A Review of First-Line Treatment for Small-cell Lung Cancer

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Although small-cell lung cancer (SCLC) makes up a smaller proportion of all lung cancers than it did 25 years ago, it remains a common cause of cancer mortality that requires more clinical and basic research than is currently underway. Trials of newer chemotherapy variations have failed to produce a regimen that is clearly superior to the two-drug combination of etoposide and cisplatin, which remains the standard of care for both limited and extensive stage SCLC. Paradoxically, advances in this systemic disease have come from radiotherapy innovations for limited SCLC, including addition of thoracic irradiation to systemic chemotherapy, more intense thoracic irradiation, early integration of thoracic irradiation with systemic chemotherapy, and prophylactic cranial irradiation.

Key Words: Small-cell lung cancer, Chemoradiation, Chemotherapy, Staging.

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In the 1970s, small-cell lung cancer (SCLC) was estimated to account for 20 to 25% of all lung cancers.[1] At the height of the lung cancer epidemic for male patients in 1986, an analysis of the Surveillance, Epidemiology and End Results database showed that the actual proportion of SCLC cases was 17.2%.[2] The percentage continued downward to 13.8% of all lung cancers in North America by 1998. This declining incidence of SCLC parallels a stalling in the pace of investigation, as reflected by the number of abstracts submitted to the American Society of Clinical Oncology over the past 25 years (Figure 1). In contrast, the number of abstracts for non–small cell lung cancer (NSCLC) has skyrocketed. The slow pace of SCLC investigation is unfortunate and puzzling because the proportion of estimated deaths from this disease is approximately 4% of all cancer mortality.[3] The number of patients dying as a result of SCLC is similar to that of ovarian cancer, leukemia, and non-Hodgkin's lymphoma, all of which have robust investigational agendas.

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THE IMPORTANCE OF STAGING

Accurate staging determines the intent and structure of the treatment program. Although there is no worldwide agreement and the origins are rooted in studies from another generation, the Veterans Administration Lung Group system[4] is most widely used in North America. That staging system, which divided patients into either *limited* or *extensive* stages, has been durable for SCLC because of its simplicity and reliable prognostic value. Limited-stage SCLC (LSCLC) is defined as tumor confined to one hemithorax and the regional lymph nodes, whereas extensive-stage small cell lung cancer (ESCLC) is defined as disease beyond these bounds. The original operational definition of limited disease was tumor quantity and configuration that could be encompassed by a "reasonable" radiotherapy treatment volume. Because long-term survival is uncommon (5–7%) when chemotherapy alone is used to treat LSCLC,[5] the "reasonable radiotherapy port" rule continues to be of practical importance in the assembly of combined-modality therapy programs that increase the long-term survival rate to over 20%. SCLC typically spreads early, with 60 to 70% of patients having ESCLC with metastases outside the limited-stage definition. Although patients with "regional" extensive stage disease such as pleural effusions and contralateral hilar and supraclavicular nodes may be given combined-modality therapy with a small chance of cure, ESCLC is typically treated with palliative intent. In addition to limited stage, other pretreatment prognostic factors associated with a favorable outcome in Cox regression analyses include good performance status, a low alkaline phosphatase level, a normal lactate dehydrogenase, and female gender.[6–8] Many have argued that the use of the TNM system used by the American Joint Committee on Cancer and the International Union Against Cancer delivers consistency with other disease sites and NSCLC. The International Association for the Study of Lung Cancer staging committee will make recommendations in the upcoming year to address these issues based on worldwide databases. What influence positron emission tomographic scanning has on staging and treatment will not be addressed for some years because of a paucity of data in SCLC.

The natural history of untreated SCLC is dismal, with a median survival of only 2 months for ESCLC and 3 months for LSCLC.[4] Over 40 years ago, it was recognized that SCLC was more responsive than NSCLC to both ionizing radiation and many cytotoxic drugs.[4,9] However, after decades of clinical research, SCLC has proved less tractable than most thought it would. It has become clear that despite higher response rates and some complete responses to combination

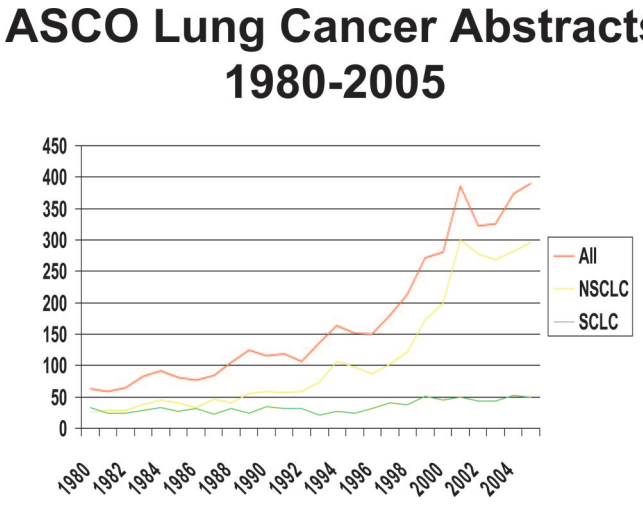

FIGURE 1. Numbers of abstracts published for American Society of Clinical Oncology annual meetings between 1980 and 2006 for (1) all lung cancer; (2) non-small-cell lung cancer; (3) small-cell lung cancer.

chemotherapy, the survival outcome for ESCLC is similar to metastatic NSCLC. Moreover, the median survival and the proportion of long-term survivors of patients treated with chemoradiation for LSCLC and stage III NSCLC are approximately the same.[10,11] The time required for treatment-resistant clones to cause a fatal outcome is similar for SCLC and NSCLC. Both are virulent epithelial neoplasms that respond somewhat to radiotherapy and chemotherapy.

STANDARD CHEMOTHERAPY REGIMENS FOR SCLC

A major step in the systemic treatment of SCLC was reported in 1969, when alkylating agents were compared to an inert compound in approximately 2000 lung cancer patients at a group of Veterans Administration Hospitals.[4] Antitumor effects of chemotherapy were analyzed according to cell type, and improvement in survival was the sole criterion of drug activity. Although the 4-month median survival for SCLC patients was only slightly better than the 1.5-month median survival of inert compound–treated patients ($p = 0.0005$), the trial was the first to show a statistically significant survival benefit of chemotherapy in lung cancer. Cyclophosphamide became a cornerstone in successful SCLC treatment, as was nitrogen mustard in the MOPP regimen (mechlorethamine, Oncovin [vincristine], procarbazine, and prednisone) in treatment of Hodgkin's disease.

Although the magic combination never emerged, the power of chemotherapy was clearly improved with multiagent chemotherapy. Many permutations and variations of protocols containing five drugs (cyclophosphamide, doxorubicin, vincristine, etoposide, and cisplatin) or their analogues have been reported and a number of regimens have been used in phase III studies. In 1975, Einhorn and colleagues[12] combined cyclophosphamide, doxorubicin, and vincristine (CAV); not only were high response rates produced but complete responses were observed in 20% of cases. It is notable and somewhat disconcerting that the CAV regimen and cyclophosphamide, doxorubicin, and etoposide (CAE) have persisted as standard combinations for 30 years. Interest in the combination of etoposide and cisplatin (EP)[13] was stimulated after it was shown to produce tumor regression in patients whose cancers had progressed following initial drug treatment with a cyclophosphamide-based regimen.[14] The consistent performance of EP or carboplatin and etoposide in clinical trials plus the bonus of its compatibility with radiotherapy has made it a standard of such durability that it persists as the treatment of choice.[15]

INVESTIGATIONAL CHEMOTHERAPY FOR EXTENSIVE STAGE SCLC

Extensive stage SCLC remains impervious to chemotherapy innovations. At the most basic level, it was easily demonstrated that monotherapy is inferior to combination chemotherapy.[16,17] However, beyond that, it has not been shown conclusively that any innovation of chemotherapy has been associated with a consistent improvement in survival. Major areas of research have been chemotherapy diversity, quantity of drugs administered (dose, dose intensity, duration of chemotherapy), and introduction of new agents. New drug development has included testing in previously untreated extensive disease patients without apparent detriment to survival, but others point out that the need is for agents that cause response in disease resistant to standard therapy. Unfortunately, no such agents loom on the horizon.

Drug diversity is a fundamental principle governing the use of combination chemotherapy that attempts to avoid or minimize the development of resistant clones.[18] Models of drug diversity acquisition include the following: standard regimen with drug addition, drug substitution studies, alternating combinations, and complex weekly regimens. An informative study by the Southeastern Cancer Study Group that compared sequential CAV (cyclophosphamide, doxorubicin [Adriamycin], and vincristine [Oncovin]), sequential EP (etoposide and cisplatinum), and alternating CAV/EP showed no differences in response rates or survival for ESCLC.[19] In addition, this trial demonstrated that an isoeffective result could be generated with four cycles of EP compared with six cycles of CAV or CAV/EP. The CODE (cisplatin, vincristine, doxorubicin, and etoposide) regimen incorporated both drug diversity and a doubling of dose intensity but failed to improve survival for ESCLC when compared with CAV/EP.[20]

Occasional examples exist of an incremental but statistically significant benefit of adding a third drug to a two-drug protocol in ESCLC such as ifosfamide to the EP regimen,[21] but the small size of the survival gain and the toxicity/logistical cost have not changed practice. Other drug addition studies such as comparing the addition of paclitaxel and granulocyte colony-stimulating factor to EP (TEP) versus EP have clearly had no impact on survival in ESCLC.[22] The addition of paclitaxel to EP did result in added toxicity. Renal toxicity, motor-sensory neuropathy, and hearing loss were more common in the TEP arm. The toxic death rate was three times as common in patients receiving the triplet combination

(6.5% versus 2.4%). The Greek Lung Cancer Cooperative Group also conducted a prospective randomized trial of TEP versus EP.[23] The trial was closed early because of unacceptable toxicity in the three-drug arm.

In a different type of drug addition study, the Eastern Cooperative Oncology Group randomized ESCLC patients that were stable or responding to four induction courses of EP to four cycles of maintenance or consolidation chemotherapy with topotecan or a control group.[24] Progression-free survival was trivially better for the topotecan arm than for the observation arm (3.6 versus 2.3 months). However, there was no difference in median survival (8.9 versus 9.3 months; $p = 0.43$), and topotecan added substantial toxicity. In this study, it is poignant that even when ESCLC patients are selected for chemoresponsive biology (patients with progressive disease were not randomized), maintenance treatment beyond four cycles of EP with putatively non–cross-resistant properties failed to improve survival.

Meta-analysis of dose intensity[25] and randomized trials[26–29] of dose intensification have consistently been negative in ESCLC. Although trials of high-dose chemotherapy with stem-cell support for SCLC are still underway in Europe, the failure of this approach to overcome drug resistance in epithelial cancers in general has marginalized this difficult line of investigation to enthusiasts.

With respect to the introduction of new chemotherapy agents, a phase III trial from Japan[30] was stopped early when the combination or irinotecan and cisplatin demonstrated survival superiority to the EP combination in ESCLC. Median survival was typical in the EP arm at 9.4 months versus 12.8 months for the irinotecan-treated arm ($p = 0.002$). At 2 years, the percentage of patients surviving was 19.5% versus 5.2%. At the 2005 meeting of the American Society of Clinical Oncology, a phase III trial of a different schedule (days 1 and 8) of irinotecan and cisplatin generated identical outcomes compared to the EP regimen.[31] A confirmatory phase III trial by the Southwest Oncology Group (S0124) is designed to reproduce the clinical data of the Japanese trial in a larger population (620 patients) and also investigate pharmacogenomic endpoints predictive of toxicity or efficacy of irinotecan and cisplatin. In addition, this study will examine polymorphisms of genes associated with drug metabolism (UGT1A1) and excision repair genes for platinum (ERCC-1, XRCC-1). In the largest phase III trial ever conducted for SCLC, Eckardt et al.[32] randomized 859 patients to EP versus cisplatin with oral topotecan. Response rates, median time to progression, and overall survival were not different. The negative results of the two North American trials[31,32] testing the utility of the substitution of topoisomerase I inhibitors for etoposide in a platinum protocol have generated a pall of pessimism that combinations with this drug class are capable of displacing EP as standard therapy for ESCLC.

Other new drugs such as pemetrexed[33] and amrubicin[34] are active and undergoing testing in combination with a platinum agent in ESCLC. However, like advanced NSCLC, it is increasingly unlikely that the plateau in the power of treatment for ESCLC will be changed with the introduction of new cytotoxic agents.

IMPACT OF CHEMOTHERAPY INNOVATIONS FOR LSCLC

Although chemotherapy alone cures a small proportion of LSCLC,[5] long-term survivors in the ESCLC population are uncommon (1%). This difference makes LSCLC a model of a curable neoplasm where incremental improvements in chemotherapy efficacy can be more easily detected than in palliative ESCLC patients. This effect has been shown in several clinical trials using a variety of chemotherapy variations.

The most notable example comes from Norway, where Sundstrom et al.[35] randomized 436 patients with SCLC to either cyclophosphamide, epirubicin, and vincristine or EP for five cycles; 218 limited stage patients were to receive thoracic irradiation between the third and fourth course of chemotherapy to a dose of 42 Gy. For ESCLC patients, there was no significant survival difference between the treatment arms. However, for LSCLC, the median survival time was 14.5 months versus 9.7 months in the EP and CEV arms, respectively ($p = 0.001$). The 2- and 5-year survival rates of 25% and 19%, respectively, in the EP arm compared with 8% and 3% in the CEV arm ($p = 0.001$). This trial provides compelling evidence that cyclophosphamide/anthracycline regimens are inappropriate first-line regimens for LSCLC.

In a drug substitution trial, Reck et al.[36] compared carboplatin, etoposide, and vincristine (CEV) to paclitaxel, etoposide, and carboplatin (TEC)—the experimental arm. The 608-patient study included 302 patients with LSCLC, and randomization was stratified by stage. LSCLC patients received thoracic irradiation after six cycles of chemotherapy. Median survival for patients in the TEC arm was superior to that achieved by patients in the CEV arm (12.7 versus 11.7 months), and the hazard ratio of death was statistically significantly higher for patients in the CEV arm (hazard ratio, 1.22; $p = 0.02$). When analyzed by stage, the median survival advantage of TEC over CEV was confined to LSCLC patients (17.6 versus 16.6 months); the difference in 3-year survival appears more impressive but was not cited in the article. There was no difference in outcome for ESCLC, where the median survival was 9.8 versus 10.0 months.

In a trial of dose intensification, Thatcher et al.[37] randomized 403 patients to a standard six cycles of doxorubicin, cyclophosphamide, and etoposide (ACE) at 3-week intervals versus the same regimen given every 2 weeks with granulocyte colony-stimulating factor support. The patient population had predominant limited stage disease (77%), and all patients had good prognostic factors as defined by this group. Survival was longer in the intensified group (hazard ratio, 0.80; 95% confidence interval, 0.65–0.99; $p = 0.04$). At 24 months, survival was 13% versus 8% in favor of the more intensive regimen. The same group examined a patient population with a higher proportion of LSCLC patients (87%) and favorable prognostic factors with a randomization between ifosfamide, carboplatin, etoposide, and vincristine (ICE-V) versus standard chemotherapy (mainly cyclophosphamide, doxorubicin, and vincristine).[38] Consolidation thoracic irradiation and prophylactic cranial irradiation was recommended after chemotherapy was complete. The median

survival was 15.6 months in the ICE-V group and 11.6 months in the control group, and the 2-year survival rates were 20% and 11%, respectively ($p = 0.0049$).

These randomized trials of LSCLC patients with good prognostic factors suggest that small but statistically significant survival gains can be achieved from chemotherapy innovations for this group. However, there is a problem. Unless profound differences exist in prognostic factors or staging methods that make these patients incomparable to other recently published LSCLC results, the median and long-term survival outcomes of all these trials are clearly inferior to what would be expected from early concurrent EP and thoracic irradiation. With initial concurrent chemoradiation, the median survival times exceed 20 months, 2-year survival is over 40%, and actual 5-year survival rates of over 20% are fairly consistently reported.[10,39,40] Concurrent administration of full doses of EP and thoracic irradiation can be accomplished with manageable toxicity without reduction of either modality. However, when chemotherapy is manipulated by dose intensification or addition of drugs that are less compatible with thoracic irradiation, the fidelity of both modalities of treatment is impaired by increased hematologic and nonhematologic toxicity. As an example, a recently reported Radiation Therapy Oncology Group phase II study[41] that incorporated paclitaxel with EP and twice-daily thoracic irradiation (45 Gy in 3 weeks) showed a favorable median survival of 24.7 months and a 2-year survival rate of 54%. Four- and 5-year survival was approximately 20%. Grade 3 and 4 esophagitis was 32% and 4%, respectively, and 6% died as a result of toxicity. After due consideration, the authors concluded that this three-drug protocol was unlikely to improve the results in LSCLC compared to the standard EP chemotherapy regimen and this line of investigation would be pursued no further.

The demographic patterns of patients diagnosed with LSCLC are not conducive to increasingly toxic combined-modality protocols. Gaspar et al.[42] examined a National Cancer Data Base including four patient cohorts diagnosed with LSCLC in 1985 ($n = 2123$), 1990 ($n = 6279$), 1995 ($n = 7815$), and 2000 ($n = 2123$). The proportion of patients aged 70 years or older increased significantly over time, from 31.6% in 1985 to 44.9% in 2000 ($p < 0.001$). Moreover, SCLC patients are generally physiologically aged beyond their chronologic age, at least in part because of heavy smoking. This analysis identified the continued need for the evaluation of new treatments in this group of patients, but more aggressive chemotherapy in combined-modality protocols is unlikely to enhance the therapeutic index.

COMBINED MODALITY THERAPY FOR LSCLC

Thirteen randomized studies, including 2140 patients, have investigated the role of thoracic radiotherapy in LSCLC. Two meta-analyses[5,43] have been published that examine these trials. Both show a modest improvement in survival rates in those patients given thoracic radiotherapy in addition to chemotherapy. Survival benefit becomes evident at approximately 15 months after the start of treatment and persists beyond 5 years. At 3 years, 8.9% of the chemotherapy-only group is alive, compared with 14.3% of the combined-modality group. The relative risk of death in the combined-modality group as compared with the chemotherapy group was 0.86 (95% confidence interval [CI], 0.78–0.95; $p = 0.001$), corresponding to a 14% reduction in the mortality rate. The analysis of local control showed a 2-year local failure rate of 23% for irradiated patients versus 48% for nonirradiated patients ($p = 0.0001$). These benefits were obtained at the cost of an increase in treatment-related deaths of 1%.

The meta-analyses[5,43] have been a valuable addition to the oncology literature, and the principal conclusion that chemotherapy combined with thoracic irradiation is superior to chemotherapy alone is undoubtedly correct. However, the meta-analyses underestimate the absolute long-term survival contribution of state-of-the-art integrated chemoradiation. Most studies in the meta-analyses commenced before 1981 and none delivered cisplatin and etoposide either as initial treatment or concurrently with thoracic irradiation. The relative risk of death method rather than the proportion of long-term survivors measured outcome. The survival curve is initially better for chemotherapy alone, and at approximately 1 year, the curves cross to show a clear benefit of combined-modality therapy on long-term survival. Chemotherapy prescriptions from a previous era that administer concurrent chemoradiation with cyclophosphamide, doxorubicin, and nitrosoureas are associated with problematic hematologic and nonhematologic toxicity. Reliable delivery of both chemotherapy and radiotherapy is uncertain. The negative impact of chemoradiation using incompatible chemotherapy regimens can be seen in two subgroups reported in the meta-analysis of Pignon.[5]

Subgroup analysis on the basis of age indicated that the benefit from radiotherapy on mortality was greatest for patients younger than 55 years of age ($p = 0.01$). The relative risk of death in favor of combined-modality therapy was 0.72 (95% CI, 0.56–0.93) for patients younger than 55 years and 1.07 (95% CI, 0.70–1.64) for patients older than 70 years. This adverse effect of age on the benefit of combined-modality therapy has been contradicted by two recent studies[44,45] that have examined treatment effects in older ($\geq$70 years) versus younger ($<$70 years) patients in studies that administered early EP with thoracic irradiation. The two groups were similar for baseline patient characteristics, treatment field sizes, toxicity, response rates, and overall survival. These analyses conclude that age does not appear to have an impact on the delivery, tolerance, or efficacy of radiotherapy, when used with platinum/etoposide, for patients with LSCLC. A plausible explanation of the discrepancy would be that toxicity of concurrent chemoradiation as used in the trials examined in the meta-analysis had a disproportionate effect on elderly patients. Clearly, fit elderly patients should not be denied the benefit from chemoradiation for LSCLC based on the meta-analysis.[5]

The same meta-analysis[5] examined the question of the timing of thoracic irradiation (sequential, alternation, and concurrent), and no statistically significant differences were found among the various treatment schedules. However, three

of the four trials that showed a significant survival advantage for combined-modality therapy used a concurrent or alternating scheme, whereas seven of the nine trials that did not demonstrate a survival advantage used a sequential plan. Comparisons between sequential and concurrent therapy depend on compatibility of chemotherapy and radiotherapy; in fact, the alternating methodology was used as a way to get around the excess toxicity of concurrent therapy with an anthracycline. The use of anthracyclines and alternating therapy has faded into the past but rises with each evidence-based assessment and review of these studies. The survival advantage of thoracic irradiation becomes important at 2 to 5 years in LSCLC when the proportion of cured patients becomes manifest.[10]

SEQUENCING AND TIMING OF THORACIC RADIOTHERAPY

Although investigation of thoracic irradiation timing is reported in seven randomized trials[39,40,46–50] of varying structure, size, and vintage, sequence and timing continue to generate controversy. Recently, a meta-analysis performed according to the Cochrane Collaboration Guidelines examined randomized controlled clinical trials comparing different timing of chest radiotherapy in patients with LSCLC.[51] Early chest irradiation was defined as beginning within 30 days after the start of chemotherapy. Seven randomized trials were eligible.[39,40,46–50] A weighted estimate of the typical treatment effect across studies was computed for 2-year survival data and for the 5-year survival data, local control, and toxicities. The odds ratio (OR) was used as the effect measure. Taking all seven studies into account, the overall survival at 2 years or at 5 years was not significantly different between early or late chest radiotherapy (OR for 2 years, 0.84; 95% CI, 0.56–1.28; OR at 5 years, 0.80; 95% CI, 0.47–1.38). When the one trial that delivered nonplatinum chemotherapy concurrently with chest radiation[46] was excluded, the OR was significantly in favor of early chest radiotherapy at 5 years (OR, 0.64; 95% CI, 0.44–0.92; $p = 0.02$). Considering studies with an overall treatment time of chest irradiation of less than 30 days,[39,40,47,49,50] the 5-year survival was even better (OR, 0.56; 95% CI, 0.37–0.85; $p = 0.006$). As expected, esophageal and pulmonary toxicity was worse with initial concurrent chemoradiation, but severe leukopenia was more frequent in patients receiving late chest radiotherapy ($p = 0.0004$).

Although a conclusion in favor of early concurrent chemoradiation for LSCLC is not definitive, analysis of relevant subsets of the data is rational. Exclusion of nonplatinum chemotherapy is supported by a meta-analysis showing superiority of SCLC regimens containing cisplatin[52] and a conclusive phase III trial showing better survival of the EP regimen compared with a cyclophosphamide/anthracycline-based regimen.[35] Early thoracic irradiation cannot be expected to perform well unless it is coupled with a chemotherapy regimen compatible with concurrent radiotherapy and efficacious enough to improve control of micrometastases outside the thoracic irradiation volume. Parenthetically, the odds ratios adduced in favor of early concurrent thoracic irradiation versus delayed thoracic irradiation (0.80, 0.64, and 0.56) in the meta-analysis by Pijls et al.[51] are more favorable than the OR of 0.86 in favor of combined-modality therapy versus chemotherapy alone (0.86).[5]

Another factor that influenced the less than robust statistics of the meta-analysis on the timing of thoracic irradiation is that the prognostic factors of the patients in the trials appear different. If a poor prognosis LSCLC population (as evidenced by a short median survival) is studied, the proportion of patients who can have their prognosis improved by better integration of chemoradiation will be low and the benefit of early thoracic irradiation timing will be diluted by a majority of incurable cases. That the study populations in the Perry et al.,[46] Work et al.,[48] and James et al.[50] trials, which failed to show superiority of early chemoradiation, contained more patients with a poorer prognosis is strongly suggested by the short median survival times reported. The average median survival of all patients (both arms) in these trials was 13.75 months for the Perry et al. trial, 11.25 months for the Work et al. trial, and 14.3 months for the James et al. study. In the trials that support early concurrent chemoradiation, the average median survival of all trial patients was 18.6 months for the Murray et al. study,[53] 23.5 months for the Takada et al. trial,[39] and 30 months for the Jeremic et al. trial.[47] These are rather large differences. Selection of patients for combined-modality trials of stage III NSCLC requires that the patient population be carefully staged and has favorable prognostic factors. Similarly, in LSCLC, patients that benefit from early concurrent chemoradiation are those with good prognostic factors and a reasonable chance of being cured.

THE CHEMORADIATION PACKAGE AND SER

The concept of the "chemoradiation package" has been discussed by Peters and Withers[54] with regard to the treatment of head and neck cancers. Most sequential combined-modality protocols emerged as pragmatic grafting of chemotherapy onto a course of radiotherapy. The failure of induction chemotherapy to improve results in the combined-modality treatment of head and neck cancer[55] can be explained by the hypothesis that the cell kill produced by induction chemotherapy is offset by tumor cell regeneration occurring during the prolonged overall course of treatment.

The duration of the chemoradiation package for LSCLC may be defined as the time elapsed from the first therapeutic intervention until the completion of the radiotherapy treatment. The use of this definition does not presume that additional chemotherapy cycles after completion of radiotherapy are unimportant but that the rapid tumor destruction caused by combined-modality therapy is crucial and markedly influences the probability that treatment will eventually eliminate the last tumor clonogen. That initial concurrent chemoradiation is the most efficient way to rapidly destroy cancer cells is self-evident. Based on data from in vitro assays of radiosensitivity of human small cell lung cancer lines,[56] numerically, more cancer clonogens are eliminated locally by the first 2-Gy fraction (SF2) than by the entire remainder of the radiotherapy course. When initial concurrent systemic chemotherapy is added to the radiother-

apy effect, inhibition of tumor repopulation and metastatic events by rapid tumor destruction will be greater than delaying radiotherapy during protracted induction chemotherapy. The theoretical basis of the superiority of initial chemoradiation is discussed in detail elsewhere.[57]

This concept has recently been statistically evaluated by De Ruysscher et al.[58] from The Netherlands. The hypothesis was that the overall treatment time available for accelerated proliferation of tumor cells could be a major determinant of tumor outcome in LSCLC. They performed a systematic overview and identified six published phase III trials[10,39,40,47,48,59] combining chest irradiation and platinum-based chemotherapy in the primary management of LSCLC and reporting 5-year survival. The following parameters and their influence on local tumor control, survival, esophagitis, and pneumonitis were analyzed: the total radiotherapy dose, the overall treatment time of chest radiotherapy, the day of the start of radiotherapy as an indicator of early versus late radiation, the SER (*s*tart of any treatment till the *e*nd of *r*adiotherapy), concurrent versus sequential radiotherapy and chemotherapy, the study period measured by the year the trial was initiated, and the Equivalent Radiation Dose in 2-Gy fractions, corrected for the overall treatment time of chest radiotherapy (EQD_2, T). The definition of SER and the chemoradiation package are the same.

Using meta-analysis methodology, the SER was the most important predictor of outcome. There was a significantly higher 5-year survival in the shorter SER arms (OR, 0.60; 95% CI, 0.45–0.80; $p = 0.0006$), which was more than 20% when the SER was less than 30 days. Although no significant relation between the SER and local tumor control was found (OR, 0.73; 95% CI, 0.46–1.14; $p = 0.16$), local tumor control was higher with increasing EQD_2, T radiation doses ($p = 0.02$). This suggests that for local tumor control, both time and radiation dose factors are important. A lower SER was associated with a higher incidence of severe esophagitis (OR, 0.47; 95% CI, 0.33–0.66; $p < 0001$). The SER was not statistically associated with pneumonitis (too few events), severe leukopenia, or thrombocytopenia.

The authors concluded that a short SER (<30 days) results in improved survival for LSCLC patients. This novel parameter, taking into account accelerated proliferation of tumor during both radiotherapy and chemotherapy, may facilitate a more rational design of combined-modality treatment in rapidly proliferating tumors.

RADIOTHERAPY TARGET VOLUME

Selection of a target to treat has evolved because of computed tomography and treatment planning systems that allow more accurate definition of structures that warrant treatment from anatomy that causes toxicity. Global mediastinal and supraclavicular irradiation dominated thoracic radiotherapy ports through the trials of the 1980s, including the Intergroup Trial,[10] where regional nodal irradiation encompassed the entire mediastinum. Relapse patterns rarely report regional nodal failure as the first or ultimate site of relapse, and this is especially true of supraclavicular nodal regions. As with other occult positive disease sites, they can be managed with systemic chemotherapy; treating uninvolved nodes with radiotherapy may not be necessary, and exposing radiographically normal nodal stations to radiation beams may add to toxicity. Diminishing mediastinal irradiation only to areas of bulky nodes reduces exposure to the esophagus, lung, and other sensitive normal tissues and reduces esophagitis and pneumonitis.

Target size can be challenging with initial concurrent therapy if the initial bulk is too large for a reasonable radiotherapy port. This fact may influence the sequence of therapy. A cycle or two of chemotherapy may reduce volume sufficiently to more facilely apply radiation beams without excessive irradiation to the lungs. The target can then become the residual mass after reduction attributable to the chemotherapy. Data supporting this are limited, but an analysis from the Mayo Clinic[60] shows support for the tactic of targeting postchemotherapy residual or at least no clear hazard by not encompassing the initial bulk. This issue has not drawn sufficient attention to construct a clinical trial to test volume-related issues in a prospective trial.

Targeting and treating only nodal structures that measure 1 cm or larger on computed tomographic scan, clinically palpable nodes in the supraclavicular fossa and disease found by bronchoscopy constitute an appropriate target. Elective treatment of uninvolved nodes does not have a good rationale, and the risk of normal tissue exposure with toxicity of esophagitis and reduction in lung function militates strongly against expansive volumes.

RADIOTHERAPY DOSE, TIME, AND FRACTIONATION

The duration of overlapping chemotherapy and thoracic radiotherapy may influence tolerability, survival, and toxicity. The 1980s issue for thoracic radiotherapy was whether it was needed at all, and the responsiveness of SCLC to either radiotherapy or chemotherapy was so great that higher doses were not contemplated. Doses commonly recommended were in the range of 40 to 50 Gy. Because of concern for spinal cord tolerance, simple techniques were used to deliver spinal cord tolerance such as a posterior shield. The fact that the spinal cord shield also blocked tumor centrally was considered a necessary problem. Since that time, treatment planning techniques allow delivery of doses to the target defined by radiation oncologists without concern for spinal cord tolerance, and toxicity to the lung and esophagus are more practical concerns. Modern planning allows delivery of doses higher than ever considered 25 years ago either by once- or twice-daily treatment.

According to the evidence, the standard dose and treatment for LSCLC is 45 Gy delivered in 3 weeks in 30 fractions of 1.5 Gy, administered concurrently with cisplatin plus etoposide.[10] The North Central Cancer Treatment Group Study,[61] which also used a twice-daily treatment arm, failed to show differences between the twice-daily treatment and once-daily treatment. However, both arms had delayed initiation of chemoradiotherapy after induction chemotherapy, and the duration of radiotherapy was not different despite a twice-daily scheme. The trial intentionally put a treatment

interruption in midcourse on the twice-daily arm, but that resulted in a reduction of toxicity. There was no significant difference in survival. The interruption muted any effect of twice-daily treatment. Although some cast doubt that twice-daily treatment is superior because of this trial, the interruption and protraction of treatment diminished the intensity of the radiotherapy. Thus, the twice-daily treatment with too much time off over too long of a period blunts esophagitis, but blunts any effect on survival as well. In Canada, 40 Gy in 3 weeks is still widely used.[40] We really do not know that longer treatments or higher doses are better for local control or survival, but we are now able to deliver doses up to 70 Gy in 7 weeks[62] without a clear signal that higher doses are superior. The Massachusetts General Hospital group[63] has consistently endorsed a policy of higher doses of once-daily treatment and have slowly escalated the dose in successive cohorts of patients to 70 Gy. Survival plots of patients treated at higher doses show no inferiority and possibly a slight benefit for protracted high-dose treatment. Both Cancer and Leukemia Group B and Massachusetts General Hospital data sets use induction chemotherapy and postchemotherapy target volumes. American cooperative groups have escalated LSCLC thoracic radiotherapy doses to doses of 61 to 63 Gy, paralleling doses used for stage III NSCLC. However, none of these doses appears superior to 40 to 45 Gy in 3 weeks, and lengthy high-dose treatments over 6 to 7 weeks are associated with a long SER. In addition, protracted thoracic irradiation overlaps with more chemotherapy cycles, leading to more dose reductions and delays. There is no evidence from controlled trials that demonstrates benefit to higher dose thoracic irradiation and no such study has been approved.

PROPHYLACTIC CRANIAL IRRADIATION

Patients with cancer control outside the brain have a 60% actuarial risk of developing brain metastases within 2 to 3 years after starting treatment. In a meta-analysis of seven randomized trials evaluating the value of prophylactic cranial irradiation (PCI), the risk of developing central nervous system metastases was reduced by more than 50%.[64] In addition, 3-year overall survival of complete responders (predominately LSCLC) was 20.7% with PCI versus 15.3% in the control group.

The selection of an optimal dose for PCI that would lead to further decreases in brain metastasis incidence with minimal toxicity is the subject of an ongoing international trial addressing the question of the optimal PCI dose for the prevention of metastases. A standard dose of 25 Gy in 10 fractions is being compared with 36 Gy in 18 fractions or 36 Gy in 24 twice-daily fractions. PCI should not be given with systemic chemotherapy because of increased toxicity.[65]

CONCLUSION

Because of the systemic nature of SCLC, the opportunity for demonstrating treatment improvement would appear to be greatest for chemotherapy, where there is a large array of drug permutations and dosing variations. In addition, the entire patient population could potentially benefit from a bona fide advance in systemic treatment. For ESCLC, a number of chemotherapy regimens have been demonstrated to be equivalent to the cisplatin plus etoposide combination for ESCLC. However, it has not been possible to unequivocally show that any chemotherapy regimen is superior to four cycles of EP. In the LSCLC patient population, the EP regimen is clearly superior to cyclophosphamide plus anthracycline regimens. Some evidence exists that incremental survival gains may be seen when dose-intensive or more complex regimens are administered before delayed thoracic irradiation. However, the best reported results for LSCLC are achieved with initial concurrent EP chemotherapy and thoracic irradiation. More intensive protocols or regimens that add another chemotherapeutic agent to the EP motif have not prospered in investigations of LSCLC because of safety concerns and fidelity of chemotherapy and radiotherapy delivery.

The frustration associated with the over 25-year tenure of cisplatin plus etoposide as standard therapy for both LSCLC and ESCLC is mitigated by favorable economic factors. The drug acquisition cost of etoposide and cisplatin for a 1.75-m^2 patient at the British Columbia Cancer Agency is US$60 per cycle (US$240 for the entire four-cycle prescription). This represents one of the best bargains for state-of-the-art chemotherapy in cancer medicine. When one considers the fact that the same model of treatment has achieved some of the best reported results for locally advanced NSCLC,[11] the importance of modest drug costs for treatment with curative intent of a common disease worldwide should not be understated. Lung cancer is a global pandemic, and the International Association for the Study of Lung Cancer has a responsibility to recognize and endorse cost-effective therapy.

Although chemotherapy advances have been disappointing in SCLC, innovations of radiotherapy from LSCLC articles published during the 1990s demonstrated that a number of radiotherapy interventions had significant survival benefits. These radiotherapy interventions include addition of thoracic irradiation to chemotherapy, early delivery of thoracic irradiation concurrently with chemotherapy, more intense thoracic irradiation, and prophylactic cranial irradiation

Over the past 20 years, there has been extensive investigation combining definitive radiotherapy and systemic chemotherapy with curative intent for a wide variety of locally advanced neoplasms. Induction or neoadjuvant chemotherapy has been popular logistically, but when evidence from randomized trials is examined, the model of treatment that has consistently generated improved survival for brain cancer, head and neck cancer, anal cancer, cervical cancer, NSCLC, and LSCLC is early concurrent chemoradiation. As there are major unanswered questions in the management of LSCLC, the rational design of combined-modality protocols and clinical trials incorporating new treatments must respect basic radiobiological principles.

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