Innovations in Multimodality Therapy for Lung Cancer
Combined Modality Management of Limited Small-Cell Lung Cancer

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Recent approaches to the treatment of limited small-cell lung cancer have combined local radiotherapy and systemic chemotherapy in an attempt to improve local control and inhibit distant metastases. Local control is a key indicator of the efficacy of radiotherapy administration in combined-modality regimens. However, even in combined-modality trials using high total radiotherapy doses, local failure rates have ranged from 30 to 50 percent. The components of radiotherapy administration—including dose, volume, fractionation, integration with chemotherapy (concurrent, alternating, or sequential), and timing (early or late administration)—are also important considerations. Hyperfractionation, or the administration of small fractions of radiation more than once daily (usually twice), and accelerated hyperfractionation, or the administration of three fourths of the standard radiation dose two to three times daily, have emerged as important concepts in radiotherapy. Although the optimal chemotherapeutic regimen for combined-modality treatment has not yet been established, use of cisplatin and etoposide combinations, which do not promote pulmonary, cardiac, or esophageal toxicity, have been particularly appropriate in patients with small-cell lung cancer.

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In the 1960s, prior to recognition of a distinction between the histologies of small-cell lung cancer (SCLC) and nonsmall-cell lung cancer (NSCLC), surgery was initially offered to many patients with lung malignancies. It quickly was recognized that these cancers had a natural propensity for distant metastasis. Radiotherapy replaced surgery as the local modality of choice in the late 1960s, but its role was rather short-lived with the appreciation that the addition of even a single chemotherapeutic agent, cyclophosphamide, improved survival over radiation therapy alone.1 With such excellent responses to chemotherapy, many predicted that lung cancer would be the next cancer cured by systemic therapy, eliminating the need for local treatment with surgery or radiation. Unfortunately, that prediction did not come true. Over the next two decades, it became increasingly clear that systemic therapy alone results in an acceptably high frequency of local failure, and that despite an excellent initial response, few lung cancer patients survive beyond 2 years, even those with limited disease.

Early attempts to integrate thoracic radiotherapy (usually large fractions given in a split course) with chemotherapy in limited SCLC failed to improve survival; local failure rates approached 80 percent for patients given doses of radiotherapy less than 40 Gy and 30 to 50 percent of those given doses of 40 to 50 Gy in combined-modality regimens.4 More recent attempts, using larger total doses usually administered sequentially, have continued to show local failure rates in the range of 30 to 50 percent.3,4

With such a frequency of local failure, local control becomes an important endpoint in assessing the value of radiotherapy. The other important endpoint is, of course, survival. Clinically, SCLC is quite responsive to external beam radiotherapy. The results of clinical cyclophosphamide-based trials evaluating chemotherapy alone versus chemotherapy combined with thoracic radiotherapy are mixed in terms of median and 2-year survivals.4 A number of nontherapeutic factors, including selection, staging, and pretreatment prognostic factors, may have influenced the outcomes of these trials. More important, and certainly more manageable, are the components of radiotherapy—including dose, volume, fractionation, integration with chemotherapy (concurrent, alternating, or sequential), and timing (early or late administration)—within the combined-modality regimen—and how they affect the results of treatment. These factors must be considered to maximize the success of a given regimen.

CONTROLLING RADIOTHERAPY COMPONENTS TO MAXIMIZE RESPONSE

Dose

Because of the excellent early responses to low-dose radiotherapy in SCLC patients, older series used doses in the range of 30 to 35 Gy. These trials, however, failed to influence demonstrably either survival or local control.4 Since the late 1970s, most combined-modality trials have employed doses ranging from 40 to 50 Gy.4 In one trial,7 a dose of 60 Gy was used, yielding excellent local control but poor long-term survival; moreover, the chemotherapy used was not a commonly employed regimen. A shortfall of using local control as an end point is that patients with brief survival and those with systemic failure may be censored from local control analysis, creating an illusory improvement in local control. When median survival is short due to suboptimal systemic therapy, local issues are less telling. The other side of the issue has been exposed by Arriagada et al,4 who recently demonstrated that local failure may be underappreciated by certain methodologies.

Volume

Radiation volume deserves attention as another variable of note. The imaging revolution has allowed better visualization and targeting of tumor. Previously, mediastinal invasion was inferred by indirect evidence or very bulky

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involvement. Splaying of the carina of the trachea and deviations in esophagograms were once among the best methods of determining the presence of bulky mediastinal disease. With computed tomography (CT) scans, we now have a better appreciation of bulky disease. Thus we can routinely define targets in ways that were impossible in the past. Knowledge of lymphatic anatomy and observations about failure patterns have influenced radiation oncologists in their definition of volume. The concept of "en bloc" irradiation harkens back to Halsted’s idea that breast tumors spread by contiguity to the next lymph node level. Thus, irradiating adjacent lymphatics would influence a tumor that spreads in an orderly fashion (eg, Hodgkin’s disease). Unfortunately, most solid tumors, even non-Hodgkin’s lymphoma, do not behave in this fashion. In lung cancer, irradiating these sites has not altered outcome measurably.

Since chemotherapy rapidly decreases tumor size in many patients with SCLC, programs that delay the use of radiotherapy until subsequent therapy cycles or until completion of chemotherapy must address the question of volume. As the tumor mass ebbs in response to chemotherapy, residual malignant cells may be left behind. Trimming the volume could leave these residual cells untouched by irradiation. On the other hand, directing radiotherapy to a prechemotherapy volume may add to the morbidity of the combined modality.

Since chemotherapy is highly cytotoxic to SCLC, it is unclear whether every cell must be irradiated to produce cure. Sites of bulk may harbor the most resistant cells. Clearly, if radiotherapy is administered concurrently with the first chemotherapy cycle, the irradiated volume must be the original target volume.

Most studies report including a margin of normal tissue in the volume to be irradiated. The volume comprises the observed tumor plus an arbitrary 1 to 2 cm of normal tissue to account for the physical dose buildup, uncertainty about tumor edges as they appear on imaging studies, technical variations in day-to-day setup of the radiation fields, and inadvertent motions of the patient (ie, involuntary squirming as well as cardiac or respiratory variable movements, which also cause tumor motion).

Fractionation

Fractionation concepts have emerged as a major issue in radiotherapy. Standard fractionation involves administering a dose in the range of 2 Gy/day, 5 days a week, usually with no treatment on Saturday and Sunday. In the past, strategies employed split-course techniques that consisted of a week or two of therapy followed by a 2- to 3-week break to allow tumor shrinkage and a subsidence of normal tissue responses; commonly, a similar interval of therapy was then reapplied, sometimes with reduced fields.

Over the last decade, two new fractionation schemes have been developed. Hyperfractionation entails giving a small radiotherapy dose per fraction (approximately half the standard dose) more than once daily (usually twice). The dose ranges between 1 and 1.2 Gy, so the total dose is generally increased by about 10 to 20 percent over the same time course used in standard fractionation. Using a smaller dose per fraction is potentially less damaging to normal tissue; therefore, hyperfractionation may produce less late normal-tissue toxicity.

The other fractionation scheme, accelerated hyperfractionation, involves giving a dose per fraction equal to three fourths the standard dose two to three times daily. Thus, a lower physical dose is applied over a shorter period.

The interval between fractions in these multiple daily fractionated schedules has generally been 4 to 6 h, and more recently, 8 h. It is believed that normal tissues are repaired within that interval and more complete repair may take place if the interval is extended. In NSCLC, a recent trial from the United Kingdom employed an accelerated hyperfractionated regimen in which fractions of 1.4 to 1.5 Gy were given three times daily for 12 days without interruption; total doses equaled between 50 and 54 Gy. This experience seemed to improve local control and survival when compared to a more standard radiotherapy scheme augmented by the radiation sensitizer, misonidazole.

There is an even greater rationale for the use of altered fractionation schemes in limited SCLC. Cell culture experiments have shown that in contrast to NSCLC, variant SCLC, and most normal tissue, SCLC has no radiobiologic shoulder, the initial area where the radiation dosage appears to accumulate prior to exponential cell killing. With smaller doses per fraction, SCLC can be killed exponentially, with no opportunity for repair, whereas accumulated toxicity to most normal tissue is minimized, allowing for easier repair. In the interval between fractions, normal tissues may repair any sublethal damage.

Small-cell lung cancer is prolific in its growth fraction. It is plausible that over time, cells could move from a relatively resistant phase of the cell cycle (the S phase) into a more radiosensitive phase (the G2-M border). Given this large growth fraction, it is less than ideal to allow opportunities for repopulation (ie, splits or breaks in or protracted duration of treatment). Using such breaks or splits may not alter median survivals in randomized trials. In order to see the effect of interruptions, it would be best to design a clinical trial isolating this factor. However, in meta-analysis or retrospective research, one must wait to analyze actuarial local control and survival.

Integration With Chemotherapy

The optimal chemotherapy regimen for SCLC in the 1990s has not been clearly established by clinical trials. Unfortunately, some of the most commonly employed drug regimens have subliminal pulmonary toxicity or are toxic to neighboring organs. The use of such drugs in combined-modality regimens poses hazards that must be balanced against potential efficacy in disease control. The cisplatin and etoposide (PE) combination has afforded the opportunity to use drugs that do not have underlying pulmonary, cardiac, or esophageal toxicity, which makes them particularly suitable for the treatment of SCLC. It is unclear whether PE alone or in combination with the commonly used regimen CAV (cyclophosphamide, doxorubicin, and vincristine) is superior in terms of survival for patients with limited SCLC. One study suggests that combination of PE and CAV is better.

Between 1984 and 1987, investigators at the University of Pennsylvania administered PE concurrently with radiotherapy to 32 patients with limited SCLC. Radiotherapy
consisted of a total dose of 45 Gy given over 3 weeks. Cisplatin was administered at a dose of 60 mg/m² on day 1, and etoposide at a dose of 120 mg/m² on days 4, 6, and 8; these full doses of both drugs were also given in cycle 2 (which began on day 22), irrespective of the toxicity encountered during the first cycle. After treatment, patients were restaged completely with chest x-rays, CT scans, and bronchoscopy. Those patients who responded received the same doses of PE alternated with CAV for six cycles.

The intense acute toxicity, particularly to the bone marrow and esophagus, that occurred in about three fourths of the patients, was manageable, typically without hospitalization. Important, very little acute pulmonary toxicity was encountered. Long-term data now available from that trial confirm that the median survival has been about 2 years and that more than 30 percent of the patients have survived for at least 5 years.14 Impressively, the local control rate has been nearly universal in the classic SCLC histologies.

Four patients with variant histologic findings (a mixture of large and small cells and prominent nucleoli observed under hematoxylin-eosin stain) were entered into this trial. From cell culture experiments, it is known that these variants produce fewer neuroendocrine products, grow in a different fashion, and, importantly, have different radiobiologic characteristics than classic small cell histologies.16 As with the non-small-cell histologies, variant histology has been shown to have the radiobiologic shoulder. As has been observed from a National Cancer Institute series,15 in the University of Pennsylvania trial, only two of the four patients with this histologic subtype were complete responders; all four patients experienced local failure and all had died by 24 months posttreatment. Among the patients with classic small-cell histology, a complete response was obtained in all 28 patients and local control in 27; the one patient with initially pure small-cell lung cancer, who experienced local failure and had variant histology, had received only 10 percent of the intended radiotherapy dose (4.5 Gy or 450 cGy).

Subsequently, other trials employing the similar combined-modality treatment have confirmed these toxicity, response, and survival results, and many investigators are now using variations of the original fractionation scheme. Table 1 shows recent 2-year survival and local failure results obtained using PE plus thoracic radiotherapy.14,16,17,21 Radiotherapy was given once daily to the same total dose in a pilot trial by the Southwest Oncology Group,16 whereas at least four trials employed altered fractionation schemes.17,21 Administering a larger daily dose of radiotherapy sequentially, the Memorial Sloan-Kettering Cancer Center achieved results similar to those of the other trials.41

Against this background, the Eastern Cooperative Oncology Group (ECOG) initiated a trial in 1988 comparing once-daily fractionation with twice-daily fractionation. Patients in both arms received four cycles of chemotherapy consisting of identical doses of cisplatin and etoposide. In one arm, radiotherapy was given once daily in 1.8-Gy fractions to a total dose of 45 Gy over 5 weeks, which overlapped with two of the four chemotherapy cycles. In the other arm, all radiotherapy was given in an intensive, twice-daily regimen over the first chemotherapy cycle; despite this, investigators were able to deliver full doses of chemotherapy on day 22 (day 1 of cycle 2). Initial results obtained from over 300 registered patients show very little difference in morbidity between the two study arms. Final analysis awaits completion of the trial and observation of long-term end points such as 2-year survival and local control.

**Prophylactic Cranial Irradiation**

The role of prophylactic cranial irradiation in the treatment of SCLC is controversial. Many believe it only increases morbidity in those that survive. Others find it to be important for addressing the failure pattern in approximately 50 percent of the previously untreated population. In the ECOG, we have opted to reserve using prophylactic cranial irradiation until completion of chemotherapy. We have adopted the schedule initially employed by the Medical College of Wisconsin and reported by Komaki et al.,22 administering fractions of 2.5 Gy ten times over 2 weeks, for a total dose of 25 Gy. There are no reports of serious late effects with this program.

Most studies reporting neurotoxicity with prophylactic cranial irradiation administered it early in the course of treatment, concurrent with systemic agents. It is plausible that prophylactic cranial irradiation may damage the blood-brain barrier, allowing penetration of larger concentrations of subsequently used chemotherapy. This, coupled with the typically large (≥3 Gy) fraction per dose of radiation, may in part be responsible for some of the observed morbidity. By using different chemotherapeutics, delaying administration of prophylactic cranial irradiation until completion of chemotherapy, and using smaller radiation doses per fraction, we may be able to avoid excessive treatment-related complications.23

Presently, ECOG is testing whether the use of prophylactic cranial irradiation alters survival, reduces brain failure, or increases neurotoxicity. Patients completing any induction chemotherapeutic regimen are randomized to receive prophylactic cranial irradiation or observation. Both patient groups are to be followed carefully with modern imaging techniques and serial psychometrics. No chemotherapy is permitted during or subsequent to prophylactic cranial irradiation. Study end points include survival, neurotoxicity,
and frequency of central nervous system relapse as both an initial site and a sole site. This study will allow us to determine how frequently central nervous system relapse occurs in this more select group of patients and what influence prophylactic cranial irradiation might have on this population.

CONCLUSIONS
Chemotherapy with PE provides an opportunity to use thoracic radiotherapy with fewer side effects and better survival. The optimal dose and duration of systemic therapy remain to be defined. Early, concurrent thoracic radiotherapy appears to produce more esophagitis and granulocyte toxicity than chemotherapy alone. Despite profound symptomatic toxicity, it's rarely fatal and usually reversible. Regimens using PE and thoracic radiotherapy are associated with better survival than in older series, but stage migration and nontreatment variables may be responsible for a portion of this difference. Optimal dose, timing, and fractionation techniques are not clearly defined and are subjects of ongoing clinical research. Issues regarding prophylactic cranial irradiation remain quite contentious—a randomized trial will attempt to shed some light on this highly contested debate.

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