Current Management of Unresectable Non-Small-Cell Lung Cancer

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The past 5 years have witnessed an evolution in the management of unresectable non-small-cell lung cancer (NSCLC) in the United States. Combined-modality treatment with chemotherapy plus irradiation has become the standard of care for stage III (locally advanced) disease. Most patients with stage IIIB disease and cytology-positive pleural effusion are now considered candidates for chemotherapy, as are those with stage IV disease.

Introduction

The American Cancer Society estimated that 180,000 patients in the United States would develop lung cancer during 1996.[1] Approximately 80% of these patients were expected to have non-small-cell lung cancer. In approximately one-third of cases, the disease is potentially resectable for cure at the time of presentation. Another third of patients have locally advanced disease (stages IIIA and IIIB) that is not surgically approachable de novo with curative intent. The remaining one-third have stage IV disease, implying hematogenous dissemination at the outset. This article describes how management strategies for the latter two groups have evolved during the past 5 years.

Stage III Disease

Patients who have stage III non-small-cell lung cancer by virtue of T3 disease, but with N0 or N1 disease, may be appropriately considered for resection. This is contingent on their having adequate pulmonary function and an expected 5-year survival rate similar to that associated with stage II disease (ie, 30% to 40% of patients).

On the other hand, N2 disease, regardless of tumor status, is generally a contraindication to initial surgical resection; the exception is when only one nodal area (or station) in the mediastinum is involved. This type of presentation is seen in a small, “favorable” subset of patients who exhibit a 5-year survival rate of 25% to 30% after complete resection. (Most also receive postoperative irradiation.)

Sequential Combined-Modality Therapy

Historically, patients with multiple sites of N2 disease (stage IIIA) and all those with T4 or N3 disease (stage IIIB) have been treated with radiation therapy alone. In the United States, however, combined-modality therapy (chemotherapy plus irradiation) has become the new standard of care, based largely on outcome data from two prospective, randomized trials. The first trial, reported by Dillman et al for the Cancer and Leukemia Group B (CALGB), compared standard continuous, daily fractionated irradiation (to 60 Gy in 6 weeks) with a regimen in which two cycles of vinblastine and cisplatin (Platinol) preceded the same radiation therapy.[2] Compared with irradiation alone, the combined-modality approach was associated with a statistically significant survival advantage (median duration, 9 vs 14 months; 2-year rate, 13% vs 26%, respectively; P < .012). The survival difference persisted at 5 years (7% vs 19%, respectively).[3]

Unfortunately, entry in this trial was closed after 155 patients had been enrolled, before patient accrual reached the level that had been initially projected. Because of concerns that the results might represent a “false-positive” finding, a second, larger trial (involving 450 patients) was mounted as an intergroup study.

As reported by Sause et al, this study also demonstrated a significant survival advantage when two cycles of vinblastine and cisplatin were given before continuous, fractionated irradiation to 60 Gy (the CALGB arm) as opposed to either of two programs of radiation therapy alone.[4] The 2-year survival rate was 32% with the combined-modality approach vs 19% with standard irradiation alone. Therefore, the combination of vinblastine and cisplatin followed by chest irradiation has been validated in consecutive randomized trials and has been widely adopted as a standard regimen.
Concurrent Combined-Modality Therapy

The Southwest Oncology Group (SWOG) pursued a different approach to combined-modality therapy in patients with stage III, inoperable non-small-cell lung cancer. These investigators chose to administer cisplatin and etoposide (VePesid) concurrently with chest irradiation (two cycles of chemotherapy plus 45 Gy of continuous, fractionated local treatment), followed by surgical resection 3 to 5 weeks after completion of the combined-modality induction phase.[5,6] The concurrent use of chemotherapy and irradiation was chosen because the SWOG had previously demonstrated its feasibility in the treatment of limited-stage small-cell lung cancer, and the results were apparently superior to those achieved when the modalities were administered in sequence.[7]

Another important distinction between this study and previous work was that before the initiation of any therapy, the investigators conducted surgical staging—including mediastinal nodal sampling, if necessary—to document N2 or N3 status. In the other studies, only clinical and radiographic criteria were used for staging.

Several important observations emerged from this phase II SWOG trial.[5,6] First, a comparable proportion of patients with stage IIIA N2 and stage IIIB disease could undergo resection (74% for patients with stage IIIA N2 disease and 58% for patients with stage IIIB disease). Second, survival rates were encouraging and were again comparable for stage IIIA and IIIB disease (median survival, 13 months for stage IIIA and 16 months for stage IIIB; 2-year rate, 34% for patients with stage IIIA disease and 38% for patients with stage IIIB disease). Third, almost 60% of the resected specimens contained no macroscopic evidence of residual tumor at the primary site, and the pathologic complete response rate was 20%.

The most striking clinicopathologic correlation, however, was between survival and mediastinal nodal status at the time of resection. Among 107 patients who underwent resection, 45% had microscopically negative mediastinal nodes; median survival duration in this group was 30 months and the 3-year survival rate was 40%. In contrast, patients with microscopically positive nodes had a median survival duration of 10 months and a 3-year survival rate of 10%. If these observations are borne out in other studies of neoadjuvant therapy, the implication will be that additional, potentially non-cross-resistant therapy may be of particular benefit in the latter group.

Other Considerations

At face value, the results of the SWOG trial appear to be better than those for sequential, combined-modality therapy without surgery. However, the rate of treatment-related fatality was higher in the SWOG trial (10%, vs 2% for most other studies without surgery), and the majority of these deaths occurred in the postoperative setting.

Another trial of triple-modality therapy was reported recently by Strauss et al for CALGB.[8] Like the SWOG trial, this study was confined to surgically staged patients. Unlike the SWOG trial, however, patients with stage IIIB disease were excluded and those with the more favorable stage IIIA disease (T3, N0; T3, N1) were included, comprising 20% of the participants.

Cisplatin, vinblastine, and fluorouracil (5-FU) were combined with concurrent chest irradiation to 30 Gy, followed by resection, when possible, and then one more cycle of chemotherapy and an additional 30 Gy to the tumor bed. Of 41 eligible patients, 25 (61%) underwent resection. The median duration of survival was 16 months, and the 2-year and 5-year survival rates were 47% and 22%, respectively. The pathologic complete response rate was 16%.

As in the SWOG study, there was a high incidence of treatment-related deaths (15%), half of which were perioperative. It is noteworthy that patients who completed therapy according to the protocol but did not undergo resection had a long-term survival rate that was nearly identical to that in patients who were resected (25% vs 24%, respectively).

A recent SWOG trial assessed concurrent cisplatin and etoposide for four cycles plus chest irradiation to 61 Gy, omitting resection, in surgically staged IIIB disease. The findings revealed a 40% survival rate at 2 years and a reduction in mortality when compared with that observed in the trial incorporating surgery.[9]

Taken together, these results suggest that a concurrent, combined-modality approach with full-dose chemotherapy (four cycles of cisplatin and etoposide) and definitive, continuous fractionated irradiation (60 Gy in 6 weeks) may be as good as the triple-modality approach with resection added. This hypothesis is the subject of an ongoing, randomized intergroup trial (INT 0139) in stage IIIA, N2 disease. If brought to successful completion, this study should resolve the question of whether surgery should play a major role in the treatment of stage III disease.

For stage IIIB disease, the SWOG has recently activated a trial of concurrent cisplatin plus etoposide (two cycles) with chest irradiation (60 Gy), followed by three cycles of docetaxel (Taxotere) consolidation, in an attempt to gain further improvement in long-term results. Another major
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question involves comparison of sequential vs concurrent chemoradiotherapy; this issue is the focus of a current study by the Radiation Therapy Oncology Group, as well as a recently completed trial in Japan. The results of these trials are awaited with interest.

**Stage IIIB (Positive Pleural Effusion) and Stage IV Disease**

**Chemotherapy vs Supportive Care**
In the United States today, most patients with stage IIIB non-small-cell lung cancer who have a cytology-positive pleural effusion are considered candidates for chemotherapy because radiation cannot be used to treat the entire pleural surface. Patients with stage IV disease are usually considered for chemotherapy if they are fully ambulatory, based on the outcome of a randomized trial by Rapp et al for the National Cancer Institute of Canada.[10] These investigators found a statistically significant survival advantage among patients who received cisplatin-based chemotherapy as compared with supportive care alone (control).

This was the only randomized trial to address this question with sufficient statistical power to detect a modest increase in duration of survival. Unfortunately, the observed benefit from cisplatin-based regimens has been modest to date; among patients with stage IV disease, the 1-year survival rate has increased from 10% to a range of 20% to 25%.

**Response Rate vs Survival Rate**
Response rate has been the end point most commonly reported as a measure of chemotherapy efficacy. The response rate is influenced by disease stage (approximately twice as high for stage III as for stage IV) and by performance status. Single institutions typically report higher response rates than do cooperative groups.[11,12] Response rate correlates poorly with the impact on survival.

The latter point is illustrated by the results of a phase III trial by the Eastern Cooperative Oncology Group (ECOG) in which single-agent carboplatin (Paraplatin) was compared with four other regimens, including a cisplatin-based combination: mitomycin (Mutamycin), vinblastine, and cisplatin.[13] Although carboplatin produced only a 9% response rate, the median duration of survival (7.3 months) and 1-year survival rate (20%) were significantly better than those associated with the other regimens (P = .008). In the same trial, mitomycin, vinblastine, and cisplatin produced a higher initial response rate of 20% but a trend toward a shorter duration of survival. Thus, the emphasis in current trials is rightly placed on survival effects as an end point of potentially effective therapy.

**Evolution of Chemotherapy**
During the 1980s, few new agents were recognized in the treatment of non-small-cell lung cancer. Dose response was studied for cisplatin in a prospective, randomized trial by the SWOG.[14] No advantage was demonstrated by doubling the dosage of cisplatin from 100 to 200 mg/m² or by adding mitomycin to the high-dose cisplatin arm. Because the results of this trial duplicated the SWOG results with other cisplatin-based combinations (ie, a median survival duration of 5.5 to 7.2 months and a 1-year survival rate of 23%), the SWOG retained cisplatin alone at a dosage of 100 mg/m² as its active control arm. Based on a similar experience with cisplatin plus etoposide, the ECOG entered the 1990s with this combination as its active control arm.

During the past 5 years, several new agents with activity in non-small-cell lung cancer have been identified (Table 1).

**Vinorelbine (Navelbine)**[A new antitubulin with a classic mechanism of action, vinorelbine has an improved therapeutic index attributable to a decreased occurrence of neurotoxicity. As a single agent, vinorelbine has produced response rates of 12% to 17%. Its median survival duration, however, is in the range of that observed with cisplatin-based combinations (28 to 32 weeks).[15,16] In a controlled trial, survival was superior with vinorelbine as compared with 5-FU plus leucovorin.[16] Of the single agents that have been tested against other regimens, only one other drug (carboplatin) has demonstrated a survival advantage.[13]

A French trial compared vinorelbine alone with the combination of vinorelbine plus cisplatin or the standard European combination of vindesine (Eldisine) plus cisplatin.[17] The new combination showed a statistically significant advantage over the standard combination (median duration of survival, 40 vs 31 weeks; P = .04), with more hematologic toxicity but less neurotoxicity. In a subsequent SWOG study, we compared cisplatin plus vinorelbine to our standard regimen of cisplatin alone.[18] The combination yielded a superior response rate (26% vs 9%) and 1-year survival rate (36% vs 18%; P = .001). Hematologic toxicity with the combination was more severe but within acceptable limits (a 1% mortality rate from neutropenic sepsis and an overall mortality rate of 3%).
Paclitaxel (Taxol)—The taxanes, of which paclitaxel is the first, are a new class of agents that exert their effects by stabilizing the polymerized form of tubulin. Paclitaxel produced a 24% response rate among 48 patients in separate phase II trials,[19,20] and the 1-year survival rate was 35% in the latter ECOG pilot study.[20] In phase II trials, paclitaxel has been combined with cisplatin or carboplatin. The former combination is active but is associated with cumulative neurotoxicity.[21] Both high-dose (250 mg/m$^2$) and low-dose (135 mg/m$^2$) paclitaxel, combined with cisplatin, produced higher response rates when compared with the standard therapy of cisplatin plus etoposide (27% to 32% vs 12%; P < .001).[22] Each paclitaxel arm also produced longer median duration of survival (9.6 to 10 months vs 7.7 months) and higher 1-year survival rates (37% to 39% vs 32%), but the differences were not statistically significant. When the paclitaxel-containing arms were combined, however, there was a statistically significant survival advantage compared with cisplatin plus etoposide (P = .04). The higher dose of paclitaxel produced more severe neurotoxicity and myelosuppression, despite its combination with granulocyte colony-stimulating factor (filgrastim [Neupogen]).

Several abstracts have been presented on the activity of carboplatin plus paclitaxel in phase II trials,[23-25] and one paper was recently published by Langer et al.[26] The overall response rate in these trials was on the order of 50% (range, 25% to 63%), with median survival duration of 38 to 53 weeks. Taken at face value, the combination of these two agents may be the most active available therapy at acceptable levels of toxicity. However, in the study by Langer et al, which found a median survival duration of 53 weeks, 37% of patients had unanticipated hospitalizations during treatment, primarily because of myelosuppression.[26]

Docetaxel (Taxotere)—The other taxane in clinical use, docetaxel, was initially administered at a dosage of 75 to 100 mg/m$^2$ every 3 weeks and without the routine premedication that is required for paclitaxel. It is now appreciated, however, that steroid premedication is useful in the prevention of hypersensitivity reactions to docetaxel. Steroids also delay and ameliorate the development of a second side effect that is peculiar to docetaxel: peripheral edema and third-space fluid accumulation related to cumulative dose.

As a single agent, docetaxel produced a response rate of 31% in initial trials. The activity of this agent in patients with previously treated, platinum-refractory non-small-cell lung cancer is of particular interest: A response rate of 19% has been observed in 72 patients, with a projected survival rate of approximately 40% at 1 year.[27,28] If these observations are validated by other investigators, docetaxel will be the first agent identified as having useful activity in the setting of platinum failure.

Gemcitabine (Gemzar)—Like cytarabine, gemcitabine is a cytidine analog. However, gemcitabine has a very different spectrum of activity in preclinical systems as well as in human cancers, possibly because of its longer intracellular half-life in its form as the triphosphorylated compound. This agent is usually given on a weekly schedule and has been reported to produce response rates in the range of 20% in phase II trials.[29-31]

Gemcitabine produces a mild flu-like syndrome and moderate neutropenia, but it has few other side effects in most patients. This favorable pattern of toxicity has led to its use in a two-drug combination with cisplatin. Three recent abstracts[32-34] reported that this combination yielded response rates of 30% to 44% in stage IV disease, with acceptable toxicity; survival data are not yet mature.

Irinotecan (Camptosar) stabilizes the topoisomerase I [cleavable complex] in a fashion analogous to the effect of etoposide on topoisomerase II. In a study in Japan, irinotecan produced a 33% response rate among 40 patients with stage IV non-small-cell lung cancer, and the median survival duration was 9.2 months.[35] Leukopenia and diarrhea are dose-limiting toxicities and have poor predictability (especially the latter, which can be life-threatening).

In other studies in Japan, irinotecan was combined with cisplatin, with or without vindesine, and yielded response rates approaching 50%.[36,37] In the United States, phase II trials of the combination of cisplatin and irinotecan are nearing completion, with results yet to be reported.

Topotecan (Hycamtin)—Also studied in non-small-cell lung cancer, topotecan has a lower reported response rate than irinotecan but a comparable median survival rate.[38] Topotecan has the advantage of producing fewer problems with diarrhea and bears investigation in combination with...
other agents.

**Conclusions**

Cisplatin, alone or in combination, probably affects survival in advanced non-small-cell lung cancer. Carboplatin and vinorelbine have had a beneficial effect on survival when used as single agents in randomized trials. The combination of cisplatin and vinorelbine has shown reproducible effects on survival when compared with standard cisplatin-based therapy; this regimen currently represents a reasonable community standard for the treatment of non-small-cell lung cancer. Paclitaxel and docetaxel are active new agents. The combination of carboplatin and paclitaxel warrants comparison with other treatments in randomized trials. Paclitaxel is of special interest because of its activity in platinum-refractory disease. Other new agents of interest include gemcitabine and irinotecan, although their roles in combination therapy have yet to be defined.

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