

The results of concomitant and sequential chemoradiotherapy with cisplatin and etoposide in patients with locally advanced non-small cell lung cancer

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Summary

Purpose: To report on the treatment results and demographic characteristics of patients with locally advanced non small cell lung carcinoma (NSCLC) who were treated with concomitant or sequential chemoradiotherapy.

Patients and methods: 132 patients with locally advanced NSCLC (stage IIIB) were evaluated. Their median age was 60 years (range 33-80). Histopathological diagnosis was epidermoid carcinoma in 96 (73%) patients, adenocarcinoma in 33 (25%) patients and large cell carcinoma in 3 (2%) patients. Karnofsky performance status (KPS) score was ≥ 70 in 112 (85%) patients. Weight loss was greater than 5% in 34 (26%) patients at presentation. One hundred and six (80%) patients were treated with sequential chemoradiotherapy which consisted of 3 monthly cycles of cisplatin (100 mg/m², day 1) and etoposide (100 mg/m²/day, days 1-3) before radiotherapy. Radiotherapy consisted of a total dose of 60 Gy in 30 fractions (2 Gy / fraction), given to a volume including primary tumor and mediastinum. Two to 4 cycles of chemotherapy were administered after completion of radiotherapy to patients whose disease had not progressed after initial chemotherapy. Twenty-six patients were treated with concomitant chemoradiotherapy. The same radiotherapy regimen was started with the 2nd cycle

of chemotherapy which consisted of cisplatin (80 mg/m², day 1) and etoposide (100 mg/m²/day, days 1-3). Chemotherapy was completed after 4 cycles in all patients.

Results: Overall survival (OS) was 14.5 months in 106 patients treated with sequential chemoradiotherapy and 14.6 months in 26 patients treated with concomitant chemoradiotherapy ($p=0.99$). Median time to progression was 9.77 months in the concomitant group and 11.6 months in the sequential group ($p=0.47$). However, progression-free survival was better in patients of both groups whose KPS was >70 (12.4 months versus 11.5 months, $p=0.02$). While presence of anemia was found as an adverse prognostic factor only in univariate analysis, non-epidermoid histology, KPS less than 70 and presence of N2-N3 disease were found as adverse prognostic factors in both univariate and multivariate analysis.

Conclusion: The addition of chemotherapy to radiation concomitantly or sequentially prolongs survival in locally advanced NSCLC patients with acceptable adverse event profiles in both arms compared with results of the trials in the literature in which radiotherapy is used as single treatment modality.

Key words: chemoradiotherapy, concomitant, non-small cell lung cancer, sequential

Introduction

Lung cancer is the leading cause of death from cancer in men, accounting for nearly 13% of all new cancer cases. NSCLC accounts for roughly 80% of all lung cancers and it is estimated that 10-15% of these patients are in stage IIIB at the time of diagnosis [1]. Patients with stage IIIB NSCLC do not benefit from surgery alone and are best managed by initial chemotherapy, chemotherapy plus radiation therapy, or radiation therapy alone, depending on sites of tumor

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involvement and PS. Surgery may be indicated only for carefully selected T4N0M0 patients with or without neoadjuvant chemotherapy or chemoradiotherapy. Patients with N3 lymph node involvement are not considered as surgical candidates. Patients with excellent PS should be considered for combined modality therapy; however, patients with malignant pleural effusion are rarely candidates for radiation therapy, and should generally be treated similarly to stage IV patients. For patients with unresectable disease, good PS, and minimal weight loss, treatment with combined chemotherapy and radiotherapy has resulted in better survival than treatment with radiotherapy alone [2-4]. Multiple daily fractions of radiotherapy have not resulted in improved survival compared with standard fractionation once daily. Concurrent chemoradiotherapy appears to be associated with improved survival compared with sequential chemotherapy and radiotherapy [5,6].

In this study, we report on the results of our NSCLC patients in clinical stage IIIB who were treated with chemoradiotherapy and discuss the treatment options.

Patients and methods

Patients

Included were 132 previously untreated patients with histologically proven NSCLC. All patients were considered to have nonresectable stage IIIB disease and were free of metastasis after physical examination and bronchoscopic, radiologic and nuclear diagnostic evaluation. Nodal and tumor stages were evaluated both with radiologic and bronchoscopic techniques. Patients with KPS less than 50% and having cardiac, hematologic, renal or liver abnormalities contraindicating combined modality therapy were not included.

Age (<60 *versus* >60 years), Hb level (<12 g/dl = anemia *versus* >12 g/dl), sex, KPS (<70 *versus* >70), weight loss (<5% *versus* >5%), histopathology (epidermoid *versus* others), T stage (T2-T3 *versus* T4), nodal stage (N0, N1 *versus* N2, N3), stage (IIIA *versus* IIIB) were evaluated as prognostic factors.

Therapy

Sequential chemoradiotherapy was administered to 106 (80%) patients. This consisted of 3 monthly cycles of cisplatin (100 mg/m², day 1) with the usual pre- and posthydration and forced diuresis, and etoposide (100 mg/m²/day, days 1-3) before radiotherapy.

Radiographic evaluation was performed before the third cycle to determine response to chemotherapy. Radiotherapy consisted of a total dose of 60 Gy in 30 fractions (2 Gy / fraction), given to a volume including the primary tumor and mediastinum. Two to 4 cycles of chemotherapy were administered after completion of radiotherapy to patients whose disease had not progressed after initial chemotherapy. The response to therapy was evaluated with radiological examination 3 weeks after the last cycle of chemotherapy.

Concomitant chemoradiotherapy was given to 26 patients. The difference in number of patients between the 2 groups was due to the changes in the treatment protocols in our clinic. At the beginning, all patients received sequential chemoradiotherapy, but afterwards the protocol changed and concomitant chemoradiotherapy was applied to all patients with locally advanced NSCLC. The same radiotherapy regimen was administered with the second cycle of chemotherapy which consisted of cisplatin (80 mg/m², day 1) with pre- and posthydration and forced diuresis, and etoposide (100 mg/m²/day, days 1-3). Chemotherapy was completed after 4 cycles in all patients. Radiographic evaluation was performed 3 weeks after the completion of chemotherapy.

Complete remission was indicated by the complete disappearance of all objective tumor without appearance of new lesions as shown by chest x-rays and thoracic CT scan. Partial remission was indicated by a decrease greater than or equal to 50% in the product of the two largest perpendicular diameters of radiologically measurable disease. Stable disease was indicated by no change shown by radiologic or endoscopic evaluation. Progressive disease was indicated by radiologic or endoscopic evidence of progression or evidence of new lesions.

Statistics

All statistical analyses were carried out with SPSS package program, version 7.5. The survival and progression times were calculated with the Kaplan-Meier method and compared with the log-rank test. Independent factors that adversely affect survival and time to progression were determined with the Cox-regression forward:LR method.

Results

The patients' mean age was 60 years (range 33-80). One hundred and twenty-five (94%) males and 7 (6%) females were evaluated. Ninety-six (72%) pati-

ents had a histopathological diagnosis of epidermoid carcinoma, 33 (25%) had adenocarcinoma and 3 (2%) had large cell carcinoma. The tumor was located in the right lung in 70 (53%) and in the left lung in 62 (47%) patients. KPS was ≥ 70 in 112 (85%) patients. The tumor stage was T2 in 8 (6%), T3 in 13 (9%) and T4 in 111 (85%) patients. The nodal stage was N0-N1 in 18 (13.5%) and N2-N3 in 114 (86.5%) patients. Patient characteristics are listed in Table 1.

In the sequential therapy group complete and partial remissions were 17% (18 patients) and 42% (45 patients), respectively. Stable disease was obtained in 24 (22%) and progressive disease was seen in 19 (18%) patients.

In the concomitant therapy group complete remission was seen in 4 (15%) and partial response in 9 (36%) patients. Stable disease was obtained in 8 (30%) and progressive disease in 5 (19%) patients.

Table 1. Patient characteristics

Characteristic	Group			
	A*		B**	
	n	%	n	%
Males	100	94	25	96
Females	6	6	1	4
Mean age, years (range)	58 (35-78)		60 (33-80)	
Histology				
Squamous cell carcinoma	73	69	23	88
Adenocarcinoma	30	28	3	12
Large cell carcinoma	3	3	–	–
Grade				
Well differentiated	43	41	10	38
Moderately differentiated	13	12	4	15
Poorly differentiated	17	16	9	35
TNM stage				
T2	6	6	2	8
T3	10	9	3	12
T4	90	85	21	80
N0	10	9	2	8
N1	4	4	2	8
N2	55	52	12	46
N3	37	35	10	38
Tumor localization				
Upper lobe	69	65	17	65
Middle lobe	17	16	4	16
Lower lobe	20	19	5	19
Right	58	55	12	46
Left	48	45	14	54
Karnofsky PS ≥ 70	69	65	20	77
Weight loss > 5%	25	24	9	35
Hb <12 g/dl	20	19	6	23

*sequential chemoradiotherapy; **concomitant chemoradiotherapy

The median overall survival of all 132 patients was 14.5 months. The survivals for 1,2,3 and 5 years were 63%, 23%, 11% and 6%, respectively. The median overall survival was 14.5 months in the sequential group and 14.6 months in the concomitant group ($p = 0.9$; Figure 1).

The median time to progression was 9.77 months in the concomitant group and 11.6 months in the sequential group ($p = 0.47$; Figure 2).

Progression-free survival was better in patients whose KPS was > 70 (12.4 months *versus* 11.5 months, $p = 0.02$).

While the presence of anemia was found as an adverse prognostic factor only in univariate analysis ($p = 0.03$), non-epidermoid histology ($p = 0.04$), KPS < 70 ($p = 0.02$), and presence of N2-N3 disease ($p = 0.004$) were found as adverse prognostic factors in both univariate and multivariate analyses.

Both treatment schedules were generally well-tolerated and toxic effects were mild to moderate in most of the cases. In the sequential chemoradiotherapy group 2 patients had grade IV anemia, one had grade IV renal toxicity after the third cycle and 2 patients had grade IV neutropenia after the fourth cycle of chemotherapy; chemotherapy was discontinued in these patients. Grade IV esophagitis was seen in 3 patients and grade IV pneumonitis in 2 during radiotherapy, but all patients completed the radiotherapy course of 60 Gy.

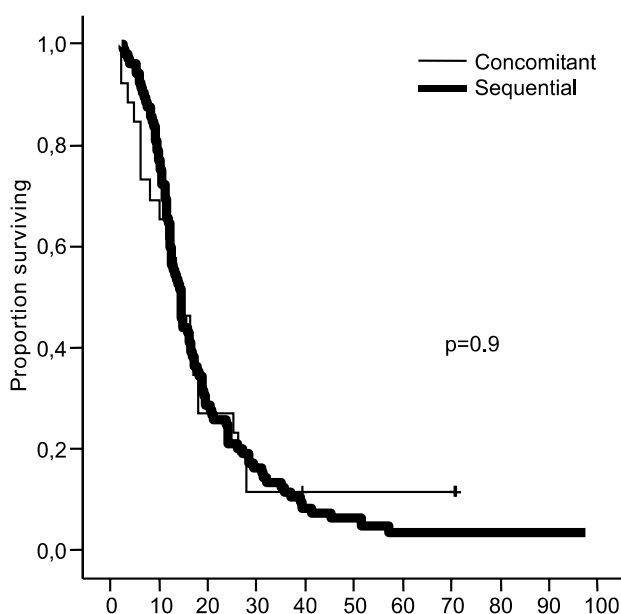


Figure 1. Overall survival of concomitant and sequential chemoradiotherapy groups.

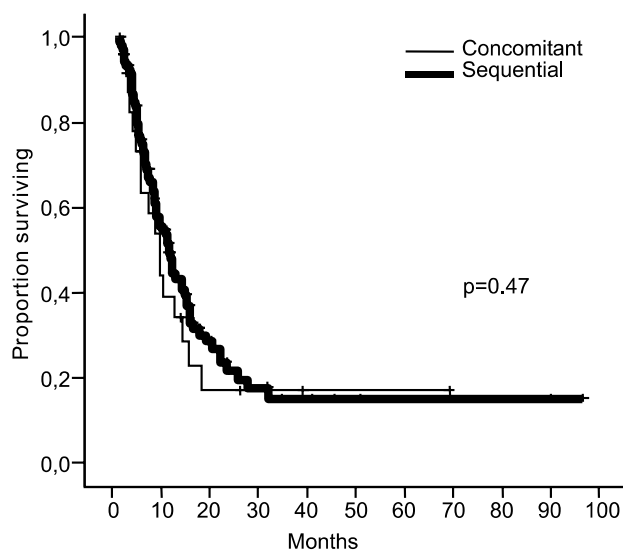


Figure 2. Time to progression in concomitant and sequential chemoradiotherapy groups.

In the concomitant therapy group 1 patient had grade IV neutropenia and 1 grade IV anemia; chemotherapy was discontinued in these patients. One patient had grade IV esophagitis and 1 grade IV pneumonitis but discontinuation of the treatment was not necessary.

Discussion

At the time of initial diagnosis 10-15% of lung cancer patients are in stage IIIB, with a median survival of 8 months and a 5-year survival of < 5% [7].

Surgery may be indicated for stage IIIB disease only in carefully selected situations. Patients who are T4N0-1 due solely to a satellite tumor nodule(s) within the primary tumor lobe have a 5-year survival of approximately 20% with surgery alone [8,9]. In another study, 5-year survival of patients with T4N0-1 disease due mainly to carinal involvement who had been treated with carinal resection with or without pulmonary resection was approximately 20% [10].

Neoadjuvant chemotherapy or chemoradiotherapy followed by surgical resection has been used in patients with N2 (IIIA) disease. However, few phase II series have included carefully selected patients with T4 primary lesions or N3 nodes. A study by the Southwestern Oncology Group employed concurrent chemoradiotherapy in 51 patients with stage IIIB disease that excluded superior vena cava syndrome and malignant effusions. That study registered a resectability rate of 80%, with a median survival time of 17

months and a 3-year survival rate of 24% [11]. These results were similar to those observed in patients with stage IIIA disease reported in that same trial. However, there are no phase III trial data demonstrating that neoadjuvant treatment followed by surgery in patients with stage IIIB disease results in prolonged survival compared with treatment with combination chemoradiotherapy.

For patients with stage IIIB NSCLC due to T4 (excluding Pancoast tumors) or N3 disease, treatment with neoadjuvant chemotherapy or chemoradiotherapy followed by surgery has been explored in limited phase II trials. At this time, there are no phase III trial data available to document that surgery adds to survival; therefore, this approach should not be considered as standard therapy.

The vast majority of patients with stage IIIB disease do not benefit from surgery and are best managed with chemotherapy plus radiotherapy or with radiotherapy alone, depending on the sites of tumor involvement and performance score status.

In a prospective trial by the Radiation Therapy Oncology Group (RTOG), ECOG, and the Southwest Oncology Group (SWOG), patients were randomized to receive 2 months of cisplatin + vinblastine chemotherapy followed by 60 Gy of radiation at 2 Gy per fraction; or radiation 1.2 Gy / fraction twice daily to a total dose of 69.6 Gy, or radiation 2 Gy / fraction once daily to 60 Gy. Overall survival was statistically superior for the patients receiving chemotherapy and radiation *versus* the other two arms of the study (13.2 months *versus* 12 months, *versus* 11.4 months, respectively; $p = 0.04$) [12]. However, the survival benefit in this trial was less than that seen in the original Cancer and Leukemia Group B (CALGB) trial [13]. Development of distant metastases was less frequent for patients who received chemotherapy [14]. In a review of chemotherapy in NSCLC patients there was also a survival benefit in favour of chemotherapy [15].

In a study which randomized patients to receive either concurrent or sequential chemoradiotherapy, the concurrent arm demonstrated statistically significant superiority in response rate (84 *versus* 66%; $p = 0.0002$) and median survival time (16.5 *versus* 13.3 months; $p = 0.040$), but myelosuppression was greater in the concurrent arm [16]. In the RTOG 94-10 trial which randomized patients into 3 arms (sequential cisplatin + vinblastine followed by thoracic radiation of 60 Gy; concurrent cisplatin + vinblastine with radiation to a total dose of 60 Gy; or cisplatin + etoposide concurrent with radiation to a total dose of 69.6 Gy delivered in twice-a-day fractions), median survival was superior in the concomitant chemotherapy plus daily radiation

arm compared with the sequential arm (17 *versus* 14.6 months; $p=0.08$), while the concomitant chemotherapy plus twice-daily radiation arm demonstrated intermediate survival compared with the other study arms. Nonhematologic toxicity was also higher in the concurrent arms [17].

These studies suggest improvement in both local control and survival with concurrent chemoradiotherapy as compared with sequential chemotherapy followed by radiation for patients with stage III NSCLC.

Different drug combinations such as carboplatin + paclitaxel, gemcitabine + cisplatin, cisplatin + paclitaxel, and cisplatin + vinorelbine have been tested with concomitant radiation in phase II trials and were found to be safe [18-20]. CALGB has completed a randomized phase II study of 2 cycles of induction chemotherapy followed by 2 additional cycles of the same drugs with concomitant radiotherapy. The 3 treatment arms included 4 cycles of cisplatin (80 mg/m²) combined with either gemcitabine, paclitaxel, or vinorelbine. Radiotherapy was completed during the last 2 cycles to a total of 66 Gy. Response rates were similar, and median survival for all patients was 17 months with no clearly superior arm evident in this randomized phase II trial [20]. One prospective, randomized trial compared sequential cisplatin + vinblastine chemotherapy followed by radiation *versus* sequential cisplatin + vinblastine plus concomitant carboplatin and radiation in 283 patients with inoperable stage III NSCLC, and was unable to demonstrate benefit with the addition of concomitant carboplatin after cisplatin-based induction [21].

The optimal duration of chemotherapy for patients with unresectable stage III NSCLC being treated with combined-modality therapy is still unclear and since no benefit was seen in studies when chemotherapy was continued until progression of disease, the duration of initial chemotherapy is recommended to be between 2 and 4 cycles of platinum-based therapy, with an upper limit of 4 cycles.

The role of surgery following induction chemotherapy or chemoradiotherapy for patients with initially unresectable cancer is being explored. In phase II testing, the use of concomitant chemoradiotherapy has led to improved resectability and overall survival compared with historical controls in patients with T3 to T4 NSCLC tumors of the superior sulcus [22]. Data from surgical series suggest that induction chemotherapy does not result in increased risk of anastomotic complications in bronchoplastic or angioplastic surgical procedures, and is unlikely to limit the type of surgery which can be performed [23-26], but these findings shall be tested in randomized trials which will

investigate the impact of induction chemoradiotherapy followed by surgical resection on survival.

In order to reduce long-term normal tissue toxicity by smaller fraction size and to reduce repopulation in rapidly proliferating tumors, accelerated radiotherapy schedules are used. Accordingly, at this time one phase III trial of continuous hyperfractionated accelerated radiotherapy (CHART) showed superior survival over standard radiotherapy. This trial compared CHART to standard radiotherapy (60 Gy/30 fractions). CHART consisted of 3 treatments per day (1.5 Gy/fraction), at least 6 hours apart, for 12 days with no break (54 Gy). Sixty-one percent of patients were IIIA or IIIB. The 1- and 2-year survival rates for the CHART arm were 63 and 29%, respectively, *versus* 55 and 20% for standard radiotherapy. Overall, there was a 22% reduction in the relative risk of death ($p = 0.008$). There was no difference in late morbidity. Recently, a phase III Eastern Cooperative Oncology Group trial of HART (same as CHART except for no treatments on weekends) *versus* standard radiotherapy after induction chemotherapy had to be closed due to poor accrual [27,28].

Oral et al. reported a preliminary analysis of paclitaxel and CHART in locally advanced lung cancer with unresectable stage IIIA and B NSCLC. The overall response rate which was evaluated in 19 patients was 84% with a grade 2-3 esophagitis in 70% and grade ≥ 3 pulmonary toxicity in 50% of the patients. Grade 3 anemia developed only in one patient [29].

Since CHART trial had only 61% of patients with stage IIIA and IIIB disease, and no data are available concerning the combination of CHART and chemotherapy at this time, neither CHART nor HART can be recommended as standard therapy. Optimal dose, volume, and fractionation schedules are evolving.

In our study cisplatin and etoposide were used concomitantly or sequentially with radiotherapy. Keeping in mind the discordance in the number of patients included in the 2 treatment methods, the overall survival and time to progression were similar in both groups with acceptable adverse effects, demonstrating that the combination of chemotherapy with definitive radiotherapy improves the patients' outcome when compared with thoracic radiotherapy alone, especially in patients with good performance status.

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