Limited Small-Cell Lung Cancer: A Potentially Curable Disease

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Patients with limited-stage small-cell carcinoma of the lung are treated with combined-modality therapy with the intent to cure. Standard therapy consists of platinum-based combination chemotherapy, thoracic irradiation, and

Introduction

During the past 3 decades, progress has inched forward in the management of limited small-cell carcinoma of the lung. Prior to the 1970s, patients were managed largely with surgery alone or radiation therapy alone. In 1969, the British Medical Research Council reported 5-year survival rates of only 1% with surgery and 4% with radiotherapy.[1]

In the early 1970s, the ability of small-cell carcinoma to disseminate early prompted clinical trials focusing on systemic management with chemotherapy.[2] Initial results with chemotherapy, yielding a four- to fivefold increase in median survival, generated great enthusiasm and the hope that outcomes similar to those achieved with other chemosensitive tumors would be forthcoming.[3] Now, almost 30 years later, high rates of local and distant relapse, including central nervous system relapse, continue to thwart efforts to achieve this elusive goal.

Nevertheless, real progress has been made, and the use of combination chemotherapy, concurrent thoracic radiotherapy, and prophylactic cranial irradiation have led to 5-year survival rates as high as 26%.[4] New chemotherapeutic agents with significant activity against small-cell carcinoma are emerging, and refinements in radiotherapeutic technique are producing not only improvements in local control, but survival benefits as well.[4] This article will review the current approach to limited small-cell carcinoma of the lung, and will explore unanswered questions and future directions.

Staging/Definition of Limited Disease

The overwhelming tendency of small-cell carcinoma of the lung is to disseminate early. This has taught us that even when a rigorous search fails to find distant metastases, the best approach is to treat limited small-cell carcinoma of the lung as a systemic disease, with chemotherapy as the cornerstone of treatment. As a result, there is less emphasis on the TNM classification, which is more appropriate when surgery is being considered. Instead, a simplified staging system of “limited disease” vs “extensive disease” is used.

The limited-disease category includes patients whose disease may be encompassed within a radiation portal. Ambiguities about pleural effusion and nodal stations cause some confusion in categorizing small-cell lung cancer as limited or extensive. The presence of an ipsilateral pleural effusion frequently, though not uniformly,[5] excludes patients from limited-disease protocols, although technically this is considered limited disease. Some investigators include within the limited-disease category patients with minimal pleural effusions not felt to be easily accessible for cytologic diagnosis; this includes those with blunting of the costophrenic angle on chest radiographs, as well as those with effusions seen only on chest computed tomography (CT).[6] Many investigators,[7-9] however, exclude all patients with demonstrated pleural effusions by any study, including chest CT.

Similar variability in the definition of limited disease occurs with reference to the extent of lymphadenopathy. Some studies include patients with bilateral supraclavicular adenopathy in the limited-disease category[10]; others[4,6] include only those with ipsilateral adenopathy. Likewise, some investigators include patients with contralateral hilar adenopathy in the limited-disease category[9]; others exclude them.[4] These variations reflect a change in approach from a time when all nodal stations were targeted by radiotherapy ports to the more recent policy of including only nodes with obvious involvement radiographically.

In addition to the variability in the definition of limited-stage disease, current imaging techniques detect more extrathoracic disease than did planar images. In many of the older studies, thoracic...
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imaging consisted only of chest radiographs.[7,11,12] Current staging minimally includes chest CT extending through the liver and adrenals (Table 1). Because the brain is a common site of metastatic disease in small-cell lung cancer, imaging of the brain by CT or magnetic resonance imaging (MRI) remains sensible. A radionuclide bone scan is also frequently performed. However, bone marrow aspiration and biopsy—once a routine staging procedure—is no longer required. Bone marrow involvement as the sole manifestation of extensive disease is quite rare, occurring in only 1.7% of patients.[13] Thus, this invasive procedure, and the associated discomfort, may be omitted.

At present, positron-emission tomography (PET) has no defined role in the routine staging evaluation of small-cell carcinoma patients. However, use of this highly sensitive imaging modality is increasingly being explored in a variety of oncologic settings. It has the potential to become a very useful staging procedure for small-cell carcinoma patients and may prove beneficial in terms of monitoring their response to therapy.[14] The precise role of PET scanning in small-cell carcinoma will emerge in the next decade.

As imaging modalities continue to improve, the ability to detect disease outside of what might be “encompassed within a radiation portal” will continue to increase. Patients who would previously have been classified as having limited-stage disease will be found to have extensive-stage disease. This stage migration will appear to improve the outcome of both limited- and extensive-disease patients, another example of the Will Rogers phenomenon.[15]

**Chemotherapy**

In the 1970s, chemotherapy regimens consisted of single-agent alkylators and then combinations based on alkylating agents (mainly cyclophosphamide [Cytoxan, Neosar]). One of the most commonly prescribed regimens throughout the 1980s was CAV (cyclophosphamide, doxorubicin [Adriamycin], and vincristine [Oncovin]). Doxorubicin was considered highly effective—“the paclitaxel (Taxol) of the 1970s.” This regimen produced excellent response rates, but the majority of patients relapsed both locally and systemically. Also, the inclusion of doxorubicin created havoc in regimens combining chemotherapy with radiation therapy, because doxorubicin potentiated radiation-induced toxicity and caused radiation recall.

**Cisplatin and Etoposide**

In the late 1970s, a regimen consisting of cisplatin (Platinol) and etoposide was developed.[16,17] Preclinical studies suggested a marked synergy with this combination, whereas single-agent therapy with cisplatin had produced a response rate of only 10%. [18] The combination was studied as salvage therapy for patients with recurrent or refractory small-cell carcinoma and was associated with response rates as high as 52%.[19] Cisplatin/etoposide was investigated as first-line therapy, and was found to be highly active and amenable to combination with concurrent thoracic irradiation. The regimen proved to be equivalent or superior to all previous combinations[20] and in the 1980s became the treatment of choice for limited small-cell carcinoma.

A prospective, randomized trial of standard-dose cisplatin/etoposide (cisplatin, 80 mg/m² IV on day 1, and etoposide, 80 mg/m² IV on days 1 to 3, repeated every 3 weeks) compared to high-dose cisplatin/etoposide (cisplatin, 27 mg/m² IV on days 1 to 5, and etoposide, 80 mg/m² IV on days 1 to 5, repeated every 3 weeks) showed no improvement in efficacy and a substantial increase in toxicity in the high-dose arm.[21] Even standard-dose cisplatin regimens, however, produce significant toxicity, most notably nausea, vomiting, nephrotoxicity, and neuropathy.

**Carboplatin**

Carboplatin (Paraplatin) may have a more favorable toxicity profile, and has been used instead of cisplatin. The carboplatin/etoposide combination has also demonstrated excellent activity in small-cell carcinoma, and in a prospective randomized phase III trial conducted by the Hellenic Cooperative Oncology Group, carboplatin/etoposide was associated with equal efficacy and less toxicity than the cisplatin/etoposide combination.[22]

Because of the equivalent efficacy and favorable toxicity profile of carboplatin, many clinicians prefer carboplatin/etoposide over cisplatin/etoposide. The combination of a platinum compound with etoposide remains 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.

**Paclitaxel**

Paclitaxel was introduced in 1993, and phase II studies demonstrated considerable single-agent activity in previously untreated and treated small-cell lung cancer patients (Table 2).[23-25] Greco and Hainsworth added paclitaxel as a 1-hour infusion to a commonly used combination of carboplatin/etoposide.[26] Hainsworth et al started with modest doses of paclitaxel (135 mg/m²) and
carboplatin (area under the concentration-time curve [AUC in mg/mL · min] = 5), but because the myelosuppression that developed with this regimen was manageable, the investigators subsequently treated a larger number of patients with increased doses of paclitaxel (200 mg/m²) and carboplatin (AUC = 6).[27] This study included previously untreated small-cell carcinoma patients with limited or extensive disease. Limited-disease patients received thoracic irradiation at 1.8 Gy/d to a total dose of 45 Gy over 5 weeks, beginning concurrently with cycle 3 of the chemotherapy. While response and toxicity data were promising, this three-drug combination is costly, and whether it will prove superior to the combination of carboplatin/etoposide chemotherapy awaits the results of a prospective, randomized trial.

Paclitaxel has also been combined with the cisplatin/etoposide regimen. This combination has produced a response rate of 94% in extensive-disease patients.[28] Recently, a multi-institutional phase I/II study of this regimen administered with concurrent thoracic irradiation to limited-disease small-cell carcinoma patients was published.[29] In this trial, four 21-day cycles of chemotherapy were administered, concurrently with thoracic irradiation given at a total dose of 45 Gy over 5 weeks, beginning on day 1 of cycle 1. Cisplatin, 60 mg/m², was given on day 2 of all cycles. Etoposide was given at a lower dose, 60 mg/m²/d, on days 1 to 3 of cycles 1 and 2 (with concurrent radiation), and at a higher dose, 80 mg/m²/d, on days 1 to 3, during cycles 3 and 4. Granulocyte-colony stimulating factor (G-CSF [Neupogen]) was added during cycles 3 and 4. During the phase I portion of the trial, the paclitaxel dose during cycles 1 and 2 was escalated to determine the maximum tolerated dose with concurrent radiation. This was found to be 135 mg/m², administered intravenously over 3 hours on day 1; grade 4 neutropenia was the dose-limiting toxicity. During cycles 3 and 4, paclitaxel was given at 170 mg/m². The overall response rate for this regimen was 96%, with 39% complete responses. Again, the question of whether this active, but costly, three-drug regimen is superior to standard cisplatin/etoposide in terms of survival cannot be answered without a prospective, randomized trial.

### Topoisomerase I Inhibitors

The topoisomerase I inhibitors, topotecan (Hycamtin) and irinotecan (Camptosar), have also been shown to have significant activity against small-cell carcinoma. Topotecan (Table 3) has been studied in the salvage setting, where it yielded response rates of 14% to 38% in patients with sensitive disease—ie, those who responded to first-line chemotherapy and subsequently relapsed more than 3 months after their chemotherapy was discontinued.[30-33] Topotecan was noted to be considerably less effective in patients with refractory small-cell carcinoma, where response rates ranged from 2% to 11%.[30-32,34] In previously untreated extensive-disease patients, a response rate of 39% has been reported.[35]

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.[36] Preliminary results show an 81% response rate.

The combination of topotecan and paclitaxel has been shown to be active by several investigators (Table 4).[37-39] A study in limited-disease patients is currently being conducted by the Cancer and Leukemia Group B (CALGB). In this protocol, patients initially undergo two cycles of induction chemotherapy with the new combination of topotecan/paclitaxel with G-CSF support. They subsequently receive the standard regimen of carboplatin/etoposide for three cycles. Thoracic irradiation is given starting with the first cycle of carboplatin/etoposide: A 60-Gy total dose is being administered to the first 10 patients; then, if well tolerated, a 70-Gy total dose. Prophylactic cranial irradiation is given starting with the first cycle of carboplatin/etoposide: A 60-Gy total dose is being administered to the first 10 patients; then, if well tolerated, a 70-Gy total dose. Prophylactic cranial irradiation is required for those who achieve complete or very good partial remissions.

Irinotecan has also shown substantial activity in previously treated small-cell carcinoma patients (Table 5).[40-42] A phase II study, including both limited-disease and extensive-disease patients, evaluated the combination of irinotecan, 60 mg/m² on days 1, 8, and 15, with cisplatin, 60 mg/m² on day 1, every 28 days.[43] Patients with limited disease received four cycles of chemotherapy followed by thoracic irradiation to a dose of 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 diarrhea.

This chemotherapy regimen has also been explored with concurrent thoracic irradiation in limited-disease small-cell lung cancer patients.[44] In this setting, the dose-limiting toxicity was fatigue, and the recommended regimen for future study is irinotecan, 40 mg/m² on days 1, 8, and 15, with cisplatin, 60 mg/m² 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 randomized phase III study in extensive-disease patients compared cisplatin/irinotecan to the standard regimen of cisplatin/etoposide.[45] The response rate was 89%
with cisplatin/irinotecan; 67% with cisplatin/etoposide. Median survival and 1-year survival rate were 420 days and 60%, respectively, with cisplatin/irinotecan; 300 days and 40% with cisplatin/etoposide. The survival benefit was statistically significant ($P = .0047$; log-rank test). Irinotecan has also been combined with etoposide in the salvage setting. Masuda et al[46] treated 25 patients with relapsed or refractory small-cell carcinoma, all of whom had received prior platinum-based combination chemotherapy. Treatment was administered with G-CSF support. The major toxicities were myelosuppression and diarrhea. This highly active regimen achieved a 71% response rate and a median survival of 271 days. 

Thus, the last several years have brought new chemotherapeutic agents with novel mechanisms of action into the therapy of small-cell carcinoma. Encouraging results obtained in both the salvage and extensive-disease settings have paved the way for using these new agents in the treatment of limited disease. The results of ongoing trials exploring various ways of combining or sequencing these agents with each other, with standard regimens, and with thoracic irradiation are anxiously awaited.

**High-Dose Chemotherapy**

As yet, there is no defined role for high-dose chemotherapy with autologous transplant in small-cell carcinoma. Humblet et al[47] treated 101 small-cell lung cancer patients with induction chemotherapy and then randomized 45 responding patients to either one cycle of high-dose therapy, consisting of high-dose etoposide, cyclophosphamide, and carmustine (BCNU [BiCNU]) with marrow support, or one additional cycle of conventional-dose therapy. Although the high-dose regimen produced more complete responses, there was a 17% toxic death rate in the autologous marrow transplant arm, and no benefit in terms of overall survival. In patients who relapsed, there was a very high incidence of chest recurrence, likely related to the omission of thoracic irradiation in this trial.

Elias et al[48] 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. The 36 patients meeting these criteria subsequently received high-dose cyclophosphamide, cisplatin, and carmustine with hematologic stem-cell support. Patients who had not received thoracic irradiation during induction therapy were treated with consolidative thoracic irradiation and prophylactic cranial irradiation after recovery from the acute toxicity of high-dose therapy.

In this study, the 5-year survival rate after high-dose therapy was 41%. For the 29 patients who 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%. While these results are of interest, the role of high-dose therapy in responding limited-disease small-cell carcinoma patients remains uncertain and requires a prospective randomized trial.

**Thoracic Irradiation**

While combination chemotherapy produces high response rates in patients with limited-disease small-cell carcinoma, the risk of relapse within the chest remains exceedingly high (> 70%)[49] after treatment with chemotherapy alone. Numerous prospective, randomized trials conducted in the 1970s and 1980s compared chemotherapy alone to chemotherapy with thoracic irradiation. The majority of these studies demonstrated a substantial improvement in local control with the addition of radiation. Based on the information provided by individual studies, however, the impact on survival was not conclusive.

Two meta-analyses[50,51] reported a benefit of about 5% in overall survival at 3 years for chemotherapy plus thoracic irradiation. Specifically, 3-year survival was 8.9% ± 0.9% among patients receiving chemotherapy only, compared with 14.3 ± 1.1% for combined-modality recipients.[51] While this increase seems modest, the improvement from 8.9% to 14.3% represents a 60% relative improvement with combined-modality treatment compared to chemotherapy alone. The trials included in the meta-analyses used induction chemotherapy regimens that were cyclophosphamide- or doxorubicin-based, not the cisplatin/etoposide regimen. Because these earlier regimens were significantly less amenable to administration with concurrent thoracic irradiation, no conclusions can be drawn from the meta-analyses regarding the optimal timing and sequencing of chemotherapy and radiation.

**Timing**

Variations in the timing of thoracic irradiation have been explored in prospective, randomized trials.
In one such study by the National Cancer Institute of Canada Clinical Trials Group, patients were treated with cyclophosphamide/doxorubicin/vincristine alternating with cisplatin/etoposide every 3 weeks for six cycles, and were randomized to receive 40 Gy of thoracic irradiation beginning concurrently with either the first or the last cycle of cisplatin/etoposide.[7] Progression-free survival and overall survival were superior in the arm that included early radiation.

In another prospective, randomized trial, however, CALGB compared three arms: chemotherapy alone (a cyclophosphamide-based regimen), chemotherapy with early radiotherapy (concurrent with cycle 1), and chemotherapy with delayed radiotherapy (concurrent with cycle 4).[40] Although the groups that included thoracic irradiation reported superior responses to those achieved with chemotherapy alone, delayed radiotherapy compared more favorably to early radiotherapy. The myelosuppression caused by early concurrent therapy and the decreased dose-intensity of chemotherapy in this study led to very modest survival rates in all arms. The diminished, less effective chemotherapy administered makes the issue of timing of thoracic irradiation harder to emphasize in this trial.

Takada et al.[52] compared concurrent vs sequential thoracic irradiation administered with cisplatin/etoposide chemotherapy. Early concurrent therapy was significantly superior to sequential treatment in which the radiation was given after four cycles of chemotherapy had been completed.

**Volume**

Firm conclusions cannot be drawn regarding the precise optimal timing of thoracic irradiation. The etoposide/platinum-based regimens, however, have made the administration of full-dose concurrent therapy possible, and this appears to convey advantages for survival. The administration of one or two cycles of chemotherapy prior to starting concurrent therapy allows an assessment of response to the chosen chemotherapy regimen and reduces the size of the target for thoracic radiotherapy in responding tumors.

A Southwest Oncology Group study randomized partial responders to induction chemotherapy to receive wide-field radiotherapy (directed at the prechemotherapy tumor volume) or reduced-volume radiotherapy (directed at the postchemotherapy target). The size of chest irradiation portals did not alter survival or relapse patterns.[12] Thus, there is a rationale for delaying the administration of concurrent thoracic irradiation briefly, to allow one or two cycles of induction chemotherapy to be administered.

Today, with improved imaging, target identification, and beam directions, avoiding irradiation of normal tissue not clearly involved with gross tumor seems to be a rational approach. Radiotherapy should be used to address gross disease that harbors chemotherapy-resistant clones, and chemotherapy can be used to manage microscopic disease in either CT- or PET-negative sites.

**Fractionation**

An in vitro radiation survival curve describes different aspects of radiation killing. The linear portion of the curve reflects the dose-regions where exponential killing is seen. For non–small-cell carcinoma and most normal tissues, higher doses of irradiation are required to overcome the initial shoulder in order to produce exponential cytotoxicity. Small-cell lung cancer cell lines are exquisitely sensitive to radiation, and even at very small doses,[53] exponential cell kill occurs. In the clinic, these low fractional doses cause less damage to normal tissues. Therefore, multiple small fractions of irradiation would be expected to effectively kill small-cell carcinoma cells and, at the same time, reduce the permanent damage and lessen late toxicity to normal tissues.

Clinical pilot studies of twice-daily thoracic irradiation combined with cisplatin/etoposide led to an Intergroup phase III trial of this approach compared to conventional once-daily irradiation with the same chemotherapy.[4] A total of 417 patients were randomized to receive 45 Gy of concurrent thoracic radiotherapy given either twice daily over 3 weeks or once daily over 5 weeks. All the patients received four 21-day cycles of cisplatin/etoposide, and irradiation began concurrently with cycle 1. For complete responders, the protocol mandated prophylactic cranial irradiation; however, it was not provided in all cases.

Twice-daily radiation proved superior, producing a 5-year survival rate of 26%, compared to 16% with once-daily radiation. While grade 3 esophagitis occurred significantly more frequently with twice-daily irradiation (27% vs 11%), there were no permanent strictures.

Bonner et al.[6] presented data on another phase III trial comparing twice-daily vs once-daily thoracic irradiation with cisplatin/etoposide. In this study, patients were treated with three cycles of induction cisplatin/etoposide before concurrent thoracic radiation therapy. After the induction chemotherapy, those in whom disease did not progress to a distant site (other than the brain) were randomized to receive twice-daily vs once-daily thoracic irradiation administered concurrently with two additional cycles of cisplatin/etoposide.
The twice-daily irradiation was administered as a split course—a 48-Gy total dose in 32 fractions, with a 2.5-week break given after the initial 24 Gy. The split course was intended to reduce acute esophagitis, and this strategy was successful. The once-daily irradiation consisted of 50.4 Gy in 28 fractions. After completion of thoracic irradiation, a sixth cycle of cisplatin/etoposide was administered. Complete responders received prophylactic cranial irradiation. In this study, 262 patients were randomized to twice-daily vs once-daily radiation. There was no difference in survival. The principal differences between this study and the Intergroup trial relate to the timing of thoracic irradiation (delayed vs early) and the split-course schedule chosen for the twice-daily radiation arm. While delayed split-course, twice-daily treatment reduced toxicity, it failed to improve survival. Although the Intergroup study showed a benefit with twice-daily radiation, one might postulate that even a slightly larger total dose given once daily could be equivalent, and a substantially higher dose might be superior.

**Dose**

Since 1990, most combined-modality trials in limited small-cell carcinoma have used total doses of thoracic irradiation ranging from 45 to 50 Gy. These moderate doses, chosen because of the high clinical responsiveness of this cell type, produced local failures ≥ 50%. This observation prompted a phase I study by Choi et al.[10] to probe for the maximum tolerated dose of radiation in standard daily and hyperfractionated-accelerated twice-daily schedules, when administered with concurrent chemotherapy. Given the predetermined dose-limiting toxicity of acute esophagitis, the maximum tolerated dose of twice-daily radiation was 45 Gy in 30 fractions over 3 weeks. For once-daily radiation, the maximum tolerated dose was at least 70 Gy in 35 fractions over 7 weeks. These doses were given to prechemotherapy volumes, and concurrent therapy was begun with cycle 3. Whether these are truly dose-limiting or maximally tolerated doses is debatable, but they do pose a reasonable question: Is a substantially larger dose given once daily better than the twice-daily dose of 45 Gy? Determining what dose to test remains a dilemma for a successor Intergroup study.

**Prophylactic Cranial Irradiation**

In 1973, when initial reports of the significant activity of chemotherapy in small-cell carcinoma were generating great enthusiasm, the risk of relapse in the brain was appreciated. Using the model of acute lymphocytic leukemia, prophylactic cranial irradiation was introduced in small-cell lung cancer to treat occult disease in this “sanctuary” site.[2] As this approach was pursued in the 1980s, numerous cases were reported of neurologic dysfunction in patients who had received prophylactic cranial irradiation as part of their treatment.[54-56] The described neurologic dysfunction ranged from subclinical decrease in memory or intellectual functioning and minimal gait or coordination deficits[47] to frank confusion, dysarthria, incontinence, inability to care for oneself, and CT evidence of leukoencephalopathy.[56] These reports appeared at a time when prophylactic cranial irradiation was considered effective in decreasing the risk of brain recurrence, but not in improving survival. Consequently, the clinical community moved away from the routine incorporation of prophylactic cranial irradiation in the treatment of small-cell carcinoma. These reports were observational and did not detail cumulative levels of brain dysfunction, nor did they include baseline cognitive function tests performed before the administration of chemotherapy or before prophylactic cranial irradiation. Prophylactic cranial irradiation was usually performed during the first one to four cycles of chemotherapy, and in many cases, the chemotherapy continued for as long as 2 years. Many of the chemotherapy agents used at that time crossed the blood-brain barrier and were associated with known neurotoxicity.

There have been no reports of central nervous system toxicity since oncologists started using the platinum/etoposide regimens, in which fewer cycles of chemotherapy are used, and no chemotherapy is given after the administration of prophylactic cranial irradiation. This is in keeping with the concept that brain irradiation increases the permeability of the blood-brain barrier, allowing greater penetration of chemotherapeutic agents that are administered concurrently with or subsequent to radiation.

Additional factors that may affect the degree of neurotoxicity encountered include total radiation dose and dose per fraction. A commonly prescribed regimen of 25 Gy in 10 fractions is considered to be both safe and effective.[57] Randomized trials that included neuropsychological assessments, comparing prophylactic cranial irradiation with no prophylactic cranial irradiation in patients with small-cell carcinoma in complete remission, were subsequently published in the late 1990s.[58,59] These studies confirmed that prophylactic cranial irradiation significantly decreases the incidence of brain metastases, and
demonstrated that there was no increase in neuropsychological dysfunction due to therapy. While individual trials confirmed the ability of prophylactic cranial irradiation to decrease the incidence of recurrence in the brain, a statistically significant survival benefit could not be demonstrated by any single trial. In 1999, Aupérin et al.[60] published a meta-analysis that evaluated data on 987 patients with small-cell carcinoma in complete remission, from seven randomized trials that compared prophylactic cranial irradiation with no prophylactic cranial irradiation. The main end point of the meta-analysis was survival. The administration of prophylactic cranial irradiation increased 3-year survival from 15.3% to 20.7%, for an absolute increase of 5.4%—similar to the survival gain achieved with thoracic irradiation.[50,51]

Prophylactic cranial irradiation 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 imaging studies required to determine response were variable, and the authors speculated that prophylactic cranial irradiation might also benefit patients who achieve a good partial remission as determined by the more sensitive imaging modalities used today.

Prophylactic cranial irradiation clearly reduces the brain relapse rate and modestly improves survival. Without prophylactic cranial irradiation, the risk of brain relapse is 50% to 60%, and patients suffer neurologic and neurocognitive deficits that are not always ameliorated by therapeutic irradiation. Prophylactic cranial irradiation is therefore mandatory for all complete responders. We lack firm data on the long-term cumulative incidence of neurotoxicity and need to determine what dose, fractionation, and timing minimizes neurocognitive damage and maximizes control of brain metastasis and survival. It seems that the magnitude of risk of brain metastasis remains underappreciated, and the risk of neurocognitive damage, remarkably inflated. While some debate may continue about excellent partial responders, the elderly, and extensive-disease patients, the risk and consequences of brain relapse seem to outweigh the toxicity associated with this treatment.

Conclusions and Future Directions

In summary, during the past 30 years we have seen the 5-year survival rate for limited small-cell carcinoma patients rise from 1% with surgery to 26% with combination chemotherapy, hyperfractionated-accelerated thoracic radiotherapy, and prophylactic cranial irradiation. In the past 10 years, we have witnessed the development of several new chemotherapeutic agents that have demonstrated significant activity in this disease. The next 10 years of trials will undoubtedly explore the various options of combining and sequencing these agents with platinum-based regimens, each other, and thoracic irradiation.

While new cytotoxic agents were emerging in the 1990s, technical advances in imaging and the administration of radiotherapy developed in parallel. Three-dimensional conformal technique, hyperfractionated-accelerated therapy, and dose escalation studies promise to contribute to improving therapeutic outcomes.

Thoracic irradiation and prophylactic cranial irradiation, once thought to be beneficial only in reducing regional recurrence and central nervous system recurrence, respectively, actually convey overall survival benefits. Questions remain regarding optimal dose, fractionation schemes, and treatment volumes. Issues surrounding the optimal timing and sequencing of thoracic irradiation with both established and new cytotoxic agents also remain to be explored.

While these advances make this an exciting period in small-cell carcinoma research, we have miles to go to improve local, brain, and systemic control rates. We have acquired many new tools to fight this disease in the past decade. Hopefully, the next decade of clinical trials will teach us how best to use them.

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