A Phase I/II Trial of Neoadjuvant Chemotherapy with Cisplatin and Vinorelbine followed by Accelerated Irradiation for Patients with Inoperable Nonsmall Cell Lung Carcinoma

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BACKGROUND. Both locoregional and distant disease control remains poor in the treatment of Stage III nonsmall cell lung carcinoma (NSCLC). This trial was conducted to evaluate the tolerance and responses of patients with NSCLC given a neoadjuvant regimen of cisplatin and vinorelbine chemotherapy followed by accelerated thoracic radiotherapy.

METHODS. Forty-two patients with Stage IIIA and IIIB NSCLC were entered into the study. Treatment consisted of cisplatin 100 mg/m^2 given on Days 1 and 29 and vinorelbine 30 mg/m^2 given weekly for 5 weeks, with a planned 50% dose reduction to 15 mg/m^2 planned for Week 2. This was followed by thoracic irradiation of 60 gray (Gy) in 30 fractions of 2 Gy over 4 weeks (once daily during Weeks 1 and 2 and twice daily during Weeks 3 and 4).

RESULTS. With a median follow-up time of 12.2 months (27–65 months for survivors), the median survival was 12.2 months (16.6 months for patients with no prior weight loss and 7.8 months for those with prior weight loss). The response rate after induction chemotherapy was 46.1%, increasing to 74.4% after radiation therapy (8 complete responses and 21 partial responses). The rate of progression was 13 of 18 (72%) for those who responded to chemotherapy (4 distant, 9 local) and 18 of 21 (86%) for those who did not respond to chemotherapy (14 distant, 7 local). The most frequent acute Grade 3 toxicity was nausea (21.4%).

CONCLUSIONS. Accelerated thoracic irradiation after induction chemotherapy is well tolerated and yields therapeutic results that compare favorably with those reported for other regimens of chemotherapy and standard fractionated radiotherapy. The data from this study suggest that the responses of patients with clinically apparent disease to induction chemotherapy might indicate a likelihood of controlling microscopic distant metastases. ***Cancer* 1999;85:2562–9.**

KEYWORDS: lung carcinoma, nonsmall cell lung carcinoma, neoadjuvant chemotherapy, accelerated radiotherapy, combined therapy.

The successful treatment of locally advanced nonsmall cell lung carcinoma (NSCLC) rests on the control of both clinically apparent intrathoracic disease and occult systemic micrometastases commonly present at the time of diagnosis. Currently available therapeutic regimens with radiotherapy alone fail to achieve these goals in more than a minority of patients.[1,2]

Cisplatin-based chemotherapy has an impact on the rate of appearance of distant metastases as well as on median and long term survival when added to thoracic irradiation.[3,4] However, better con-

trol of systemic micrometastases might be achievable with the introduction of new agents in the treatment for locally advanced NSCLC. A randomized trial of chemotherapy treatment of advanced NSCLC reported superior response rates (RR) and median and 1-year survival rates with a combination of cisplatin and vinorelbine (30% RR) compared with a combination of cisplatin and vindesine (19% RR; $P = 0.04$).[5] A large randomized trial of the Southwest Oncology Group showed better response rate, progression free survival, and overall survival with a combination of cisplatin and vinorelbine over single-agent cisplatin in advanced NSCLC at the cost of an increased hematologic toxicity.[6] These findings support the potential benefit of using vinorelbine in combination with cisplatin in locally advanced NSCLC.

Local control remains poor in most series. When reevaluated by bronchoscopy after radical treatment with thoracic irradiation (65 grays [Gy]) and chemotherapy, viable tumor persists in 83% of patients within the irradiated volume at 1 year.[7] This lack of local control after conventionally fractionated thoracic irradiation may be due in part to accelerated repopulation of clonogenic tumor cells, which can occur during the later phase of standard or hyperfractionated treatments and jeopardize their efficacy.[8,9] A logical exploitation of this phenomenon would be to decrease the overall treatment time (accelerated fractionation) and/or to increase the doses of irradiation delivered in the last phase of the treatment. In a previous Phase I/II study, we piloted a treatment approach in which patients with locally advanced NSCLC received treatment to a large field encompassing the clinically detectable tumor as well as regional lymph nodes to a dose of 40 Gy in 20 daily fractions. An additional dose of 10 Gy was delivered to a smaller field limited to the clinically apparent disease concomitantly with the last 5 fractions of the original volume, with an interfraction interval of 6–hours.[10]

In randomized trials, sequential treatment with induction chemotherapy improved survival when added to conventional thoracic radiotherapy.[7,11,12] We decided to build on these results and combined the recent advances in chemotherapy for advanced NSCLC[5,6] with intensified thoracic radiotherapy designed to overcome the accelerated repopulation of clonogenic cells. We report here on a trial that expands our prior experience of accelerated fractionation by increasing the delivered dose of irradiation to 60 Gy (40 Gy to the original volume with a boost of 20 Gy over 4 weeks) in association with cisplatin and vinorelbine induction chemotherapy.

The 42 patients entered in the current study were ineligible for entry into other programs with stringent selection entry criteria and typically had weight loss and supraclavicular adenopathy. Despite these poor prognostic features, the overall survival rate was 26% at 3 years, and the median survival was 12.2 months, figures comparable to those obtained with standard fractionation irradiation in other studies.[7,11,12] It is noteworthy that local complications were moderate, and the treatment was well tolerated. Similar to results in other schemes, local control was obtained in only a minority of patients.

MATERIALS AND METHODS

Patient Selection

Eligible patients had to meet the following criteria: histologic or cytologic confirmation of NSCLC; clinical Stage IIIA, Stage IIIB, or inoperable Stage II; presence of measurable disease by chest radiograph or computed tomography (CT); age $>$ 18 years; Karnofsky performance status $\geq$ 70; life expectancy $>$ 12 weeks; no prior therapy for NSCLC; and, at least 2 weeks from prior major surgery, granulocytes $\geq 2000/\mu L$, platelets $\geq 100{,}000/\mu L$, hemoglobin $\geq$ 12 g/dL (patient could be transfused to this level prior to entry), serum creatinine $\leq$ 1.5 mg/dL, and serum bilirubin $\leq$ 2.0 mg/dL. Prior weight loss was allowed. Informed consent was obtained prior to entry into trial, satisfying the regulations of our institutional review boards. Patients with any unstable, preexisting, major medical condition; with a history of another malignancy other than basal cell carcinoma of the skin or carcinoma in situ of the cervix (unless the patient had been curatively treated and remained disease free for a period $>$5 years); or with evidence of metastatic disease (Stage IV) were excluded.

Pretreatment evaluation was completed within 3 weeks of the first day of induction chemotherapy and included a complete history and physical examination (including neurologic examination). Staging work-up included blood counts, blood chemistries, full pulmonary function tests, chest radiograph, CT scan of the chest (including upper abdomen), total body bone scan, and CT scan of the brain.

Treatment Plan

Chemotherapy

The induction chemotherapy phase of this study lasted 5 weeks, during which cisplatin 100 mg/m^2 and vinorelbine 30 mg/m^2 were administered on Days 1 and 29. Vinorelbine alone was administered at 15 mg/m^2 on Day 8 and at 30 mg/m^2 on Days 15 and 22. Cisplatin was administered with aggressive hydration and a prophylactic antiemetic regimen of ondansetron and dexamethasone (see Fig. 1).

Modifications were based on blood counts ob-

	Induction chemotherapy						Accelerated RT			
Week	1	2	3	4	5	6	7	8	9	10
Cisplatin (mg/m^2)	100				100					
Vinorelbine (mg/m^2)	30	15	30	30	30					
RT 10 Gy/wk AM							X	X	X	X
RT 10 Gy/wk PM									X	X
Documentation of response to induction chemotherapy						X				

FIGURE 1. A schematic representation of study design is shown. Note the 50% dose reduction of vinorelbine on Week 2 and administration of radiotherapy twice daily on Weeks 9 and 10. RT: radiotherapy; Gy: gray.

tained on the day of treatment, with a full dose of both agents to be given in the presence of granulocytes $\geq$ 2000/μL and platelets $\geq$ 100,000/μL, a 50% reduction in the dose of vinorelbine alone if granulocytes were 1500–1999/μL or platelets were 75,000–99,999/μL, and both agents were withheld if granulocytes were $<$1500/μL or platelets were $<$75,000/μL. When counts were too low to allow administration of single-agent vinorelbine on the day it was scheduled, that day was omitted. However, administration of Day 29 cisplatin and vinorelbine could be delayed for up to 1 week to allow blood count recovery. Dose modification for nonhematologic toxicity included a 50% decrease in cisplatin if serum creatinine was 1.5–2.0 mg/dL. Cisplatin was stopped if serum creatinine increased to $>$2.0 mg/dL. Dose modification of vinorelbine included a decrease to 50% for a total bilirubin 2.1–3.0 mg/dL and a decrease to 25% for total bilirubin $>$ 3.0 mg/dL.

Patients underwent repeat clinical assessment, chest radiograph, and CT scan of the chest during Week 6 to assess the objective response rate of the induction chemotherapy regimen. Patients without evidence of disease progression outside of the planned irradiation field began radiotherapy on Day 43, i.e., 14 days after the last dose of chemotherapy. Radiotherapy was delayed until granulocytes $>$ 2000/μL and platelets $>$ 100,000/μL. Patients with tumor progression within the planned irradiation field during chemotherapy remained on study and proceeded to accelerated fractionation thoracic irradiation. Patients with tumor progression outside of the planned irradiation field were removed from the study and were treated at the attending physician's discretion.

Radiotherapy

Radiation therapy was delivered to the primary tumor, ipsilateral hilum, and mediastinum with 2 cm margins. The contralateral hilum and mediastinum were included with a 1 cm margin: If it was grossly involved, the margin was 2 cm. The ipsilateral supraclavicular fossa was included only for upper lobe tumors or if it was clinically involved. This initial volume was treated to a total tumor dose of 40 Gy in 20 fractions of 2 Gy over 4 weeks. The boost volume consisted of the primary tumor and grossly involved lymph nodes with 2 cm margins and was taken to an additional dose of 20 Gy in 10 fractions of 2 Gy over 2 weeks. The total dose to the tumor was 60 Gy, and the total treatment time was 4 weeks, because the treatment to the boost volume was delivered concomitantly with the last 2 weeks of the large volume (Plan 1), with an interval of 6–8 hours between treatments. Tumor volume definition was based on preinduction chemotherapy tumor volume. There was no correction for lung heterogeneity. Compensating filters and wedges were used, when necessary, to respect a homogeneity of $\pm$5% within the treatment volume. The maximum dose allowed to the spinal cord was 42 Gy, and the use of posterior spinal blocks was not allowed. The ipsilateral whole lung could receive 25 Gy, and the contralateral normal lung could receive 20 Gy. Maximal doses to the entire heart and esophagus were 45 Gy and 60 Gy, respectively. Patients were treated on a linear accelerator with accelerating potential between 4 MV and 18 MV or on an isocentric cobalt-60 machine using CT scan planning. Radiotherapy was to be held until resolution if granulocytes fell below 1000/μL, if platelets fell below 75,000/μL, or if severe esophagitis requiring intravenous fluids administration developed.

Response and Toxicity Evaluation

Patients were evaluated clinically weekly during the treatment phase of this study, at 2 and 4 weeks after completion of therapy, every 3 months for 2 years, and every 6 months thereafter. A full history and physical

examination, with particular attention to any acute and late toxicities, as well as repeat blood work were recorded on these occasions. A chest radiograph was obtained at the 4-week follow-up visit and on each visit thereafter. A CT scan of the chest and pulmonary function tests were obtained at 1 month, at the first 3-month follow-up visit, and every 6 months thereafter. Patients showing evidence of local recurrence were evaluated for the presence of systemic metastases by undergoing a CT scan of the brain, a bone scan, and a CT scan or ultrasound of the abdomen. Patients who showed evidence of systemic metastases were evaluated for the presence of intrathoracic recurrence by CT scan of the chest.

The following definitions were used to assign response status: complete response (CR), disappearance of all signs of tumor on radiologic studies and physical examination for a period of at least 4 weeks, with no appearance of any new lesions; partial response (PR), reduction of 50% of the sum of the products of the perpendicular greatest dimensions of all measurable lesions for a period of at least 4 weeks; stable disease, <50% reduction or 25% increase in the sum of the products of perpendicular greatest dimensions of all measurable lesions or no major change in evaluable disease with no new lesion appearing; and disease progression, increase of 25% or more in the sum of the products of all measurable lesions, or a definite increase in size of evaluable lesions, or the appearance of new lesions. Toxicities were graded by using the World Health Organization (WHO) criteria.[13]

Statistical Analysis

We had planned to enroll 40 evaluable patients so that response rates could be estimated within a standard error of 8%. Survival and recurrence curves were estimated by using the Kaplan–Meier method[14] and were measured from the time of registration. The overall survival and toxicity results are presented on an intent-to-treat basis. Differences in survival were tested for statistical significance by using the Student's *t*-test and for difference in incidence of recurrences by chi-square test.

RESULTS

Patients Characteristics

From October 1992 to November 1994, 43 patients were entered onto this study. One patient was found to be ineligible because of the presence of distant metastases at baseline (Stage IV). Among the 42 eligible patients, 34 were men and 8 were women, and the median age was 62 years. There was an equal distribution of clinical Stages IIIA and IIIB (n = 21 each), and most tumors (n = 26) were of a nonsquamous histology. It is noteworthy that 35.7% of patients had reported significant weight loss (>5%) in the 3 months preceding their diagnosis. Patients characteristics are shown in Table 1.

TABLE 1
Patient Characteristics

Characteristic	No.	%
Patients registered	43	100.0
Ineligible	1	2.3
Assessable for toxicity to chemotherapy only	3	7.0
Assessable for response to treatment	39	97.7
Age (yrs)		
Median	62	
Range	35–75	
Gender		
Male	34	81.0
Female	8	19.0
Histology		
Squamous	16	38.1
Nonsquamous	26	61.9
UICC 1992 stage		
IIIA	21	50.0
IIIB	21	50.0
Prior weight loss		
<5% weight loss	27	64.3
>5% weight loss	15	35.7

UICC: International Union Against Cancer.

Thirty-nine patients completed the treatment plan. Three patients did not receive radiotherapy for the following reasons: one patient developed renal toxicity after receiving the first dose of cisplatin and received no further treatment; one other patient developed a deep venous thrombosis at week 3, which led to termination of study treatment; and another patient elected to leave the trial and seek an attempt at surgical resection while showing stable disease postchemotherapy. These three patients are included in our statistics on overall survival and toxicity of treatment but not in statistics on response to treatment.

Response to Treatment

Response to induction chemotherapy was assessed by repeat CT scan of the chest during Week 6, i.e., 1 week after completion of cisplatin/vinorelbine regimen. At that time, 18 of 39 patients (46.1%) had an objective partial response, and 20 were stable. Following completion of the induction chemotherapy and accelerated irradiation, there was an overall response rate of 74.4%, with 8 CRs and 21 PRs. Weight loss prior to study entry seemed to influence the likelihood of response. In patients with no prior weight loss, the response rate was 14 of 25 (56%) after induction chemo-

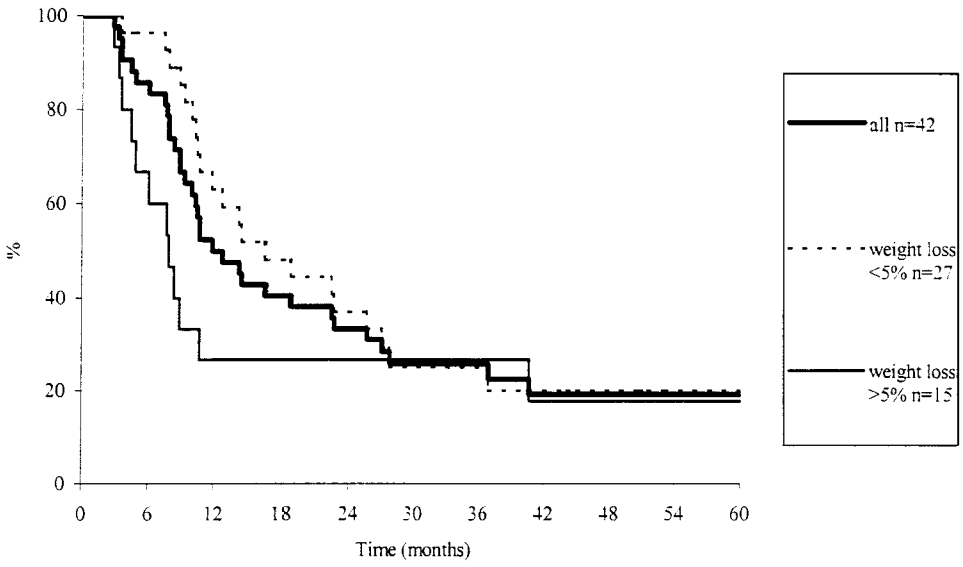

FIGURE 2. Overall survival rates are shown, based on follow-up of 27–65 months for survivors. The median survival is 12.2 months for the whole group, 16.6 months in patients without weight loss, and 7.8 months in patients with weight loss.

TABLE 2
Cumulative Patterns of Relapse at Any Time

Pattern	All (n = 39)	Chemo responders (n = 18)	Chemo nonresponders (n = 21)
Local only (inside radiation field)	12 (30.8%)	8 (44.4%)	4 (19.0%)
Distant only	14 (35.9%)	3 (16.7%)	11 (52.4%)
Both local and distant	4 (10.3%)	1 (5.6%)	3 (14.3%)

therapy and increased to 22 of 25 (88%) after the completion of accelerated radiotherapy. In contrast, patients with weight loss prior to study entry showed a response rate of 4 of 14 (28.6%) after induction chemotherapy and 7 of 14 (50%) after the completion of radiotherapy ($P < 0.01$).

Survival

The median follow-up is 12.2 months, with a minimum follow-up of 27 months in surviving patients (range, 27–65 months). Of the 42 patients, 33 have died, 26 with and 7 without documented evidence of disease progression. Of the 9 patients still alive, 5 have evidence of recurrent disease, and 4 are clinically progression free from 27 months to 65 months from the start of chemoradiotherapy. The median survival for the 42 eligible patients is 12.2 months. However, the median survival for the subgroup of 15 patients with weight loss $\geq$ 5% is 7.8 months, and, for the 27 patients with no prior weight loss, it is 16.6 months (Fig. 2). Response to chemotherapy also seemed to influence survival, with median survivals of 24.2 months and 10.4 months for chemotherapy responders and nonresponders, respectively.

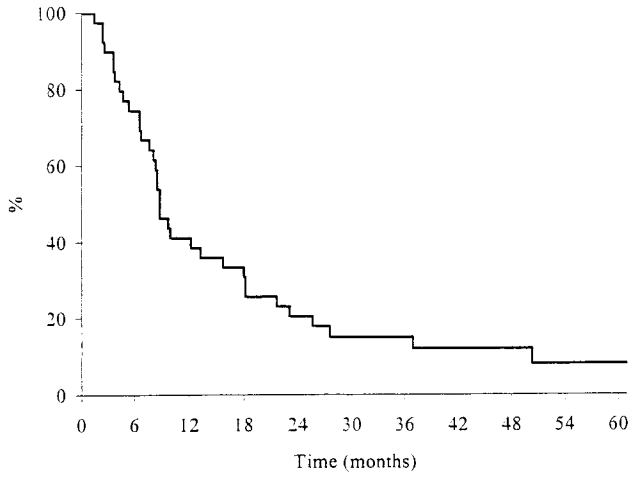

FIGURE 3. Overall progression free survival is shown, based on the percentage of patients alive and without any local or distant disease progression (n = 39; all patients were assessable for response to treatment).

Patterns of Relapse

The median progression free survival was 8.7 months, with 59% of failures and/or deaths occurring within 1 year (Table 2, Fig. 3). Of the 38 patients who experienced treatment failure or who died, 14 patients had

TABLE 3
World Health Organization Grade 3/4 Acute Toxicity of Treatment

Type	No. of patients	%
Lung	2	4.7
Esophagus	7	16.6
Nausea	9	21.4
Weakness	2	4.7
Skin	2	4.7
Chest pain	2	4.7
Hypotension	1	2.4
Infection	1	2.4
Febrile neutropenia	2 (1 life threatening)	4.7
Kidney	1	2.4
Thrombosis	1 (life threatening)	2.4
Neurologic	2	4.7
Other	2	4.7

initial evidence of tumor progression within the irradiated field, 3 had first evidence of relapse within the thorax but outside the irradiated field, 12 had distant metastatic disease as first evidence of relapse but without tumor progression within the irradiated field, and 1 showed both concurrent thoracic (outside radiation field) and distant metastatic progression at the time of initial failure. Overall, 18 patients developed metastatic disease (including the 3 patients with intrathoracic metastatic disease) at a median of 5.1 months, and 16 developed tumor progression within the irradiated field at a median of 14.5 months after initiation of this chemoradiation treatment regimen. The pattern of relapse was evaluated according to the response rate achieved after chemotherapy. Of the 21 assessable patients with tumors that were nonresponsive to induction chemotherapy, 14 later developed distant metastases, whereas only 4 of 18 patients with objective tumor response later developed distant metastases ($P = 0.006$). In contrast, no such trend was apparent for the cumulative incidence of in-field recurrence.

Toxicity of Treatment

WHO Grade 3 or 4 toxicity encountered in 42 patients during the treatment and follow-up phases of this study are listed in Table 3. Hematologic toxicity was frequent, but complications were rare: Of 42 patients, 16 (38.1%) experienced Grade 4 neutropenia (neutrophil count $\leq 1000/\mu L$), two of whom had a febrile episode during neutropenia: One was life threatening. Delivered dose intensity was not recorded prospectively during this protocol, but dose reduction was significant; Twenty-one patients did not receive vinorelbine in Week 3 because of a neutrophil count $< 1500/\mu L$ despite the 50% planned dose reduction at Week 2.

WHO Grade 3 or greater nonhematologic early toxicity usually was self-limited and transient. Nausea and vomiting occurred in 9 patients (21.4%), and esophagitis occurred in 7 patients (16.7%). One patient developed a lower limb deep venous thrombosis at week 3 and died 12 weeks later with an unknown tumor status. Relation to induction chemotherapy was uncertain. A second patient received one dose of cisplatin and developed severe renal toxicity. He received no further chemotherapy or radiotherapy and died at Week 44 with an unknown tumor status. Late effects of treatment were reported in two patients: One patient had symptomatic pulmonary fibrosis, and a second patient developed an esophageal stricture.

DISCUSSION

Initial efforts to improve treatment results for patients with Stage III NSCLC by adding chemotherapy to thoracic irradiation were universally negative, probably because of the marginal efficacy of the drugs used in these trials.[15–17] However, randomized trials have reported an improvement in the median survival and the proportion of long term survivors when thoracic irradiation was combined with cisplatin-containing chemotherapy.[11,12,18] However, local disease control and control of systemic micrometastases remain poor.[3]

Random trials have demonstrated that the combination of cisplatin and vinorelbine results in higher response rates than either cisplatin or vinorelbine alone.[5,19,20] The response rate of 46% to induction chemotherapy in our study is higher than rates usually reported for similar induction therapy,[11] despite the dose reduction at Week 2. This may be due in part to better response evaluation by systematic three-dimensional measurements on CT scan or different tumor and patients characteristics.

The optimal sequential integration of modalities and the best platinum-based combination remain to be determined. Furthermore, despite promising initial results,[21,22] altered fractionation using a hyperfractionated regimen (69.6 Gy delivered at 1.2 Gy per fraction twice daily) did not demonstrate superiority over conventionally fractionated radiotherapy (60 Gy in 30 fractions over 6 weeks) with neoadjuvant chemotherapy in a Radiation Therapy Oncology Group (RTOG)/Eastern Cooperative Oncology Group randomized trial.[12] Accelerated repopulation of clonogenic tumor cells that occur during the later phase of standard or hyperfractionated treatments is one of the mechanisms that could explain the poor local control obtained by conventionally fractionated radiotherapy.[8,9] To potentially circumvent this phenomenon, we used the accelerated concomitant boost radiotherapy

technique, which seemed to be well tolerated in our previous experience[10] and in head and neck carcinoma.[23] Similar results have been obtained in two RTOG Phase I/II studies of accelerated fractionation via concomitant boost in NSCLC.[24,25] Diminution of total treatment time and intensification of the last phase of treatment is a logical approach to prevent tumoral repopulation, but it is associated with the risk of increased acute side effects. The biologically equivalent dose (BED) of our regimen would be similar to 60 Gy delivered in 30 fractions over 6 weeks for late effects, assuming an α/β ratio of 3. For early effects, the BED of our accelerated scheme is 66.5 compared with 60.9 for the 60 Gy/30 fractions regimen, assuming an α/β ratio of 8 and an estimated doubling time of 5 days after 2 weeks of radiotherapy.[26]

The median survival of 12.2 months for patients in this study is comparable to the results obtained in recent literature with chemoradiation (range, 11–14 months).[18] However, 35.7 % of our patients reported a weight loss of >5% in the 3 months before registration and study entry. This population consistently fared worse with radiation in the recursive analysis of 1592 inoperable NSCLC patients in RTOG protocols.[27] When these unfavorable patients are excluded of our data, the median survival increases to 16.6 months and compares favorably to studies with similar populations.[7,11,12] However, these data must be interpreted with caution in view of the small numbers of patients in this subset.

Another interesting finding is the observation of a different pattern of disease progression in patients who were documented to respond to induction chemotherapy and compared with chemotherapy nonresponders. When the primary tumor responded to the induction chemotherapy, only 22% of patients developed distant metastases versus 67% with a nonresponding primary. This observation suggests that objective response of clinically apparent disease to the induction chemotherapy may be associated with a higher likelihood of control of systemic micrometastatic disease commonly present at the time of diagnosis and may be an indication for intensifying the therapy in these patients. Similar to other studies, local control remains a problem for our patients, with 16 of 39 (41%) experiencing clinical treatment failure inside the radiation field. In our study, local control became the most important issue in patients responding to induction therapy. Local recurrences were more frequent in chemotherapy responders (50% vs. 33.3% in nonresponders), suggesting that the lower rate of distant metastases in chemotherapy responders was not likely to be a consequence of better local control. Chemotherapy nonresponders were more likely to die of metastatic disease before manifesting potential local recurrences, explaining in part the differences in local recurrence. Underestimation of local recurrences in patients with distant metastases also is possible, although our study design minimized this bias by careful thoracic evaluation at any relapse. Trials intensifying local therapy by dose escalation using three-dimensional conformal planning or by concomitant chemoradiotherapy after response to induction chemotherapy could lead to better local control rates and potentially to better cure rates.

In conclusion, in patients with inoperable Stage IIIA and Stage IIIB NSCLC, induction chemotherapy with vinorelbine and cisplatin followed by accelerated concomitant boost thoracic irradiation is feasible, generally well tolerated, and yields therapeutic results that compare favorably to those reported for other regimens. A 3-year survival rate of 26% is an encouraging result, given that 36% of patients had lost weight, and 50% had Stage IIIB disease. Despite our accelerated radiotherapy course, local control remains poor. Our data suggest that the response of the clinically apparent disease to induction chemotherapy might indicate a high likelihood of controlling microscopic distant metastases. Intensification of local therapy in this subgroup should be investigated in future studies.

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