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ARTICLE

Concurrent Paclitaxel–Cisplatin and Twice-a-Day Irradiation in Stage IIIA and IIIB NSCLC Shows Improvement in Local Control and Survival with Acceptable Hematologic Toxicity

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Non-small-cell lung cancer (NSCLC) has one of the highest death rates among the various forms of cancer. In attempts to improve on this unsatisfactory outcome, different radiation schedules and chemotherapy agents have been examined in phase II or III studies. These have led to modest improvements in local control and survival, but combined therapies are associated with substantial hematologic toxicity. In this phase II study, 80 consecutive stage IIIA or IIIB NSCLC patients were treated with concomitant chemotherapy and twice-a-day irradiation in a total dose of 60 Gy in 1.5 Gy fractions. Patients scheduled for surgery received 45 Gy only. Paclitaxel (30 mg/m^2) on days 1-4 and cisplatin (100 mg/m^2) on day 5 were administered in the first and fourth weeks of treatment. Granulocyte colony stimulating factor (30 ng/m^2) was given on days 10-15. The local control, the 1- and 2-year survival rates and the occurrence of acute hematologic toxicity in the non-surgically treated patients were examined. Fifty-two patients were treated without and 28 with surgery. Among the non-surgically treated cases, 43 were evaluable for response and 47 for acute toxicity during a median follow-up of 22 months. The rate of local control was 65% (28/43), and the 1- and 2-year survival rates proved to be 68% and 48%, respectively, with a median survival of 28 months. Severe acute grade 3-4 toxicities included grade 4 leukopenia in 6 cases (13%), grade 3 leukopenia in 4 cases (9%), grade 3 esophagitis in 3 cases (6%) and grade 3 anemia in 3 cases (6%). Our results and the relevant data from the literature support the application of twice-a-day irradiation with concomitant chemotherapy in stage IIIA and IIIB NSCLC. Local control and survival were improved relative to once-a-day irradiation with sequential or concomitant chemotherapy. (Pathology Oncology Research Vol 8, No 3, 163–169)

Keywords: Non-small-cell lung cancer; concomitant chemotherapy; hyperfractionated irradiation

Introduction

It is evident from the latest cancer statistics that non-small-cell lung cancer (NSCLC) has one of the highest death rates among the different types of cancer.[10] The main reason for this high mortality is the advanced stage of the disease at presentation. Radiation therapy alone resulted in a 5-year survival rate of 5-8%, with a median survival of 10-12 months.[2,7,8,21]

To test the effects of sequential chemo-radiation in NSCLC, the Cancer and Leukemia Group B (CLGB) initiated a phase III randomized trial in 1984. The overall survival at 2 years was higher in the chemo-radiotherapy arm than in the radiation-alone patients.[9] In 1993, Lager et al. reported on a phase II study with concomitant chemo-radiation therapy.[18] The 2-year overall and event-free survival rates were 38% and 25%, respectively.[18] Schaake-Koning et al. and the Radiation Therapy Oncology Group (RTOG 88-04 and RTOG 90-15) investigated the effects of sequential and/or concurrent chemo-radiation.[3,24,26] Radiation was administered once or twice a day. The 1- and 2-year overall survival rates with chemo-radiation were improved as compared with radiation alone.[3,24,26] In the phase II Southwest Oncology Group

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Table 1. **Characteristics of non-surgically treated patients (n = 52)**

Age (median)	*61 (range: 47-79)*
Gender	
Male	28
Female	24
Performance status	
ECOG 1-2	47
ECOG 3 (borderline)	5
Histology	
Squamous cell carcinoma	14
Adenocarcinoma	24
Poorly differentiated carcinoma	14
Stage	
IIIA	18
IIIB	34
Location of tumor	
Right upper lobe	24
Left upper lobe	18
Right lower lobe	7
Other	3

Table 2. **TNM classification of non-surgically-treated patients (n = 52)**

	N0	*N1*	*N2*	*N3*	*Total*
T1	0	0	2	1	3
T2	1*	0	7*	6*	14
T3	0	0	11*	0	11
T4	3	2	19	0	24
Total	4	2	39	7	52

*Four patients with solitary brain metastases were treated with resection and radiotherapy.

Table 3. **Reasons for not evaluating non-surgically treated patients for response (n=9) or for acute toxicity (n=6)**

Disease progressed outside treatment field, and treatment was stopped Adrenal gland (3) Liver (1) Bone (1)	5
Expired on treatment from pulmonary embolism	1
Suicide 3 days after treatment completed	1
Expired 1 week post treatment from lymphangitis spread	1
Lost to follow-up at 0 month	1

(SWOG) study, the patients were treated daily with cisplatin and concurrent chest irradiation, and promising improvements in local control and survival were observed.[11] In all of these combination trials, the rate of local recurrence was decreased, but still presented a considerable problem.

On the basis of these studies, we treated 80 consecutive, unselected NSCLC patients with stage IIIA or IIIB disease in a phase II study by using concurrent chemotherapy with twice-a-day radiation. We anticipated that this combination would lead to local control and survival benefits.

Patients and methods

Patient eligibility

Eighty consecutive patients (median age: 60 years, range: 35-79 years) with stage IIIA or IIIB NSCLC were treated from December 1994 to June 2001. A cardiopulmonary status adequate to tolerate hydration was mandatory. An Eastern Cooperative Oncology Group (ECOG) status of 1-2 was required, but in rare situations (e.g. a young age or a specific request by the patient) we treated patients with borderline ECOG 3 (5 subjects). An adequate hematologic status (white blood cell count >3,000 mm^3, absolute neutrophil count >1,500 mm^3, platelet count >100,000 mm^3) and an appropriate renal function (creatinine <1.5/dl) were required. Patients underwent complete physical examination, chest X-ray, and CT scans of the chest, abdomen and pelvis. Pathological material was obtained by means of transbronchial biopsy or cytol-

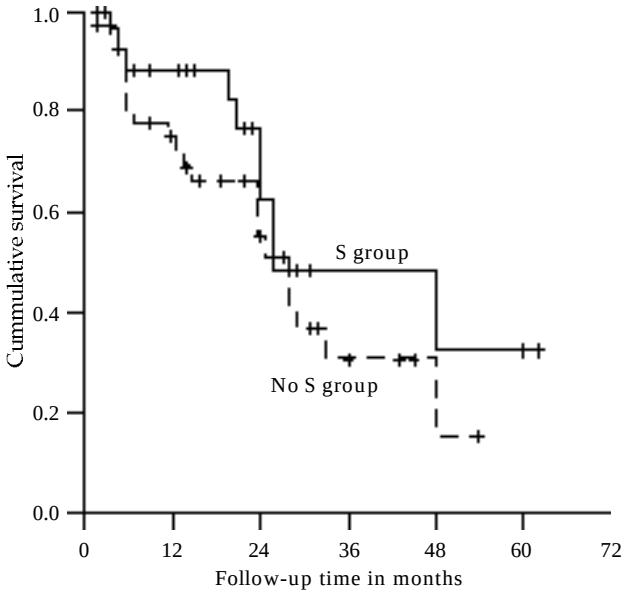

Figure 1. Kaplan-Meier estimates of probability of survival for 28 patients with (S group), and 43 patients without surgery (no S group)

Table 4. **Status of non-surgically-treated patients (n=43)**

	No. (%) of patients with tumorous signs					
	Local	*Local+Distant*	*Regional*	*Distant*	*Total*	*(%)*
No evidence of disease					10	(23)
Alive with disease	4	1	2	3	10	(23)
Died with disease	4	6	2	8	20	(47)
Died without disease					1	(2)
Lost to follow-up					2	(4)
Total	8	7	4	11	43	(100)

Remarks: Because of rounding, percentages did not total 100.

ogy, CT-guided needle biopsy, mediastinoscopy, scalene node biopsy or video-assisted thoracoscopy. All patients gave their signed informed consent before treatment.

Treatment

Radiation therapy was administered in a dose of 1.5 Gy, twice daily, with a 5-6-hour interval between the two treatments. Irradiation was started with antero-posterior and postero-anterior fields on a 6- or 10-MV linear accelerator, using appropriate blocking. The planning CT scan was used for 2D, and in the past 4 years for 3D treatment planning. Depending on the tumor location and the mediastinal node status, the fields were changed to obliques, laterals or a combination of them to exclude the spinal cord at 36-39 Gy. The treatment area included the mediastinal nodes and the ipsilateral hilar nodes. The ipsilateral supraclavicular nodes were included only for upper lobe tumors or for positive scalene nodes. For 3D planning, all margins for primary tumors followed the ICRU 50 and 62 recommendations.[12,13] The total dose to the primary tumor was 60 Gy for patients not undergoing surgery (52 subjects) and 45 Gy for patients undergoing surgery (28 subjects). No inhomogeneity correction was applied.

Patients received two courses of chemotherapy, started on day 1 and day 21 of irradiation. Chemotherapy via an intravenous infusion route, was begun with paclitaxel (30 mg/m^2, Mead–Johnson, Oncology products, a Bristol-Myers-Squib Company, Princeton NJ 08543 USA) for 4 days. On the fifth day, the patient received cisplatin (100 mg/m^2, Bristol Laboratories, Oncology Products, a Bristol-Myers-Squib Company, Princeton NJ 08543 USA). Filgrastim (30 ng/m^2, granulocyte colony stimulating factor=GCSF, Amgen Inc. One Amgen Center Drive, Thousand Oaks, CA 91320-1789) was given subcutaneously on days 10-15. In the fourth week of treatment, the patients participated in a CT scan of the chest and upper abdomen for restaging. If there was evidence of an adequate local response (tumor size shrinkage to resectability) without evidence of distant spread, the patient was scheduled for surgery. Surgery was planned for 3-4 weeks after the second course of chemotherapy. Following irradiation or surgery, the patients received two additional courses of paclitaxel-cisplatin chemotherapy.

Table 5. **Acute treatment-related toxicities in non-surgically-treated group (n=47)**

	No. of patients	*(%)*
Leukopenia (grade 4)	6	(13)
Leukopenia (grade 3)	4	(9)
Esophagitis (grade 3)	3	(6)
Anemia (grade 3)	3	(6)
Excessive salivation	2	(4)

Evaluation of response and toxicity

The response to treatment was evaluated only in patients not receiving surgery. Regular follow-up visits were scheduled every 2 months in the first year, every 4 months in the second and third years, and then every 6 months. Physical

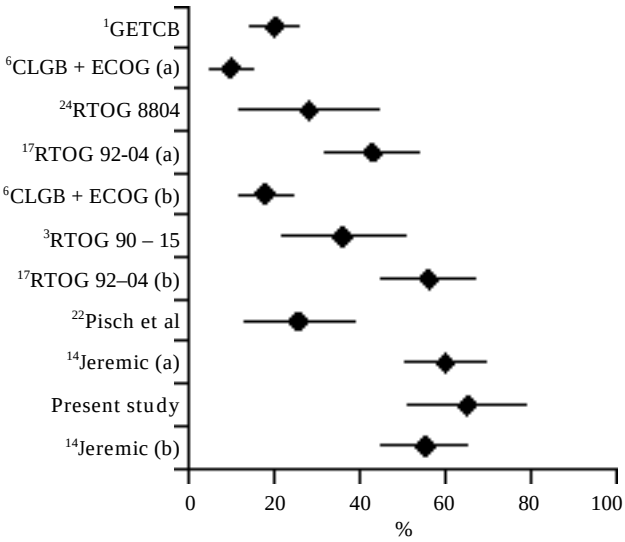

Figure 2. Percent of local control (± 95% CI) in different clinical studies with arms a and b (same sequence as in Table 6)

Table 6. **Local control and survival in phase II and III studies**

Study	*Phase*	*Treatment*	*No. of patients*	*Local control (%)*	*Survival (%)*			
					1. year	*2. year*	*3. year*	*4. year*
Sequential chemotherapy and qd RT								
CLGB 84-33[9]	III	Arm a: sequ + qd RT	78	n.s.	54	26	24	–
GETCB[1]	III	Arm a: sequ + qd RT	176	20	–	21	–	–
CLGB+ECOG[6]	III	Arm a: sequ + qd RT	130	10	57	28	21	–
Concomitant chemotherapy and qd RT								
RTOG 88-04[24]	II	1-arm: sequ + conc + qd RT	30	28	68	–	–	–
RTOG 92-04[17]	III	Arm a: sequ + conc + qd RT	80	43	65	30	–	–
CLGB+ECOG[6]	III	Arm b: conc + qd RT	146	18	57	28	21	–
Concomitant chemotherapy and b.i.d. RT								
RTOG 90-15[3]	II	1-arm: conc + b.i.d. RT	42	36	54	28	–	–
RTOG 92-04[17]	III	Arm b: conc + b.i.d. RT	82	56	58	30	–	–
Pisch et al.[22]	II	1-arm: conc + b.i.d. RT	47	26	60	49	–	28
Choy et al.[5]	II	1-arm: conc + b.i.d. RT	42	n.s.	62	35	–	–
Jeremic et al.[14]	III	Arm a: conc + b.i.d. RT (5-day chemotherapy)	97	60	78	49	34	–
Recent study	II	1-arm: conc + b.i.d. RT	43	65	68	48	–	–
Jeremic et al.[14]	III	Arm b: conc + b.i.d. RT	98	55	80	47	29	–

Abbreviations: b.i.d. = twice-a-day; conc = concomitant; n.s. = not stated; qd = once-a-day; RT = radiotherapy; sequ = sequential

examination was performed at every visit, with chest radiographs every 2 months in the first year, every 4 months in the second year and every 6 months for the third-fifth years, and CT scans after 2, 4 and 6 months, then twice a year in the second year, and thereafter once a year. Other appropriate tests were based on the symptoms observed. No bronchoscopy and/or biopsies were required or performed. Patients not undergoing surgery were scored as complete responders if the CT scan at 2, 4 or 6 months or at the last follow-up revelaed resolution of the tumor, or the fibrotic tissue did not change on CT. Acute toxicity reactions were scored according to the Common Toxicity Criteria, Vesion 2.0.[4]

Statistics

Survival curves were calculated according to the Kaplan-Meier estimate,[15] while the log rank test was used to test for significant differences in survival. The level of significance applied for all comparisons was 0.05. The 95% confidence interval (CI) for percentages was used to compare the rates of local control and survival in the present study with those in past studies.

Results

Fity-two patients were treated without and 28 with surgery. Of the non-surgically treated cases (*Tables 1, 2*), 43 were evaluable for response and 47 for acute toxicity during a median follow-up of 22 (range 2-54) months. Reasons for not evaluating patients are listed in *Table 3*.

Figure 1 presents data on the actuarial survival of the patients. In the non-surgically-treated group, the 1-and 2-year survival rates were 68% and 48%, respectively, with a median survival of 28 months. There was not a statistically significant difference between the surgically and

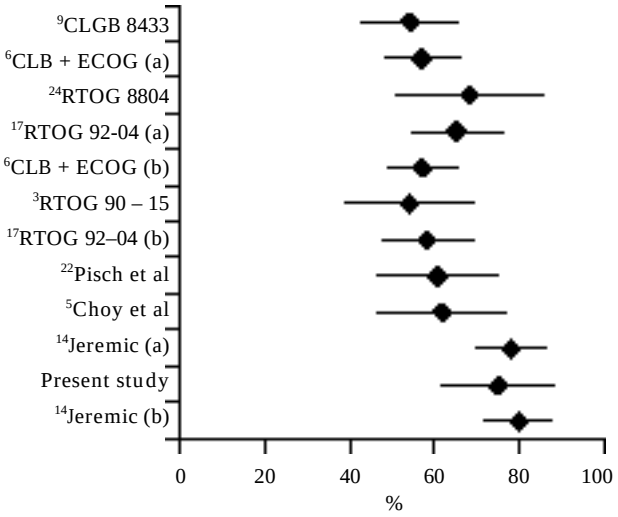

Figure 3. Percent of 1-year survival (± 95% CI) in different clinical studies with arms a and b (same sequence as in Table 6.)

non-surgically treated groups. At the end of the follow-up, the local control rate in the non-surgically-treated group was 65% (28/43), including 10 patients (23%) without evidence of the disease (*Table 4*). Ten additional patients are still alive with the disease (either local or distant or a combination of them), 2 patients were lost to follow-up, 1 died without disease and 20 died with NSCLC *(Table 4)*.

Acute toxicity in 47 patients *(Table 5)* included grade 4 leukopenia in 6 (13%, 4 cases with fever), grade 3 leukopenia in 4 (9%), and grade 3 esophagitis in 3 patients (6%) Three patients (6%) received blood transfusion (one or two times), which is equivalent to grade 3 toxicity. Two patients

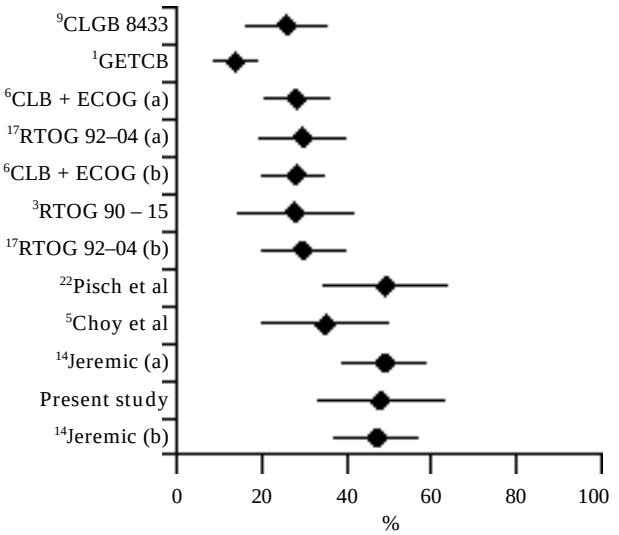

Figure 4. Percent of 2-year survival (± 95% CI) in different clinical studies with arms a and b (same sequence as in Table 6.)

(4%) developed an electrolyte imbalance, treated with water restriction and/or K^+ or Mg^{++} supplementation, and excessive salivation developed in 2 additional subjects (4%).

Discussion

Tumors with the potential for rapid proliferation have a poor outcome when treated with conventional once-a-day irradiation. Such tumors undergo accelerated repopulation during treatment, which may contribute to or be one of the reasons for local failure in lung cancer.[19,27,28] To test this hypothesis, a number of national and international groups have launched accelerated irradiation, involving irradiation two or three times a day or a concomitant boost technique.[2,7,20,23] The results of these trials confirmed that accelerated radiation is tolerable with acceptable acute and late toxicity. The overall survival rate improved for all the patients, but the local failure rate was still high. It was felt that partial control of the accelerated repopulation itself is not sufficient to improve the local control, and that more effective local and systemic therapies are needed.

Combination chemo-radiation therapy regimens have been introduced in clinical trials. *Table 6* and *Figures 2-4* compare the rates of local control and survival for phase II and III studies.[1,3,5,6,9,14,17,22,24] All combination trials revealed moderate improvements in local control and the 1- or 2-year survival rate, as compared with the historical data[2,7,8,21] (median survival 10-12 months) for radiotherapy-alone schedules. For sequential chemotherapy with once-a-day irradiation, the local control and 2-year survival rates were 10-20% and 21-28%, respectively. The corresponding data for concomitant radiotherapy and once-a-day radiotherapy proved to be 18-43% and 28-30%, respectively. The concomitant radiotherapy and twice-a-day irradiation yielded more favorable results of 26%-60% and 28%-49%, respectively. The best 1-year survival rate (80%) was reported by Jeremic[14] for continuous concomitant chemotherapy and twice-a-day irradiation, but the local control (55%) and 2-year survival (47%) rates were similar to those achieved in other concomitant twice-daily irradiation studies.[5,16,17,22]

The local control (65%), 1-year survival (68%) and 2-year survival (48%) rates in our patients compare well with the best results reported in the literature.[3,5,6,14,16,17,22,24] This underscores the benefit of twice-a-day irradiation in local control and survival by reducing the treatment time, thereby possibly preventing accelerated repopulation. We recognize that the number of patients treated is small, but is not unlike the numbers enrolled in many phase II-III trials,[3,5,17,22,24] and, to prevent a selection bias, we treated consecutive, unselected patients.

Table 7 compares the acute grade 4 hematologic toxicity with CLGB 84-33, RTOG 88-08, 88-04 and 90-15 studies.[3,9,24,25] The 13% acute grade 4 toxicity is substantially

Table 7. **Comparison of acute grade 4 hematologic toxicity of chemo-radiotherapy trials**

Study	*Treatment*	*Acute grade 4 toxicity (%)*
	Induction chemo+radiotherapy	
CLGB 84-33[9]	once daily radiotherapy	23
RTOG 88-08[25]	once daily radiotherapy	55
	Concurrent chemo+radiotherapy	
RTOG 88-04[24]	once daily radiotherapy	30
RTOG 90-15[3]	twice daily radiotherapy	45
Recent study*	twice daily radiotherapy	13

Remarks: CLGB and RTOG studies used vinblastin+cisplatin or VP16+cisplatin combinations.
*Paclitaxel+cisplatin and GCSF.

less than the 23-55%[9,25] observed for induction chemotherapy, or the 30-45%[3,24] reported with concurrent treatment. The reason for this appreciable difference may lie in the different toxicity profiles of the chemotherapies (CLGB and RTOG with vinblastin+cisplatin or etoposide+cisplatin, while our patients were treated with cisplatin+paclitaxel) and the added benefit of GCSF for our patients.

Conclusions

Our results and the relevant data from the literature support twice-a-day irradiation with concomitant chemotherapy in Stage IIIA and IIIB NSCLC. This schedule gives better local control than that achieved with once-a-day radiation. There is also a trend to an improvement in the 1- and 2-year survival rates.

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