

ORIGINAL PAPERS

CONCURRENT CHEMORADIO THERAPY IN LIMITED-STAGE SMALL-CELL LUNG CANCER. RESULTS OF A PILOT STUDY

Radkowski A, Korzeniowski S, Sas-Korczyńska B, Małecki K, Skołyszewski J

Department of Radiation Oncology, Centre of Oncology - Marie Skłodowska-Curie Memorial Institute, Kraków

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ABSTRACT

Between January 1994 and February 1998, 32 limited-stage small-cell lung cancer patients were treated with concurrent chemoradiotherapy. Follow-up time ranged from 4 to 34 months, (median 14 months). Complete regression was obtained in 22 of the 30 patients, who received at least four courses of EP chemotherapy and a tumour dose of 50 Gy or more. In all, 2-year actuarial disease-free survival was 21%. Brain metastases occurred in 8 (36.4%) patients with CR, in 5/7 (71.4%) patients without prophylactic cranial irradiation (PCI) and in 3/15 (20%) patients after PCI. The survival rate was lower in patients with PCI, in whom chest irradiation was started later than one month from the beginning of course 1 of EP chemotherapy. We have suggested a modification of the treatment protocol.

Small-cell lung cancer (SCLC) is the second most frequent histologic subtype, accounting for 25% of all lung tumours. About one third of cases is diagnosed at a stage of the disease limited to one side of the chest. SCLC is highly sensitive to chemotherapy, which can lead to a response rate of 70-80% and, in patients with limited-stage disease, achieve even up to 50% complete remissions. Nevertheless, most patients experience a relapse. Despite improvement of the median survival obtained with multidrug chemotherapy the prognosis remains poor. Only about 10% limited - stage patients are long-term survivors (Sandler et al., 1993; Coy et al., 1993).

To improve the results of treatment results the following main subjects are investigated in clinical trials: (a) optimum number of chemotherapy courses and the value of maintenance therapy, (b) application of alternating chemotherapy regimens with non-cross resistant drugs, (c) weekly versus monthly regimen, (d) increase in radiation dose and in high-dose chemotherapy with bone marrow or peripheral blood progenitor cell transplantation, (e) addition of new drugs and use of new regimens, (f) combined chemo- and radiotherapy and optimum timing of chest irradiation (Elias, 1998; Thatcher et al., 1998; Tomeczko et al., 1997; Brugger et al., 1998). Two meta-analyses have shown a small but

significant improvement in survival for patients treated with chemotherapy plus radiation versus chemotherapy alone. Especially interesting are updated results of CALGB Study 8083. In a group of 399 patients, with a follow-up of 10 years, modes which included thoracic radiation therapy remained superior to chemotherapy alone. Addition of thoracic radiation therapy to combination chemotherapy improves complete response rates and survival, with increased, but acceptable, toxicity (Perry et al., 1998; Albain et al., 1990; Bonomi, 1998).

Since January 1994, at the Department of Radiation Oncology, Centre of Oncology in Kraków (COK) phase II of the clinical trial for the assessment of effectiveness and toxicity of concurrent chemoradiotherapy has been carried out.

The aim of this paper is to present our results in the pilot group of patients with limited-stage SCLC.

MATERIAL AND METHODS

Between January 1994 and February, 32 patients with a limited-stage SCLC were treated with concurrent chemoradiotherapy.

The inclusion criteria were as follows:

- histologically proven SCLC limited to one side of the chest, i.e.: T1-4, herein with

positive cytology of pleural liquid, N1-3, herein with metastases to opposite hilar lymph nodes, but with exclusion of patients with metastases to opposite supraclavicular lymph nodes,

- performance state, $\geq 60\%$ (Karnofsky scale), adequate respiratory functions ($FEV_1 \geq 1000$ ml), normal renal and blood tests.

Obligatory staging included bronchoscopy with biopsy, chest X-ray (PA and lateral), spirometry, trepanobiopsy, bone scan, abdominal USG, chest and brain computed tomography (CT), and biochemical profile.

Chemotherapy consisted of PE regimen (cisplatin 30 mg/m^2 day 1, 2, 3 and etoposide 120 mg/m^2 day 1, 3, 5) started immediately after staging work-up was completed. Five courses of EP regimen were applied with three - week intervals, with concurrent chest irradiation. Radiotherapy was introduced 2 - 16 weeks after the beginning of chemotherapy. Patients were irradiated with megavoltage photon beam (either ^{60}Co teletherapy or 10 MV photons). The clinical treatment volume included the primary tumour with a 2-3 cm margin of normal tissue as visualised on the

chest CT scan, and regional lymph nodes. A total dose of 44 - 45 Gy, in fractions of 1.8-2 Gy, was delivered to this large volume and then a boost to the primary tumour of up to 54 -55 Gy was applied. In the case of lack of complete regression of primary tumour, further escalation of dose was possible. The overall response was assessed four weeks after the fifth course of chemotherapy. Restaging examination included chest X-ray, chest CT if needed, bronchoscopy with biopsy or brushing of suspicious areas.

At the beginning, we did not use prophylactic cranial irradiation (PCI) in our protocol. In May 1995, after our first analysis, because of the high incidence of brain metastases in the initial group of patients, the strategy was changed and all patients with CR received 30 Gy PCI in 15 fractions.

Survival was calculated from the first day of chemotherapy until treatment failure (death or recurrence of the process), survivors being censored at the date of their last control visit. The Kaplan-Meier estimate was used to calculate survival curves. The data were processed using the Statistica program.

RESULTS

Characteristic		Range (median)	N (%)
No of patients			32 (100)
Time of follow up		4 - 34 (14) months	
Sex	Female		14 (43.8)
	Male		18 (56.2)
Age		28 - 73 (49) years	
Localisation	Right		18 (56.2)
	Left		14 (43.8)
Time interval between the first course of CHT and RT		5 - 114 (30) days	
		≤ 30 days	17 (53.1)
No. of CHT courses		> 30 days	15 (46.9)
		5	24 (75)
		4	6 (18.8)
		3	1 (3.1)
		2	1 (3.1)
Total dose of RT		29.4 - 69.6 (55) Gy*	
Overall treatment time		25 - 67 (45) days	

*- 69.6 Gy was given to one patient, CHT - chemotherapy, RT - radiotherapy

Table 1. Clinical characteristics of 32 patients.

	N0	N1	N2	N3	
T 1	0	0	1	0	1
T 2	3	0	6	0	9
T 3	0	7	4	2	13
T 4	1	0	5	3	9
Total	4	7	16	5	32

Table 2. Distribution of patients by TNM stage.

Clinical characteristics of 32 patients treated are presented in tables 1 and 2. The time of follow-up ranged from 4 to 34 months, median 14 months. Complete regression was obtained in 22 of 30 patients (i.e. 73.3%), who received at least 4 courses of EP chemotherapy and a tumour dose of 50 Gy or more. Two patients did not receive this therapy: one of them died of pulmonary haemorrhage after the third course of chemotherapy, and in another patient we had to change the chemotherapy regimen because of renal insufficiency after the first course of EP. In the whole group of 32 patients, the 2-year actuarial disease-free survival was 21%. (Figure 1).

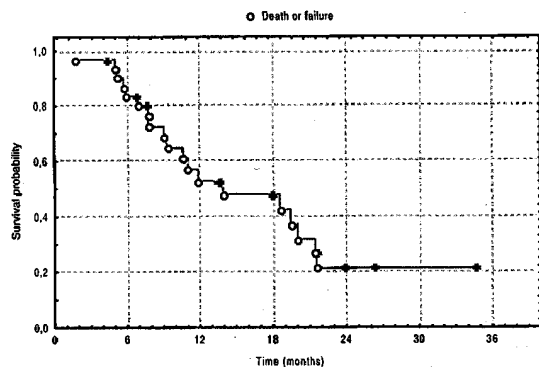


Fig. 1. Actuarial disease-free survival in 32 patients with SCLC treated in COK between 1994-98.

Fifteen patients are still alive, 11 with no evidence of disease, two with incomplete regression and two with distant metastases after initial CR. Seventeen patients died, one patient with CR, and one patient with partial regression during treatment, due to of pulmonary haemorrhage.

Brain metastases (BM) were found in 8 (36.4%) patients with CR, in 5/7 (71.4%) without PCI and in 3/15 (20%) with PCI.

Survival curves of patients with and without PCI were compared using the log rank test. The two-year actuarial survival rates were 35% and 0% respectively, $p=0.06$ (Figure 2).

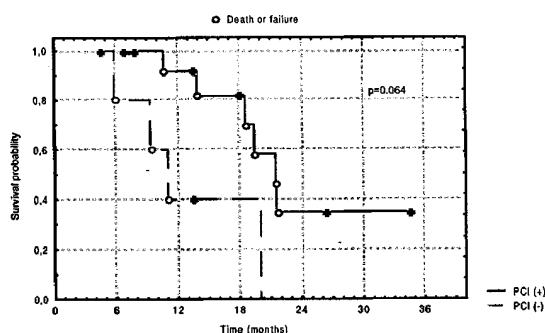


Fig. 2. Comparison of survival rates in groups of patients with and without PCI (only in CR).

To assess whether the delay in radiotherapy could adversely influence survival, we compared the survival time of chest irradiated patients treated with before and after one month after the first course of chemotherapy, using the Mann-Whitney U test. The mean survival time was 15.5 vs. 9.5 months, respectively. The difference was statistically significant, $P=0.025$.

The early toxicity of concurrent chemoradiotherapy was mild to moderate (table 3). The most frequent side effect was anaemia, and 34.4% of patients required blood transfusion. Transient alopecia developed in all patients. Severe oesophagitis was observed in 12.5% patients. PCI tolerance was good. Since we routinely used antiemetics during chemotherapy, nausea and vomiting did not affect the schedule of treatment. Up to now we have not observed any severe late effects.

Trombocytopenia		
76 – 100 x10 ⁹ /l	4	12.5
50 – 75 x10 ⁹ /l	4	12.5
Leukopenia		
2.51 – 3.0 x10 ⁹ /l	6	18.8
2.01 – 2.5 x10 ⁹ /l	4	12.5
1.01 – 2.0 x10 ⁹ /l	7	21.9
Infection (treated with antibiotics)	13	40.6
Anaemia		
G 1*	15	46.9
G 2	2	6.3
Transfusions	11	34.4
Oesophagitis		
G 1-2	9	28.1
G 3-4	2	12.5
Weight loss < 5%	7	21.9
Other: haemorrhage, stomach ulcer, renal insufficiency	3	9.7

* - toxicity scale according to WHO.

Table 3. Toxicity in 32 patients treated with concurrent chemoradiotherapy.

DISCUSSION

The analysed group of patients treated is small. Our patients had relatively more advanced tumours than those treated at other centres. According to the Manchester score system, about 50% of our patients would have scored two or above (Thatcher et al., 1998).

This classification comprises the total estimation of 6 parameters which influence the prognosis (one item for each parameter): LDH activity <450 U/l, extended disease (there are some differences in the definition of limited-stage disease), serum sodium level <132 mmol/l, performance status on the Karnofsky scale, of below 60%, alkaline phosphatase activity >165 U/l (1,5 times the x upper limit of norm), bicarbonates >24 mmol/l. The best prognosis is for values 0-1, moderate for 2-3, and poor for 4 or more.

In the group of 32 patients the 2-year actuarial disease-free survival was 21%. No patient who survived longer than two years, recurred.

The high incidence of brain metastases (BM) caused a modification of our treatment protocol. All patients treated before May 1995 died and 71.4% of them because of BM. In the literature, the value of PCI remains controversial. The critical issues are the value

of PCI, the optimum irradiation dose, and the time interval between the treatment of the primary tumour and the initiation of PCI („early” vs. „late” PCI). All large trials have shown a consistent survival advantage in favour of the PCI mode (Gregor et al., 1997; Le Chevalier and Arriagada, 1997). Until now, no individual sample size was large enough to statistically confirm this survival benefit, but a meta-analysis is in progress and will results are expected soon (Gregor, 1998). In a group of 199 patients Work et al., tested the hypothesis that the benefit from PCI would be expected mainly among the patients with the best prognosis. In the group of patients with favourable prognostic parameters, the survival advantage from PCI was statistically significant: the 3-year disease-free survival was 35.5% in patients with PCI vs. 14.1% in patients without PCI, P=0.029 (Work et al., 1996). Our results indicate that patients in CR could benefit from PCI (Figure 2).

In our study, due to logistic problems, the interval between chemotherapy and chest irradiation varied from 5 to 114 days (average 1 month). Extension of this interval over one the month seems to have had a negative influence on survival time.

In 1993, Murray et al. reported that cisplatin-etoposide chemotherapy in combination with

radiotherapy beginning at cycle 2 of chemotherapy was superior to concurrent radiotherapy beginning at cycle 6.

Similar results were published by Jeremic et al. in a randomised study on the optimal timing of chest irradiation in combination with concurrent chemotherapy in limited-stage SCLC. One-hundred and seven patients were enrolled in the study. Patients who received concurrent chemoradiation at weeks 1 to 4 had a significantly higher local control and survival rate. The five-year survival rate in these patients was 30% compared with 15% in the group irradiated at weeks 6 to 9 (Jeremic et al., 1997).

Two other randomised studies addressing the timing of chest irradiation in combination with chemotherapy in limited-stage SCLC have been reported. The Danish trial, presented by Work et al., showed that the timing of chest irradiation had no impact on the outcome. However, careful examination of the treatment design for this trial shows that chest irradiation was not administered concurrently with chemotherapy in either arm (Work et al., 1997). The survival rates in this trial were poorer in comparison with results presented by those groups where early chest irradiation was combined with concurrent chemotherapy (two-year survival 19% and 20% vs. 40%).

The trial presented by EORTC Lung Cancer Cooperative Group also failed to confirm the superiority of an alternating (early) versus sequential (late) schedule of delivery of chest irradiation. In this trial, five courses of CDE chemotherapy followed by continuous chest irradiation 50 Gy in 20 daily fractions (arm S) were compared with the same total dose of chemotherapy and irradiation split into four courses of five daily fractions delivered on days 14 to 21 of the second and subsequent chemotherapy courses (arm A). For combination of chemotherapy and radiotherapy in arm A, haematological toxicity compromised treatment delivery and could have contributed to the overall results. The poorer rates of local control are disappointing and require intensification of the radiation therapy strategy (Gregor et al., 1997).

The latest data published by Turrisi et al. suggest that twice-daily accelerated chest radiotherapy has potential advantages over once-daily radiotherapy. Four cycles of cisplatin plus etoposide and a course of radiotherapy (45 Gy, given either once or twice daily) beginning with the first cycle of chemotherapy, resulted in overall 2- and 5-year survival rates of 44% and 23%, respectively. These results constitute a considerable improvement in survival rates over the previous results in patients with limited stage SCLC, but the optimum manner of delivering radiotherapy is yet to be defined.

The tolerance of concurrent chemoradiation in our study was good. Basing on our results and on data from literature, we modified our treatment protocol as follows: (1) all patients with CR are routinely treated with PCI, (2) we try to begin chest irradiation no later than two weeks from the first day of chemotherapy and (3) in treatment planning, we apply CT scans to minimise treatment - related oesophagitis. We also intensified our chemotherapy regimen by adding ifosphamide to cisplatin and etoposide.

CONCLUSIONS

1. In patients with complete remission prophylactic cranial irradiation (PCI) reduces the incidence of brain metastases. We found brain metastases in 5/7 (71,4%) patients without PCI, and in 3/15 (20%) patients after PCI.
2. Our results suggest that the timing of chest irradiation may affect the outcome, but observation of a larger group of patients is required.

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