To Treat or Not to Treat Non–Small-Cell Lung Cancer Patients? Current Perspectives

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In the 1980s, the introduction of cisplatin (Platinol)-based chemotherapy prolonged survival and improved quality of life in patients with stage III and IV non–small-cell lung cancer. More recently, the use of five new

**Introduction**

The third most common cancer in the United States, lung cancer, is the leading cancer killer of both men and women.[1] Because of the low cure rate (14%), lung cancer kills more individuals than cancers of the breast, prostate, colorectum, and ovary combined.[1] Less than 25% of lung cancer patients present with stages I and II, and nearly all patients die with disseminated systemic disease. Thus, improved systemic therapies are critical to improving the cure rate.

Great pessimism developed regarding the role of chemotherapy in non–small-cell lung cancer, largely because alkylating agent–based chemotherapy produced low response rates and considerable toxicity. Moreover, these drugs worsened survival at all stages, even when used as postoperative adjuvant therapy.[2]

The treatment of lung cancer improved considerably in the 1980s, when cisplatin (Platinol)-based chemotherapy was shown to prolong survival and improve quality of life in patients with stage III and IV non–small-cell lung cancer as shown by randomized trials and meta-analyses of these randomized trials.[2,3] In resectable non–small-cell lung cancer, postoperative cisplatin-based chemotherapy improved 5-year survival rates by 5% (a value of borderline significance given the small number of patients enrolled in these trials).[2]

In the 1990s, a renewed optimism has emerged with the introduction of five new chemotherapeutic agents, each of which produces higher response rates and longer survival than cisplatin.[4]

**Therapy for Stage IV**

At least one-third of all non–small-cell lung cancer patients present with metastatic disease, and the vast majority of patients will develop metastases during their course. The prognosis for patients with metastatic disease is dismal, with median survivals of about 4 months and 1-year survival rates below 15% when best supportive care (including radiotherapy but excluding chemotherapy) is the only therapy.[2]

Randomized trials and meta-analyses of these trials showed that cisplatin-based chemotherapy significantly improves survival in these patients, although the improvements are modest.[2] The median survival is improved by an average of 10 weeks and the 1-year survival rate is increased by 10%.[2] Although there has been limited study of this issue, available data suggest that cisplatin-based therapy also improves quality of life as assessed by patients, despite the drug’s toxicity.[3]

These data were derived primarily from studies restricted to patients with good performance status. Since response rates are lower and toxicity rates are higher in patients with poor performance status, the role of chemotherapy in poor performance status is unproven.

During the 1990s at least five new chemotherapeutic agents were tested in 100 or more advanced-stage non–small-cell lung cancer patients and were shown to produce responses in more
than 20% of those patients. Results from these studies are summarized in Table 1 where they are compared to results with cisplatin alone.

The survival results from these studies were as striking as the response-rate results. The average median survivals in these studies ranged from 33 weeks to 41 weeks, and the 1-year survival rates ranged from 24% to 52%. These results can be contrasted with a median survival of 4 months and 1-year survival rates of 10% to 15% with best supportive care.

Randomized trials are necessary to confirm results from phase II studies. Results from randomized studies comparing new single agents to other therapies are summarized in Table 2. The original Eastern Cooperative Oncology Group (ECOG) study of paclitaxel (Taxol) showed that it was superior to both merbarone and piroxantrone with respect to both response and survival. Vinorelbine (Navelbine) was compared to fluorouracil (5-FU)/leucovorin and was shown to be superior with respect to response, time to progression, and survival. Single-agent vinorelbine was also compared to the combination of vinorelbine plus cisplatin. As shown in Table 2, the combination proved superior to single-agent vinorelbine with respect to both response and survival.

Single-agent gemcitabine (Gemzar) was compared to a standard two-drug combination consisting of etoposide plus cisplatin in two randomized trials. In both studies, gemcitabine produced response rates and survival that were equivalent to the standard two-drug combination, but gemcitabine produced significantly less toxicity (Table 2).

The activity of these new chemotherapeutic agents led to phase II studies in which they were combined with cisplatin. The results of these phase II studies are summarized in Table 3. Each combination produced response rates exceeding 35%, whereas single-agent response rates were always less than 26%. A comparison of Table 1 and Table 3 shows less striking differences with respect to median survival and 1-year survival rates although the combination results were always superior.

Randomized trials to confirm these results are now appearing in the literature and are summarized in Table 4. The results of these studies suggest that survival is improved when combinations of vinorelbine plus cisplatin, gemcitabine plus cisplatin (Eli Lilly, unpublished data), and paclitaxel plus cisplatin are compared to cisplatin alone or etoposide plus cisplatin. As in the phase II studies, the increases in response rates are somewhat more striking than the increases in survival. Nonetheless, the median survival exceeded 35 weeks and the 1-year survival rates exceeded 30% in all groups receiving a new drug plus cisplatin.

The costs of these new chemotherapeutic agents are higher than the costs of chemotherapeutic agents no longer under patent protection. Because survival is prolonged by chemotherapy, the costs of chemotherapy per year of life gained can be calculated. Such calculations have been published by Evans and his coworkers from Canada and are summarized in Table 5. An earlier study from Canada showed that patients treated with outpatient chemotherapy incurred lower costs than patients given best supportive care (including radiotherapy). The costs were lower because the chemotherapy-treated patients received less radiotherapy and spent fewer days in the hospital. These results were confirmed in a more recent Canadian study. This led to lower costs for patients receiving etoposide plus cisplatin, compared to best supportive care.

The new chemotherapeutic agents are associated with higher costs than etoposide/cisplatin therapy, as indicated in Table 5. The costs per year of life gained are under $20,000 (in 1995 Canadian dollars) for each of these therapies. Costs of this magnitude are generally deemed to be cost-effective in the medical community and are considerably lower than commonly used procedures such as organ or marrow transplantation, dialysis, or mammography.

In summary, there is now convincing evidence that chemotherapy can relieve symptoms, improve quality of life, and prolong survival at acceptable medical costs in patients with advanced non-small-cell lung cancer. Newer drug combinations appear to be superior to older cisplatin-based...
Therapy for Stage IIIIB

For many years, radiation therapy was the standard treatment for stage IIIIB non–small-cell lung cancer. The recognition that cisplatin had radiosensitizing properties and could be given safely before, after, or with chest radiotherapy led to randomized trials comparing radiotherapy alone to combined chemotherapy and radiotherapy in stage IIIIB non–small-cell lung cancer. These randomized trials and meta-analyses of these trials established that the combined-therapy approaches significantly prolonged survival.[2] On average, the median survival was improved by about 4 months.[2,16] The long-term survival was also extended, with two- to threefold improvements in 5-year survival rates.[2,16]

Several approaches to combining the modalities were studied including sequential approaches[16], alternating approaches[17], and concurrent approaches.[18,19] Each of these approaches was superior to radiotherapy alone in randomized trials, and the meta-analyses were unable to show whether one of these approaches was preferred over others.[2] Table 6 summarizes the results of some of the randomized trials.

More recently, a randomized trial comparing the sequential and concurrent approaches was completed (Table 6).[20] The study showed that the concurrent administration of mitomycin (Mutamycin), vinblastine, and cisplatin chemotherapy (MVP) and chest radiotherapy (56 Gy) produced a higher response rate (84% vs 66%) and longer survival compared to a sequential approach. There was more toxicity in the concurrent arm, but the authors concluded that the improvements in efficacy outweighed the increases in toxicity.

The addition of chemotherapy to chest radiotherapy also improves quality of life as assessed by patients. In a phase III study conducted in the United Kingdom, patients were randomized to receive chest radiotherapy (56 Gy) and best supportive care measures or chest radiotherapy and chemotherapy with mitomycin, ifosfamide (Ifex), and cisplatin. Survival was significantly longer in patients receiving the combined modality (median, 13 vs 9.9 months).[3] The quality-of-life score, whereby a lower score represented better quality of life, was 287 in the combined modality arm vs 394 in the radiotherapy arm (P = .0002).

Since all of the new chemotherapeutic agents have radiosensitizing properties in vitro,[4,21] it is logical to combine these agents with chest radiotherapy. The most extensive experience with this combination involves paclitaxel. Phase II studies evaluating chest radiotherapy with paclitaxel alone or with paclitaxel and other agents are summarized in Table 7.[22-26]

Choy and coworkers studied the weekly administration of concurrent chest radiotherapy and paclitaxel alone[22] or paclitaxel and carboplatin (Paraplatin).[23] They reported that these combined approaches produced exciting preliminary results with acceptable toxicity. Belani and coworkers also evaluated concurrent radiotherapy with paclitaxel and carboplatin.[24] They, too, reported extremely favorable survival results with acceptable toxicity.

Curran et al studied paclitaxel in combination with carboplatin given alone for two cycles and then followed by concurrent radiotherapy with the same paclitaxel combination given at 3-week intervals.[25] This trial had impressive survival results with acceptable toxicity. Finally, Greco et al used a three-drug combination of paclitaxel, cisplatin, and etoposide given at 3-week intervals and combined with chest radiotherapy.[26] They reported an 82% response rate, a 1-year survival of 65%, and acceptable toxicity.

It appears that the simultaneous delivery of gemcitabine and radiotherapy is extremely dangerous, producing marked increases in normal tissue toxicity.[4] Several patients experienced toxic deaths when near-full doses of gemcitabine were given weekly with chest radiotherapy. Phase I studies are now evaluating very low doses of weekly gemcitabine (200 to 300 mg/m²) with chest radiotherapy. Fewer results are available for docetaxel (Taxotere), vinorelbine, and irinotecan (Camptosar) combined with radiotherapy. Further study of these combinations will be required before standard
recommendations can be made.

Therapy for Stage IIIA

The vast majority of stage IIIA patients have involvement of mediastinal lymph nodes (T1-3, N2, M0). When mediastinal lymph node involvement is documented preoperatively, the results of surgical therapy alone are very poor, with 5-year survival rates of only 10% to 15%.[27] The vast majority of relapses in these patients occur in distant sites. Thus, effective systemic therapies are required to improve cure rates.

A group from Memorial Sloan-Kettering Cancer Center found that the combination of cisplatin, vinorelbine, and mitomycin produced high response rates in advanced non–small-cell lung cancer.[28] They then tested this combination as a preoperative regimen to reduce tumor burden and downstage patients with clinical stage IIIA, N2 non–small-cell lung cancer.[29] They reported better than expected survival, with a 5-year survival rate of about 25%.[29]

This phase II study and other similar studies were followed by three phase III studies in which patients were randomized to surgery alone or pre- and postoperative cisplatin-based chemotherapy in addition to the surgery.[30-32] The results are summarized in Table 8.

In all three trials, survival was superior in the chemotherapy arms, and the differences were statistically significant in two of the trials.[30,31] These studies have been criticized because of their small size and because of the poor outcome in the patients receiving surgery alone. Nonetheless, most investigators have concluded that surgery alone is no longer adequate therapy for stage IIIA, N2 patients.

Another neoadjuvant approach used combined chemotherapy and radiotherapy prior to surgery. This approach was used by the Southwest Oncology Group (SWOG) and other groups.[33] The SWOG investigators reported that 59% of 126 patients had an objective response to the preoperative therapy and another 29% had stable disease. Surgical resections were performed in these stable and responding patients. There was no pathologic evidence of tumor in 21% of the patients, and the projected 4-year survival rate was just above 20%. These results were not markedly superior to those obtained with chemotherapy and radiotherapy alone, and 6% of patients experienced operative mortality.

These results led to an ongoing intergroup trial in which patients with preoperatively identified N2 nodes are randomized to receive chemoradiotherapy alone or chemoradiotherapy induction followed by surgery. This trial should determine whether using all three of these modalities together is superior to using only two modalities. If there are equivalent results with all three modalities vs chemoradiotherapy, other trials will be necessary to determine whether chemotherapy plus radiotherapy or chemotherapy plus surgery would be preferred.

To date, no randomized studies have used the new chemotherapeutic agents in patients with stage IIIA disease. It is likely that the new agents will provide at least as much advantage in stage IIIA as they do in stage IV, so these trials should be performed in the near future.

Therapy for Stages I and II

Surgery alone produces 5-year survival rates of 50% to 60% in clinical stage I patients and 33% to 50% of clinical stage II patients.[27] The results are better still for patients with surgical stages I and II in whom node biopsies were negative at the time of surgery. In these instances, 5-year survival rates are about 70% for stage IA, 60% for stage IB, 60% for stage IIA, and 50% for stage IIB.

For patients with stage IA, the rate of development of a second primary cancer exceeds the rate of relapse, especially after 2 years and in those who continue to smoke.[34] Some investigators believe that stage IA patients should not be included in adjuvant and neoadjuvant studies because of their relatively favorable prognosis. This philosophy, however, can be questioned. About 30% of these patients develop a recurrence (usually within 2 years), and a 20% reduction in the hazard rate would
increase the cure rate from 70% to 76%. These patients should also be considered for chemoprevention studies.

Meta-analysis of randomized trials using postoperative alkylating agent-based chemotherapy showed that survival is significantly shortened by this approach.[2] In contrast, cisplatin-based postoperative therapy reduced the hazard rate of death by 13%.[2] This was translated into an absolute increase of 5% in the 5-year survival rate. These differences were of borderline statistical significance given the small number of patients in these trials. The magnitude of the reduction in hazard rate was not dissimilar from that observed in breast and colon cancers, for which trials were larger and adjuvant therapy was usually recommended.

These data have been interpreted in different ways. Patient surveys have shown that more than 95% of patients would choose to receive chemotherapy that would improve their cure rate by 5%.[35] Yet, after these results were published, physicians in Wales overwhelmingly indicated that they would not offer such therapy to their patients.[36]

Fortunately, a number of randomized trials are being conducted around the world to determine whether other cisplatin combinations, including those with new agents, will improve survival and cure rates. Due to the promising results of neoadjuvant therapy in patients with stage IIIA disease, as well as the fact that the new-agent combinations appear to be better than older cisplatin-based combinations, trials of new combinations used in a neoadjuvant manner have been instituted. For example, the biomodality lung oncology team in the United States is evaluating the combination of paclitaxel and carboplatin given for two cycles before surgery and then three cycles after surgery. Preliminary results of this study are encouraging, and there are plans to institute a randomized trial.[37]

References:


