Concurrent Chemoradiotherapy for Unresectable Stage III Non–Small Cell Lung Cancer
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Abstract
Over the last two decades, several approaches to multimodality therapy have been investigated in patients with advanced unresectable non–small cell lung cancer. These include induction chemotherapy and concurrent chemoradiotherapy. Both approaches have been shown to be superior to radiation therapy alone. However, in several randomized trials, concomitant chemoradiotherapy was shown to be superior to the induction chemotherapy approach. It has been hypothesized that the addition of systemic dose sequential chemotherapy to concurrent chemoradiotherapy, either as induction or as consolidation chemotherapy, might further improve survival rates. Recently, the Cancer and Leukemia Group B reported on a randomized phase III trial directly evaluating the addition of two cycles of carboplatin and paclitaxel to concurrent chemoradiotherapy. In this study, induction chemotherapy failed to further improve survival rates of concurrent chemoradiotherapy. A previously conducted randomized phase II study also suggested no benefit from the addition of induction chemotherapy to concomitant chemoradiotherapy. Favorable phase II data have been published supporting the use of consolidation chemotherapy. However, to date, no large randomized study evaluating a possible benefit from consolidation chemotherapy has been completed. In addition to evaluating optimal sequencing strategies of combined modality therapy, current investigations are also focusing on the integration of novel agents, including chemotherapeutic and targeted therapies. Currently ongoing trials involving novel approaches are reviewed here.

Regionally advanced unresectable non–small cell lung cancer (NSCLC)—stage IIIA with bulky N2 and stage IIIB (T4 without pleural effusion or N3)—is characterized by large primary lesions and/or widespread involvement of the ipsilateral or contralateral mediastinum or supraclavicular regions (1). Eradication of bulky widespread disease poses a major therapeutic challenge, because radiation therapy alone can achieve locoregional control in only a small minority of such cases. In addition, patients are at high risk of distant failure due to initial micrometastatic spread (2–6). Thus, an effective systemic therapeutic component needs to be incorporated into curative intent treatment plans. In the past, radiation therapy alone was considered standard therapy. However, 3- to 5-year survival rates achieved by single modality radiotherapy are <10%, and locoregional or systemic control is infrequently attained. As a result, combined modality approaches have been studied intensively, including sequential chemotherapy and radiotherapy (induction or consolidation) and concomitant chemoradiotherapy.

From the experience of the last 20 years, it is clear that a sequential approach is mainly directed at eradication of micrometastatic disease. Induction chemotherapy, in particular, allows for early delivery of full systemic doses of chemotherapy and thus is a strategy best suited to eradicate micrometastatic disease (7–9). Although it can also result in a decrease in locoregional tumor burden, it is unlikely that it can increase the activity of subsequent radiation therapy unless significant volume reduction of the primary tumor occurs. There has also been concern that the delay of radiotherapy resulting from the initial administration of chemotherapy allows for the accumulation of treatment-resistant clonogenic cells and decreased locoregional control (“leaner but meaner tumors”; ref. 10). Concomitant chemoradiotherapy, on the other hand, promises a radiation-enhancing effect possibly associated with improved locoregional control. However, unless the chemotherapy component is administered at full doses, a systemic benefit is less likely (11). Thus, both sequential and concomitant combined modality approaches have a theoretical benefit and potentially complementary activities.

Induction Chemotherapy
A sequential combined modality therapy approach starting with two to three cycles of induction chemotherapy followed by radiotherapy has been compared with radiotherapy alone. Several randomized trials indicating an increase in median survival of ~3 to 4 months (from 10 to 13-14 months) have suggested that the benefit was derived mainly through better control of distant disease (7–9). Overall, the use of induction...
chemotherapy is feasible and effective. It is also logistically less challenging than a concurrent approach, because most chemotherapy-related toxicities are readily managed and similar to those encountered in patients with stage IV disease receiving the same regimen. Thus, induction chemotherapy remains an option for a selected group of patients who may not be candidates for a more intensive concomitant chemoradiotherapy approach.

Concomitant Chemoradiotherapy

Several initial trials comparing concomitant chemoradiotherapy to radiotherapy alone failed to show an improved treatment outcome. These trials frequently used single-agent chemotherapy at suboptimal doses or agents lacking proven single-agent activity (4, 11). Nevertheless, an early study conducted in Europe indicated that daily doses of cisplatin added to split-course radiotherapy resulted in better local control and survival than split-course radiotherapy by itself (11). The major criticism of this trial was that it lacked a standard radiotherapy control arm of daily fractionated radiotherapy without planned interruption. Of note, a trial conducted by the Hoosier Oncology Group comparing single-agent cisplatin at a dose of 70 mg/m² every 3 weeks for three cycles with concomitant radiotherapy to radiotherapy alone was negative for a survival benefit (12).

By the mid-1990s, however, positive data were generated in trials using combination chemotherapy at systemically active doses. The Southwest Oncology Group (SWOG) published their phase II experience with a combination of cisplatin, etoposide, and radiation followed by cisplatin and etoposide maintenance chemotherapy. In both resectable and unresectable disease, favorable phase II data were obtained (13–15). Positive phase II data were also generated in trials by the Radiation Therapy Oncology Group (16). In Europe, a study comparing carboplatin and etoposide with radiotherapy versus radiotherapy alone showed an increased median survival of 22 versus 14 months (17, 18). These trials and subsequent studies directly comparing concomitant chemoradiotherapy with induction chemotherapy have led to the adoption of concomitant chemoradiotherapy as the currently preferred standard treatment for patients with good performance status (19).

Induction versus Concomitant Therapy

Several randomized phase III studies have compared induction chemotherapy with concomitant chemoradiotherapy using an identical chemotherapy regimen (20–25). The first of these was a Japanese study using the MVP regimen (mitomycin C, vinblastine, and cisplatin) either followed by radiotherapy or administered during split-course radiotherapy (20). This important trial reported median survival times of ~13 months for the induction chemotherapy approach with an improvement to 16 months when using a concomitant approach. Radiation Therapy Oncology Group 9401 expanded on these observations (21). The base regimen here was cisplatin and vinblastine administered either before or during radiotherapy. A third arm used cisplatin with oral etoposide and hyperfractionated radiotherapy. This trial confirmed the Japanese observations with median survival times of 13 months for the sequential approach and 17 months for the concurrent approach. Patients over the age of 70 years, in particular, seemed to benefit from concurrent therapy. The intensification of radiation did not result in a further improvement in outcome (median survival of 15 months). More recently, additional trials comparing sequential and concomitant combined modality therapies have been presented. All of them show either a trend to or a statistically significant improvement in survival. However, all of these studies noted increased toxicity with a concurrent therapy, primarily consisting of intensified toxicities within the radiation therapy field, notably, esophagitis with associated nutritional problems and potential dehydration. There may also be a small increase in the risk of pneumonitis. Thus, concomitant chemoradiotherapy may be too toxic for selected patient groups with NSCLC, especially elderly patients and those with poor performance status. The identification of milder and more effective treatment approaches, therefore, remains a high priority.

Sequential and Concomitant Combined Modality Therapy

The most successful concomitant chemoradiotherapy regimens to date are those using systemic doses of chemotherapy (20, 21, 26). It can be postulated that these regimens can result in eradication of micrometastatic disease while also providing a radiation-enhancing effect. The early introduction of both chemotherapy and radiation therapy may, therefore, be responsible for the superiority of the concomitant approach in direct comparison. It has been postulated that the addition of a sequential chemotherapy component to concomitant chemoradiotherapy may further improve treatment outcome. Induction and consolidation strategies have both been pursued.

The consolidation chemotherapy approach has mainly been investigated by SWOG. Initial phase II data using cisplatin/etoposide both during and following radiotherapy at systemic doses yielded a median survival of 15 months (14). In a subsequent trial, the consolidation chemotherapy regimen was altered to single-agent docetaxel (26). This was based on a hypothesis of at least partial non-cross-resistance of this agent with other chemotherapy regimens derived from preclinical data and the clinical responses observed in the second-line stage IV treatment setting. In this phase II study of 83 patients with biopsy-proven stage IIIIB disease, the median survival was >2 years and the 3-year survival rate ~40%. Although these data are highly encouraging, it must be pointed out that the final analysis included only 83 of 98 patients registered. Furthermore, eligibility criteria differed from those used in stage III trials in that pathologically proven stage III disease was required. This may have led to inclusion of patients with less bulky disease. Nevertheless, these data are encouraging. Furthermore, because they seem superior to those of the prior SWOG study using cisplatin/etoposide as consolidation therapy, it is possible that the positive survival effect is indeed mediated by the administration of docetaxel for three cycles of consolidation therapy. The Hoosier Oncology Group is currently investigating consolidation chemotherapy in a randomized phase III trial to determine whether consolidation therapy with three cycles of docetaxel, compared with observation, following
concurrent chemoradiotherapy (cisplatin/etoposide) will improve progression-free and overall survival for patients with unresectable stage III NSCLC.

An alternative strategy has been explored by the Cancer and Leukemia Group B (CALGB). After identifying the efficacy of induction chemotherapy (7), we investigated whether the addition of carboplatin as a radiation-sensitizing agent could further improve treatment outcome (27). In CALGB 9130, all patients received two cycles of induction chemotherapy with cisplatin and vinblastine followed by either standard single daily fraction radiation therapy or identical radiation therapy with weekly doses of carboplatin at 100 mg/m². Median survival on both study arms was 13 months with no difference in survival, time to progression, or pattern of failure. Thus, the use of low-dose carboplatin as a sensitizer was not further investigated.

CALGB 9431 continued to employ the sequence of induction chemotherapy followed by concomitant chemoradiotherapy and aimed to explore in a randomized phase II setting the use of doublet chemotherapy during induction and concomitant chemoradiotherapy focusing on the new drugs of the 1990s (28–30). In this randomized three-arm phase II study, all patients received four cycles of cisplatin at 80 mg/m². Two cycles were administered as induction chemotherapy and two during radiation therapy. Patients were randomized to receive a second chemotherapy agent consisting of paclitaxel, gemcitabine, or vinorelbine (Table 1). Mature data from this study have been published (Fig. 1; ref. 30). Dose-limiting toxicities were not identified and the strategy was feasible on all three arms. Nevertheless, in-field toxicities, in particular, esophagitis, were pronounced on the gemcitabine arm, necessitating more frequent radiotherapy interruptions. There was also a higher incidence of grade III and IV thrombocytopenia on that study arm. The overall median survival time was 17 months, with study arm-specific survival times of 14.8 months for paclitaxel, 17.7 months for vinorelbine, and 18.3 months for the gemcitabine arm. In a similar parallel trial, CALGB investigated the combination of carboplatin and paclitaxel. Again, two cycles were administered as induction chemotherapy with weekly low doses of both agents given during radiation therapy (31). As reported by others, this regimen was also found to be tolerable (25, 32–34). Median survival time was 15.1 months. The data from these four regimens given as induction and concomitant chemoradiotherapy suggested the feasibility of the approach. Furthermore, median survival times exceeded that of any prior CALGB study. Nevertheless, the median survival times of ~15 to 17 months were compatible with a concomitant chemoradiotherapy effect alone (20, 21). Of note, the two paclitaxel-based arms were associated with the lowest numerical survival times.

CALGB conducted a randomized study to specifically test the contribution of induction chemotherapy. In CALGB 39801, all patients received concomitant chemoradiotherapy with weekly carboplatin and paclitaxel (35). Patients were randomized to receive only concomitant chemoradiotherapy or to first receive two cycles of carboplatin and paclitaxel followed by concomitant chemoradiotherapy. An analysis of this study has been presented. It indicated no significant survival benefit from the addition of induction chemotherapy. Furthermore, median survival times on both study arms were disappointing (11 months for concomitant only and 13 months for concomitant plus induction chemotherapy). The data suggested that the addition of induction chemotherapy to concomitant low-dose chemoradiotherapy does not result in a statistically significant survival benefit. Furthermore, given the disappointing survival times on both study arms, they suggested that the identification of a more effective chemoradiotherapy platform remains a high priority.

For the large majority of patients with stage III NSCLC, concomitant systemic dose chemoradiotherapy represents the current standard. The use of an additional chemotherapy component remains investigational. CALGB 39801, investigating the addition of induction chemotherapy, does not support that strategy. A randomized trial evaluating consolidation chemotherapy is currently in progress. These two strategies have also been evaluated in a comparative randomized phase II trial (25). In the Locally Advanced Multimodality Protocol trial, patients received either induction chemotherapy followed by radiation, induction chemotherapy followed by chemoradiotherapy, or chemoradiotherapy followed by consolidation chemotherapy. Chemotherapy regimens on all three study arms were based on the combination of paclitaxel and carboplatin. Approximately 60 patients were entered on each study arm. Median survival times were 13, 12, and 15 months, respectively. Although the small sample size prohibits firm conclusions and the study lacked a control arm of concurrent chemoradiotherapy alone, the data allow the suggestion that the consolidation strategy might deserve further investigations.

### Current Trials

The addition of targeted therapies to concomitant chemoradiotherapy is currently under investigation. Phase I and II studies are evaluating the addition of gefitinib or erlotinib during radiation therapy to the CALGB or SWOG platform (36–38). The SWOG is currently conducting a large phase III study evaluating the administration of gefitinib following

| Table 1. Schema for CALGB 9431 |
| Days | 1 | 8 | 15 | 22 | 29 | 36 | 43 | 50 | 57 | 64 | 71 | 78 |
| All: cisplatin (mg/m²) | 80 | — | — | 80 | — | — | 80 | — | — | 80 | — | — |
| Arm I: gemcitabine (mg/m²) | 1,250 | 1,250 | — | 1,250 | 1,250 | — | 600 | 600 | — | 600 | 600 | — |
| Arm II: paclitaxel (mg/m²) | 225 | — | — | 225 | — | — | 135 | — | — | 135 | — | — |
| Arm III: vinorelbine (mg/m²) | 25 | 25 | 25 | 25 | 25 | 15 | 15 | 15 | 15 | 15 | 15 | 15 |
| X-ray therapy | — | — | — | — | — | — | — | — | — | — | — | 66 Gy |
The latter agents can be administered at systemically active full data evaluating cisplatin and etoposide as radiation enhancers. Multimodality Protocol study have been somewhat disappoint-treatment outcomes in CALGB 39801 and the Locally Advanced tions of this regimen suggested a high degree of activity, administered at 40 to 50 mg/m²/wk. Although early evalua-
an area under the curve of 2 mg/mL min with paclitaxel Typically, this regimen consists of carboplatin administered as radiation-enhancing agents. The Eastern Cooperative Oncology Group is evaluating thalidi-
mide as an antiangiogenic agent in a randomized phase III study (39). Antiangiogenic therapies have been shown to enhance radiotherapy in preclinical experiments (40). In the Eastern Cooperative Oncology Group study, patients receive induction chemotherapy with carboplatin/paclitaxel followed by concomitant chemoradiotherapy with or without thalidomi-
and/or the administration of an erythropoiesis-stimulating agent would improve treatment outcome has not been assessed. Predictive factors have been evaluated. In a comprehensive review of CALGB studies, performance status, the use of com-
mixed modality therapy, and pretreatment anemia were identi-
fied as predictive (44). Whether an early correction of anemia and/or the administration of an erythropoiesis-stimulating agent would improve treatment outcome has not been assessed. Similarly, continued smoking has been shown to have a negative effect in survival (45).

It must be pointed out that most of the above studies used carboplatin and paclitaxel as radiation-enhancing agents. Typically, this regimen consists of carboplatin administered as an area under the curve of 2 mg/mL min with paclitaxel administered at 40 to 50 mg/m²/wk. Although early evaluations of this regimen suggested a high degree of activity, treatment outcomes in CALGB 39801 and the Locally Advanced Multimodality Protocol study have been somewhat disappoint-
ng (25, 31, 35), particularly when compared with the SWOG data evaluating cisplatin and etoposide as radiation enhancers. The latter agents can be administered at systemically active full doses during radiation. It is possible that they could result in better systemic antitumor activity than the low doses of paclitaxel and carboplatin. Efforts are currently under way to identify newer chemoradiotherapy platforms that administer chemotherapy agents at systemic doses. At the University of Chicago, a phase I study has recently been completed evaluating the administration of carboplatin and pemetrexed during standard chest radiotherapy based on preclinical data (46). Early data suggest that these agents can be administered at systemically active doses of carboplatin at an area under the curve of 6 mg/mL min with pemetrexed at 500 mg/m², both administered every 3 weeks (47). A phase II evaluation of this regimen by the CALGB is currently planned.

Performance Status 2 Patients

The above-mentioned trials usually involved patients with a good performance status of 0 or 1. Few data exist evaluating the use of combined modality therapy in less optimally selected patient groups (48, 49). The SWOG has evaluated carboplatin and paclitaxel in a cohort of patients with poor performance status or compromised organ function (49). Their phase II study suggested that this approach was feasible, with a median survival time of 15 months. However, a follow-up trial adding adjuvant paclitaxel had a lower median survival time of 10 months and a higher rate of treatment-related deaths (50). Thus, a milder treatment regimen for this population of patients remains highly desirable. The recent identification of several targeted agents with single-agent activity in NSCLC may facilitate the identification of treatment regimens for these patients in the future (51–53). CALGB is currently investigating a strategy in which patients with performance status 2 receive two cycles of carboplatin and paclitaxel as induction chemotherapy followed by radiation therapy with daily doses of orally administered gefitinib. It is hoped that the addition of gefitinib will result in independent antitumor activity and, more particularly, radiation enhancement. In fact, recent data using the monoclonal antibody cetuximab during radiation therapy for patients with advanced head and neck cancer suggest that an anti–epidermal growth factor receptor–directed strategy can improve treatment outcome without increasing radiation-related toxicities (54). Early data from the CALGB studies support the feasibility of this approach and suggest acceptable tolerance (36).

Summary

Much progress has been made in recent decades in treating stage III NSCLC. Combined modality therapies clearly repre-
ent the current standard, and concomitant chemoradiotherapy is the preferred approach over induction chemotherapy. There have been no phase III comparisons of different chemo-
radiotherapy regimens. Therefore, a specific standard regimen cannot be recommended at this time. Nevertheless, the trial data reviewed above suggest that regimens using full-dose chemotherapy might be preferred. That would suggest the use of cisplatin with etoposide or cisplatin and vinblastine as identified by SWOG and Radiation Therapy Oncology Group trials. Clearly, improved treatment strategies are needed, and participation of academic and practicing physicians in clinical trials remains of high importance.
Chemoradiotherapy for NSCLC

Open Discussion

Dr. David Gandara: What is the purpose of this proposed phase II CALGB trial of pemetrexed with or without cetuximab? What would you hope to learn?

Dr. Vokes: For us to have a positive signal following the results achieved in 39801, what we need to show is a survival somewhere above 14 to 15 months depending on whether we include patients with weight loss over 5%. I think we will have to look at this in the context of your randomized trial in SWOG. If that still shows median survival times of 2 years in both arms or better survival in one arm over the other, I think we would want to aim at a similarly effective regimen in a similar population of patients.

Dr. Gandara: My question is rather about the design. Are you going to compare one of these to concurrent paclitaxel/carboplatin?

Dr. Vokes: Yes, the idea is eventually to pick a winner between these two. I'm not sure that carboplatin/paclitaxel is going to be the control. We could also choose cisplatin/etoposide with or without consolidation at the end.

Dr. Bruce Johnson: So I'll ask you one of the dullest questions: What about using cisplatin instead of carboplatin in your pemetrexed platform?

Dr. Vokes: That is not a dull question. In concurrent treatment, if you give full-dose chemotherapy you probably get away with using carboplatin for four cycles at an AUC of 6. Carboplatin and cisplatin have never been directly compared in the stage III setting and carboplatin has been adopted based on its more favorable toxicity profile. I think that a possible difference in activity between the two agents, even if it favored cisplatin, would be so small that we don’t need to look at that issue. We are trying to redefine a whole new chemo-radiotherapy platform that is more tolerable.

Dr. Walter Curran: The same issue was observed in LAMP as in the CALGB 39801 study: a decision was made to include patients with up to 10% or 15% weight loss, thinking performance status would be effective surrogate, and there was a huge drop-off in survival. If you really wanted to compare to the CALGB 8433 trial or the Intergroup phase III trial [Chest 2000;117:358–64], you had to strip out the greater than 5% weight loss. As a further point, is there anywhere a group like this that can collect data on the shrinking denominator of patients eligible for these studies? Our pemetrexed study is picking up quickly, so I think if you have a study that people like, it accrues, but I’m interested in figuring out where is there a means, population-wise, to get an updated staging in lung cancer to see what is happening in nonoperative management of stage III cancers.

Dr. Gandara: There is the Intergroup survey done where you can actually assess this, and clinicians get credit for filling out a survey on every patient who comes in.

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Clin Cancer Res 2005;11:5045s-5050s.

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