete responders were offered prophylactic cranial irradiation.

Bonner and colleagues [6] presented data on another phase III trial comparing twice-daily versus once-daily thoracic irradiation with cisplatin/etoposide. In this study, patients were treated with three cycles of induction cisplatin/etoposide. For those patients that did not progress, a subsequent randomisation to receive twice-daily versus once-daily thoracic irradiation given concurrently with two additional cycles of cisplatin/etoposide was offered. In this trial, the twice-daily irradiation was administered as a split course: 48 Gy total dose in 32 fractions, with a 2.5-week break given after the initial 24 Gy. The once-daily irradiation consisted of 50.4 Gy in 28 fractions. After completion of thoracic irradiation, a sixth cycle of cisplatin/etoposide was given. Complete-responders received prophylactic cranial irradiation. In this study, 262 patients were randomised between the twice-daily and the once-daily radiation regimen. There were no significant differences between the arms in terms of progression rate or survival. Again, oesophagitis was encountered more frequently with the twice-daily radiation. The principal differences between this study and the positive intergroup trial relate to the timing of thoracic irradiation (delayed versus early) and the split-course schedule chosen for the twice-daily radiation arm of this study. The rationale for choosing split-course therapy was in part an attempt to reduce toxicity, and in part based on theoretical considerations suggesting that the cells would be entering an accelerated repopulation phase at the start of the second portion of twice-daily irradiation, making them more sensitive to the effects of treatment. At any rate, when administered according to this schedule, twice-daily radiation conferred no benefit over the conventional once-daily treatment.

7. The issue of total dose given in a daily method

Historically, most combined modality trials in limited small-cell carcinoma have employed total doses of thoracic irradiation in a rather modest dose range

between 45 and 50 Gy. These total doses, apparently chosen in light of the high radiosensitivity and responsiveness of this cell type, appear to be empirical and not based on tumour control, survival or toxicity data. The risk of locoregional failure remains high, certainly in excess of 50% and perhaps as high as 90%. This prompted a phase I study by Choi and colleagues in the Cancer and Leukemia Group B (CALGB) [10]. The study was designed to determine the maximum-tolerated dose of radiation in standard daily and hyperfractionated-accelerated twice-daily schedules, administered with concurrent chemotherapy, added concurrently at the third cycle. The maximum-tolerated dose of the twice-daily radiation was found to be 45 Gy in 30 fractions over 3 weeks; the dose-limiting toxicity was oesophagitis. For once-daily radiation, the maximum-tolerated dose was found to be at least 70 Gy in 35 fractions over 7 weeks.

The intergroup trial [4] reported a significant improvement in 5-year survival with twice-daily radiation compared with once-daily radiation, both using a dose of 45 Gy. Although the twice-daily regimen employed a maximum-tolerated dose achievable with this schedule; the once-daily regimen did not. Since the total delivered dose may be as important as dose intensity in radiation therapy, a reasonable hypothesis is that daily treatment administered to a maximum-tolerated dose, or at least a substantially higher dose than 45 Gy, might improve local control and survival. It would, therefore, be of interest to perform a phase III prospective randomised trial comparing hyperfractionated-accelerated twice-daily radiation with higher total dose daily radiation, with each given at or near the maximum-tolerated dose. Many US Cooperative Groups have employed pilots with doses of thoracic radiotherapy ranging between 60 (33% increase) and 70 (56% increase) Gy. It will take a trial to determine what radiotherapy dose given once daily is superior to the current best treatment, 45Gy administered in 3 weeks with a twice daily scheme.

Presently, there is no limited small-cell trial open in the United States. However, several groups are conducting pilot studies mostly of new agents. Moreover, no new agent study using two or three drug regimens has sufficient survival or long enough follow-up to endorse its use or propose it as a challenger to the established therapy, cisplatin etoposide and 45 Gy administered in 3 weeks. The NCI and its pilot assessing panel have rejected a dose comparison trial, and have refused to reconsider its verdict. Table 3 highlights facts to remember regarding thoracic radiotherapy.

8. Prophylactic cranial irradiation

In 1973, the high risk of brain relapse was appreciated, and the concept of the brain as a sanctuary site evolved from success in childhood leukaemia. PCI began as a way to head off relapse in this sanctuary site [2]. Not until the 1980s were numerous isolated reports of neurological dysfunction in patients who had received PCI as a part of their treatment reported [44–46]. The neurological problems included memory loss or intellectual/cognitive functional impairment and minimal gait or coordination deficits [46]. More serious problems: frank confusion, dysarthria, incontinence, inability to perform self-care, and requirement for custodial care were also reported. Computed axial tomography sometimes found evidence of leucoencephalopathy [44]. These reports arrived when PCI was considered to be effective in decreasing the risk of brain-recurrence, but had not yet been demonstrated to improve survival. These warnings dampened enthusiasm for the use of PCI and many abandoned it completely. Survival improvement was sought as a justification for its use. These reports arose from an era when PCI was used very early in the systemic treatment, commonly with doxorubicin, procarbazine, vinca alkaloids and nitrosoureas—some of which cross intact blood–brain barriers, others of which clearly enhance radiation toxicity normal tissue.

In the early 1990s, more scientific analyses of the aetiology of the neurotoxicity deficits were published, and the importance of the interaction between PCI and chemotherapy became suspect [47,48]. The sequence of treatment associated with the least neurological sequelae was found to be the administration of all the chemotherapy first, followed sequentially by PCI without further systemic treatment after the PCI. This was in keeping with the hypothesis that the brain irradiation increases the permeability of the blood–brain barrier, allowing passage of chemotherapeutic agents that are administered concurrently with or subsequent to radiation. Thus, the more severe toxicity encountered after concurrent chemotherapy and PCI should more accu-

Table 3
Radiotherapy in SCLC: summary

- ● The *de facto* standard is 45 Gy BID in 3 weeks
  - ○ We do not know the best total dose with daily radiotherapy
  - ○ 45–50 Gy is associated with >50% local failure

US Cooperative Group Study Pilots use >60 Gy

- ○ Inadequate experience at 70 Gy for safety

- ● Timing
  - ○ Data best: concurrent cycles 1 and 2
  - ○ Data worst: sequential post >4 cycles
- ● What is the target?
  - ○ Areas of actual involvement
  - ○ NOT elective nodes, NOT supraclavicular nodes
- ● What limits dose?
  - ○ Oesophagus—stricture, not acute toxicity
  - ○ Lung toxicity
  - ○ Spinal cord (unlikely)

SCLC, small-cell lung cancer; BID, twice daily.

rately have been attributed to the combined modality therapy, and not simply to the radiation. Additional potential factors include total radiation dose and dose per fraction. A commonly prescribed regimen of 25 Gy in 10 fractions of 2.5 Gy was widely used in the United States and has been considered to be both safe and effective [47]. However, the optimal dose to reduce brain relapse and maintain a survival advantage is not established.

Randomised trials, which included prospective neuropsychological assessments, comparing patients with small cell carcinoma in complete remission treated with PCI or with no PCI treatment, were subsequently published in the late 1990s [49,50]. These studies confirmed the fact that PCI significantly decreases the incidence of brain relapse and that there was no increase in neuropsychological dysfunction associated with the PCI. The Arriagada report used 3 Gy fractions and showed a cognitive dysfunction rate of less than 10% regardless of treatment with PCI or not [49]. Their strategy delivered the PCI after completion of all systemic therapy and did use 3 Gy fractions. While this should stem substantially concern about brain injury, the minimum follow-up was only 3 years so late brain problems remain a possibility. Importantly, the risk of brain relapse without PCI was 60% for patients observed without PCI.

While the individual trials confirmed the ability of PCI to decrease the incidence of recurrence in the brain, a statistically significant survival benefit could not be demonstrated from PCI when compared with a no PCI standard. Aupérin and colleagues [5] published a meta-analysis, which evaluated data on 987 patients with small-cell carcinoma in complete remission, who participated in seven randomised trials comparing PCI with no PCI. The main endpoint of the meta-analysis was survival. The administration of PCI increased 3-year survival from 15.3 to 20.7%, for an absolute increase of 5.4%. (This degree of improvement echoes the survival gain achieved with thoracic irradiation, also demonstrated by meta-analysis [40,41]. PCI was also shown to increase disease-free survival and decrease the cumulative incidence of brain metastases. While the meta-analysis included only patients who had achieved complete remission, the required imaging studies to determine response were variable and the authors speculated that PCI might also benefit patients who achieve a good partial remission as determined by the more sensitive imaging modalities used today. Some still doubt the benefit or fear the toxicity of PCI, but the facts point towards this as established therapy.

9. Surgery

The role of surgery in the management of limited small-cell carcinoma has been proposed, but remains unestablished. By itself, it is ineffective in small-cell lung cancer. Its role may be for a subset of the population that has a continued high risk of local failure and a population that is sufficiently fit to undergo thoracotomy and resection. Several studies have attempted to assess the contribution of surgical resection in these patients.

In 1982, Shields published a retrospective analysis of the results of small cell carcinoma patients that were included in the Veteran's Administration Surgical Oncology Group adjuvant trials. These were a series of randomised studies of adjuvant chemotherapy following surgical resection of all cell types of lung cancer [51]. Some of these trials demonstrated improved survival associated with the administration of adjuvant chemotherapy for resected small-cell carcinoma. Additionally, this analysis illustrated the profound prognostic importance of utilising the more detailed TNM staging classification for small-cell patients treated with surgery. The 5-year survival of $T_1N_0M_0$ patients was 59%, in comparison to 28% for $T_2N_0M_0$ and 31% for $T_1N_1M_0$ patients.

In 1984, Meyer published a retrospective review of limited small-cell carcinoma patients who had been treated with surgery and chemotherapy [52]. All of these patients underwent pre-operative mediastinoscopy. 10 patients with stage I or stage II disease underwent surgical resection followed by a full course of chemotherapy. 8 (80%) remained disease-free at 30 months of follow-up. 4 patients with T_3N_1 disease and 16 patients with N_2 disease were treated with two cycles of induction chemotherapy, followed by surgery in those who responded, and then additional chemotherapy and PCI. 2 (50%) of the T_3N_1 patients were disease-free at 30 months. The patients with N_2 disease did very poorly; only 10 of the 16 were resected, and all of them relapsed. The TNM staging system predicted different prognostic subgroups within the broad category of 'limited disease' that might benefit from surgery.

Surgery appears to provide no advantage to patients with N_2 disease. Therefore, it would seem prudent to perform mediastinoscopy prior to considering resection. In a series of 63 patients treated with surgery followed by adjuvant chemotherapy, with or without thoracic irradiation, and PCI published by Shepherd in Ref. [53], pre-operative mediastinoscopy had been performed in only 25 patients. 39 patients (62%) were upstaged at the time of surgery. The projected 5-year survival was 48% for $T_{1\text{-}2}N_0$ patients, 24.5% for N_1 patients, and 24% for T_3 or N_2 patients. The surgical pathology revealed pure small-cell carcinoma in 54 patients, but showed mixed small-cell and non-small cell carcinoma in 9. On pathological principle, surgery might be more beneficial for those patients with mixed histology tumours, in whom the non-small cell component would be expected to be less sensitive to chemotherapy. In this series, surgery

appeared to decrease the frequency of chest recurrence. Only 2 patients suffered an isolated locoregional relapse, and 5 others relapsed concurrently in the mediastinum and at distant sites. 3 of the 7 patients who had locoregional relapse had also received thoracic irradiation (25–35 Gy), a dose that would be considered inadequate by today's standards.

The following are précis of a small series suggesting a benefit of surgical treatment. Davis published a prospective study of 37 clinical stage I–II small cell carcinoma patients treated by surgery followed by six cycles of chemotherapy and PCI [54]. Despite pre-operative mediastinoscopy in all patients, many were upstaged at the time of surgery. Pre-operatively, there were 15 stage I and 22 stage II patients. Post-operatively, there were only 10 stage I, 14 stage II, and 8 stage III patients and 5 patients were not resected. 5-year survivals were 50, 35 and 21%, respectively, not including the unresected patients. Some investigators explored the approach of induction chemotherapy followed by surgery. These studies assess the feasibility of surgery; determine the influence of surgery on local recurrence and on long-term survival. Prospective surgical series still require selection of patients sufficiently fit medically to tolerate resection. Shepherd described a prospective study in which limited disease patients were treated initially with five to six cycles of chemotherapy and then restaged [55]. Responders were then offered resection, and subsequently received thoracic irradiation (25–35 Gy) and PCI afterwards. 72 patients were entered onto this study. After induction chemotherapy 57 (79%) patients were candidates for surgery, but only 38 (53%) actually underwent thoracotomy. Of these, 4 could not be resected, and 1 additional patient was not resected because there was no visible tumour present. Of the other 33 patients, less than half (46%) were resected. However, no survival advantage could be demonstrated for patients with N_2 disease. The patients who were found to have pathological stage I disease at surgery had a projected 5-year survival of 71%. In contrast, 0 of 6 clinical stage I patients who did not undergo surgery remain alive without recurrence. In addition, the risk of local recurrence was diminished by the addition of surgery in clinical Stage I patients, but not in stage II or III patients. Zatopek performed a prospective study in stage II–IIIB patients who received three cycles of induction chemotherapy followed by surgical resection [56]. Patients who failed to respond to chemotherapy or who had persistent T_4 or N_3 disease *were not* operated upon. The post-operative treatment in this trial consisted of three more cycles of chemotherapy with hyperfractionated thoracic irradiation integrated with chemotherapy, a boost of radiation to the areas where gross residual disease had remained after induction chemotherapy, and PCI. The therapy was tolerable demonstrating the feasibility of such an approach. 14 (56%) of 25 patients were able to undergo thoracotomy. 10 were resectable; 4, unresectable. 5 patients had achieved pathological complete remission.

These retrospective reviews and phase II studies suggest the feasibility of the combined modality approach and produced encouraging survival results in the select early-stage patients. Whether the favourable outcomes achieved were because of the surgery itself, the selection factors enabling surgery, or exclusion of the progressing and debilitated fraction of patients remains uncertain. It is clear that everyone cannot undergo surgery, and that everyone does not necessarily benefit.

A randomised trial was conducted by the Lung Cancer Study Group between 1983 and 1989 [57]. In this study, 328 patients with limited small-cell lung cancer were treated with five cycles of induction chemotherapy. Unfortunately, less than half achieved sufficient remission to be considered fit for a thoracotomy and were subsequently randomised to surgery versus no surgery. All of the 146 patients randomised also received thoracic irradiation and PCI. The resection rate was 83%. Pathological complete remission was achieved by 19% of patients. Nine percent were found to have residual cancer of non-small cell histology only; the small-cell component had been eradicated. The survival curves for the two arms of this study overlapped. Thus, this prospective randomised study, including only patients fit for surgery, did not support the inclusion of surgery in the management of limited small-cell carcinoma. While the previously cited literature would suggest that patients with N_2 disease might be the least likely to benefit from the inclusion of surgical resection in their care, this group actually constituted the majority of the patients randomised to surgery in the Lung Cancer Study Group trial. The exclusion of patients with peripheral nodules and the inclusion of a large proportion of N_2 patients likely contributed to the negative results of this randomised trial.

More recently, Eberhardt and colleagues report a phase II trial of combined modality therapy in selected stages IB to IIIB small cell carcinoma [58]. All of the patients were staged with mediastinoscopy. Those with IB to IIA disease were managed by four cycles of chemotherapy followed by surgery, followed by PCI. Patients with IIB to IIIA disease, however, were managed with an aggressive pre-operative regimen consisting of three cycles of induction chemotherapy, followed by a fourth cycle with concurrent hyperfractionated thoracic irradiation to 45 Gy. Subsequently, mediastinoscopy was repeated in those patients who had previously shown N_2 involvement. Those who had cleared their mediastinal nodes went on to surgery; those who had persistent mediastinal node involvement, received a boost of thoracic irradiation taking the total dose up to 60 Gy. All of these patients received PCI as well. At the beginning of this trial, IIIB patients were approached in

a non-surgical fashion with chemotherapy and radiation only. However, towards the end of the study, 2 of the IIIB patients were managed with the tri-modality approach described above for IIB to IIIA patients. 46 patients entered this trial. 24 of these were initially planned to undergo tri-modality therapy. 17 of these went on to surgery, while 2 refused, 1 had a decline in performance status precluding surgery, and 4 had other contraindications. 11 of 14 IIIA patients with initial N_2 involvement, and both of the IIIB patients who had repeat mediastinoscopy performed in anticipation of going on to thoracotomy, cleared their mediastinal nodes with the pre-operative regimen (81% were down-staged).

The 4 IIB patients and 18 IIIA patients were analysed together and achieved an impressive 50% 5-year survival. In this phase II study, the total number of patients amongst all stages who went to thoracotomy was only 24 (52% of the initial group). 23 of these were able to undergo complete resection. The 5-year survival of the completely resected group was 63%. 9 of the 23 have relapsed, 8 with isolated central nervous system relapse and 1 with liver metastasis. There have been no locoregional failures in this group. In contrast, amongst the 23 patients in the study who were not resected, there have been 6 (26%) locoregional failures as the first site of relapse; in 4 of these, it was the only site of relapse.

The potential role of surgery in the combined modality approach to limited-stage small cell remains undefined. For those patients with mixed histology tumours, the resection of the less chemotherapy-sensitive non-small cell component may be beneficial. In addition, at least in some circumstances, surgery appears to enhance locoregional control, and this in turn could potentially lead to an improvement in overall survival. Whether the inclusion of surgery as a portion of the combined modality treatment actually improves survival, however, remains a question that can only be answered by another prospective randomised trial.

10. Vaccine therapy

Small cell has tantalised clinicians with its high frequency of complete response rates and increasing 2- and 5-year survival, but the majority still fail and die of cancer. Dealing with this phenomenon has led to theories about identifying signals for who will fail and diagnosing a group with subclinical microscopic disease. Molecular biology has defined typical loss of heterozygosity of certain chromosomes, and even gene products residing in these regions on these chromosomes. We expect much from the bench in the next decade to perhaps identify specific targeted therapy that might be added to or even supplant traditional chemo-radiotherapy.

Vaccination has been proposed as a form of adjuvant treatment for those patients that have achieved a remission with standard therapy. The ganglioside GD3, a cell surface glycosphingolipid antigen expressed mostly on cells of neuroectodermal origin, seems to be expressed on most clinical small cell tumours tested and *in vitro* cell lines as well [59]. A mouse monoclonal antibody, BEC2, has been developed against the binding region of mouse monoclonal antibody R24, which binds to GD3 [60]. BEC2, when combined with Bacillus Calmette-Guérin (BCG) as an immune adjuvant, can then be utilised to induce an immune response against GD3.

Grant and colleagues immunised 15 small cell carcinoma patients who achieved partial or complete remission with standard therapy [61]. Each patient received a series of five immunisations of BEC2 plus BCG. Immunisation was confirmed by serum titres of anti-BEC2 human antimouse antibody (HAMA) and anti-GD3. All of the patients developed anti-BEC2 HAMA antibodies, and 5 of 13 patients who were evaluable for a serological response developed anti-GD3 antibodies. The median survival of the immunised patients was 20.5 months. The median time to relapse was 10.6 months for extensive disease patients and had not been reached for the limited disease patients after a median follow-up of 47 months.

The success of this approach has spurred the European Organization for Research and Treatment of Cancer (EORTC) to initiate the SILVA trial: 'Survival in an International Phase III Prospective Randomized Limited Disease Small Cell Lung Cancer Vaccination Study with Adjuvant BEC2 and BCG'. This study will determine in a randomised prospective manner, the role of adjuvant BEC2 plus BCG vaccination after the achievement of a partial or complete response with standard therapy.

11. Conclusions and future directions

Beyond the scope of this article is the potential exploitation of molecular distinctions of small-cell lung cancer. Small cell has fingerprinted defects in loss of the short arm of chromosome 3, defects in p-53 function, and mutations in the *rb* gene. Interestingly, there are not parallel losses in these factors in non-small cell lung cancer. Tumours produce potent stimuli to make their own vasculature. Anti-angiogenesis, a target attack on these abnormal vessels, has great intuitive appeal. These strategies may also be investigated in small-cell lung cancer. While offering great promise, these agents have not had successful first attempts in non-small cell lung cancer adjuvant settings, but the concept remains solid and the potential viable.

Table 4
SCLC issues

- ● How to integrate the new drugs
- ● Dose of thoracic radiotherapy (TRT)
- ● Is twice daily really the best TRT and is there a once daily equivalent?
  - ○ US trial proposal blocked by National Cancer Institute/Concept Evaluation Panel
- ● Volume of irradiation
- ● TRT Timing with chemotherapy
  - ○ Concurrent; early; perhaps a chemotherapy issue—need to use a compatible regimen
  - ○ NOT doxorubicin
- ● Timing and dose of prophylactic cranial irradiation
- ● Role of surgery
- ● Are vaccines ready?

SCLC, small-cell lung cancer; US, United States.

12. Summary of standard therapies

Table 4 emphasises the current issues facing clinical researchers. Despite the fact that we know we need radiotherapy, we do not know what dose, what volume, or what timing produces the best effects. The Intergroup results [4] are the *de facto* standard despite the reluctance of many to use twice-daily radiotherapy. The obvious necessary trial, a comparison of the twice daily 45 Gy in 3 weeks to a higher dose once daily has been stubbornly rejected in the United States. The variables of volume and timing are also worthy of trial, but perhaps a little less pressing in importance. PCI is an established modality with proof in principle studies showing remarkable reduction of brain relapse and a meta-analysis clearly showing a survival advantage. There remains a small army of the unconvinced who require more safety data. However, the nay-sayers occupy a position in the minority. They may be right, but they need to make their case with more than ideas and theory.

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