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A Randomized Clinical Trial Comparing Systemic Radiotherapy Versus Chemotherapy Versus Local Radiotherapy in Small Cell Lung Cancer

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Abstract—*Between* 1982 *and* 1987 *a prospectively randomized trial of sequential hemibody irradiation (SHBI) (A), a non-cross-resistant chemotherapy drug combination (B) and local and/or locoregional radiotherapy (C) in small cell lung cancer (SCLC) was conducted. Previously untreated patients with extensive SCLC were randomized into three arms: A = 31 patients, B = 37, C = 31. In the chemotherapy combination, the following were used: etoposide, doxorubicin, methotrexate (VAM) and procarbacine, vincristine, cyclophosphamide, lomustine (POCC) and prophylactic cranial irradiation* (30 Gy). *The results show that the median survival was significantly* ($P < 0.01$) *better in chemotherapy* (44 *weeks*) *compared with* 17 *and* 20 *weeks in arms A and C, respectively. One year and 2 year survival rates were better for the chemotherapy arm. No differences were found between groups A and C. In comparing the total hospitalization time expressed as a percentage of overall survival, an advantage for group B was shown. In conclusion, high dose SHBI cannot be recommended as a standard therapy for extensive SCLC.*

INTRODUCTION

THE PROGNOSIS of small cell lung cancer (SCLC) is known to be poor and, up to now, all kinds of treatment have not significantly improved this situation [1–3]. Even using combination chemotherapy with or without radiotherapy, median survival times of only about 7–10 months (for extensive disease) can be achieved and the group of long-term survivors is disappointingly small. Conventional radiotherapy, however, has rarely been successful and is less effective than chemotherapy in SCLC patients [3–6]. Nevertheless, hemibody irradiation (HBI) was introduced by Fitzpatrick and Rider as a systemic treatment in SCLC [7] and immediately after their first promising reports in 1977 we began to use sequential HBI for SCLC patients. From 1977 to 1982, more than 70 patients were treated with HBI and a number of modifications were introduced to reduce the frequency of toxic reactions, i.e. pulmonary complications [8, 9]. On the basis of our preliminary promising results, we created a randomized clinical trial comparing systemic or locoregional radiotherapy with combination chemotherapy in SCLC, to confirm or to reject this first impression. We used a POCC–VAM combination according to the protocol of the North California Oncology Group [10]. Using this combination, Sikic *et al.* obtained 44% complete remissions with a disease-free interval of 6 months and an overall survival of 10 months.

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MATERIALS AND METHODS

All patients admitted to the Central Institute for Cancer Research of the Academy of Sciences in Berlin (GDR) with histologically proven small cell carcinomas of the lung were extensively staged, using history and physical examination: X-ray of the lung, CT of the thorax and abdomen, brain, liver and bone scanning, bone marrow puncture, complete blood count with differentiation and serum chemistry, including parameters of renal and liver function, electrolytes and blood clotting. Patients with extensive disease (T3 or M1 tumors) were eligible for our study if they had a Karnofsky performance status greater than or equal to 50% and had no prior treatment of lungs with chemotherapy, irradiation or surgery. Patients with limited disease, severe renal, hepatic or cardiac impairment, diabetes mellitus and patients older than 70 years were excluded. For every patient, written informed consent was obtained.

Patients were randomized to receive one of three possible forms of treatment: systemic radiotherapy (group A), chemotherapy (group B) or local radiotherapy (group C). Systemic radiotherapy consisted of two parts—locoregional irradiation of the primary tumor and the mediastinum and sequential HBI for the upper and lower hemibody.

Treatment planning was CT-based in every case.

1. Locoregional irradiation: 40 Gy photon irradiation (linac, 9 MeV), mostly as two opposing fields, with dose reduction up to 20 Gy in cases of very extensive disease or rapid growth of metastases. The total dose was delivered with single doses of 2 Gy in 20 or 10 fractions over 4 or 2 weeks respectively. Locoregional irradiation was followed by a treatment-free interval of 1 week maximum.
2. Sequential HBI: upper hemibody irradiation (UHB) 8 Gy midline dose (max. dose at lungs 9.4 Gy) separated into a 6 Gy dose given in the morning and a 2 Gy dose given in the afternoon (5 h later); UHB was followed by a lower hemibody irradiation (LHB) at the same regimen, 6 weeks later. Upper and lower hemibody were divided at the level of the navel; hands, forearms, feet and lower legs were always situated out of the field.

Local radiotherapy was given for the primary tumor and the mediastinum as well as for all distant metastases, confirming at the beginning of the trial or during the follow-up.

We used a 40 Gy photon irradiation (9 MeV, linac) with CT-based treatment planning. Depending on tumor extent and performance status, a dose reduction of up to 20 Gy was allowed. The total dose was delivered with single doses of 2 Gy in 20 or 10 fractions over 4 or 2 weeks respectively.

Chemotherapy consisted of two non-cross-resistant drug combinations, including procarbacine, vincristine, cyclophosphamide and lomustine (POCC) and etoposide, doxorubicin and methotrexate (VAM). Drug doses and schedules are described in Table 1. Chemotherapy was started with five cycles of VAM, followed by alternating cycles of POCC and VAM (up to 12 cycles of VAM and eight cycles of POCC). Maximum duration of treatment was 18 months.

Table 1. Dosing schedule of the POCC-VAM combination

VAM regimen	
Etoposide	200 mg/m² i.v. inf., day 1
Doxorubicin	50 mg/m² i.v., day 1
Methotrexate	30 mg/m² i.v., day 1
	(21 days cycle)
POCC regimen	
Procarbacine	100 mg/m² p.o., day 2–day 15
Vincristine	1.5 mg/m² i.v., day 1 + day 8
Cyclophosphamide	600 mg/m² i.v., day 1 + day 8
Lomustine	60 mg² p.o., day 1
	(28 days cycle)

All patients included in the chemotherapy arm received prophylactic cranial irradiation (30 Gy). Patients were evaluated for response, duration of survival and toxicity. Quality of life was estimated, comparing the time spent in hospital with the overall survival.

For statistical analysis, we used the life table method according to Peto *et al.* [11], as described by Berchtold [12], the Mann–Whitney–Wilcoxon test [13] and the chi-square test [14].

RESULTS

From 1982 to 1987, 114 patients with T3 and/or M1 small cell lung cancer were randomized between the three treatment groups: 36 into group A (systemic radiotherapy), 44 into group B (chemotherapy) and 34 into group C (local radiotherapy). Of these, 99 patients (31, 37 and 31 patients, respectively) were evaluable for the study; 15 patients had to be excluded for protocol violations. This was due to a rapid worsening of the general condition of patients after randomization and before hospitalization (this interval was no longer than 1 week), to a Karnofsky index of less than 50% or due to death of patients during the first 15 days independent of causes of death. To evaluate whether our treatment groups A, B and C are comparable, we regarded a number of stratification parameters known to have a prognostic value [15], such as age, sex, Karnofksy index (greater or less than 70%), weight loss >2 kg and the number of tumorous lesions. The characteristics of the treatment groups are shown in Table 2. According to these parameters, the study was well balanced between the groups.

All patients evaluated for this study had a follow-up of at least 12 months.

Survival curves are shown in Fig. 1. Median survival was 19 weeks for group A (systemic irradiation), 46 weeks for group B (chemotherapy) and 23 weeks for group C (irradiation). Survival

Table 2. Patient stratification with respect to staging and prognostic factors

Stratification parameters	Treatment groups A	B	C
No. of patients	31	37	31
Mean age	55.7	56.4	57.7
Women (%)	26	16	16
Percentage of patients with Karnofky index <70	23	30	29
Weight loss >2 kg (%)	55	68	71
No. of tumorous lesions (mean)*	4.0	4.1	3.8
No. of M1 patients	25	29	25

*Including primary tumor, mediastinum and distant metastases.

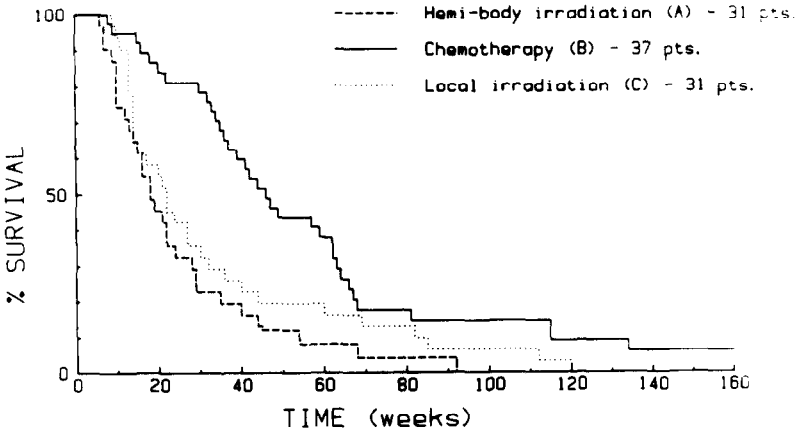

Fig. 1. Survival curves for extensive SCLC treatment groups.

was significantly better for chemotherapy, compared with systemic as well as with local irradiation ($P < 0.01$). No difference between groups A and C could be found.

The 37 patients treated with chemotherapy were assessed for their response to the POCC–VAM combination: 24 (65%) experienced objective regression of the tumor; of these, four patients (11%) had complete remission and 20 patients (54%) partial remission. Fourteen patients failed to respond to chemotherapy.

One year and 2 year survival rates are reported in Table 4. In every case, better results were obtained for the chemotherapy arm, while no difference was found between the two irradiation groups.

Table 3a. Leucopenia following radiotherapy (incidence according to the WHO scheme as a percentage)

	WHO grade				
	0	1	2	3	4
Therapy arm A					
LRT	65	32	3	0	0
UHBI	13	32	48.5	6.5	0
LHBI	6.5	13	61.5	16	3
Therapy arm C					
(LRT partly, different regions)	26	35	30.5	8.5	0

LRT—local radiotherapy; UHBI—upper half-body irradiation; LHBI—lower half-body irradiation.

Table 3b. Leucopenia following chemotherapy (incidence according to the WHO scheme as a percentage of chemotherapy cycles)

	WHO grade				
	0	1	2	3	4
Therapy arm B					
VAM 239 cycles	64	12	20.5	2	1.5
POCC 75 cycles	38.5	16	45.5	0	0

Number of leucocytes (Gp/l) grade 0: ≥4.0; grade 1: 3.0–3.9; grade 2: 2.0–2.9; grade 3: 1.10–1.9; grade 4: <1.0 [18].

Table 4. Survival rates for small cell lung cancer patients following half-body irradiation (A), chemotherapy (B) and local irradiation (C)

	Treatment		
	A	B	C
½ year	32%	81%	42%
1 year	10%	43%	19%
2 years	0	13%	8%

Toxicity

The principal side-effects we noticed following systemic radiotherapy were modest leucopenia (Table 3a) and a complex of general symptoms, i.e. nausea, weariness, dry mouth and anorexia, lasting about 1–2 days. Forty-five per cent of our patients had slight locoregional inflammatory reactions (esophagitis, stomatitis, pneumonitis), so that the treatment had to be discontinued for 2–4 days and symptomatic treatment was carried out.

The clinical signs of the general pneumonitis occurring in two patients were improved by means of prednisolone and antibiotics. Following local radiotherapy, the main side-effects were esophagitis and local pneumonitis, occurring in 29% of patients and needing symptomatic treatment as well as discontinuation of therapy for 2–4 days. Hematological toxicity was mild and did not influence the treatment schedule (Table 3a).

In patients receiving chemotherapy, typical side-effects were modest leucopenia (Table 3b) and thrombocytopenia, mild nausea and only rarely vomiting. In 15 patients, leucopenia caused dose reduction or prolongation of the treatment-free interval.

Vincristine-induced neurotoxicity, occurring during POCC treatment (six patients), was moderate and transient. Only in one patient was a

doxorubicin-induced cardiomyopathy found (cumulative dose 570 mg).

Estimating the quality of life for our patients, we analyzed the time a patient had to spend in hospital for therapy and general medical care (until death) and compared total hospital days with survival days, expressed as percentage of overall survival (Table 5).

Although no difference was found in the total number of hospital days, an advantage for chemotherapy was shown in the survival time ratios.

DISCUSSION

High dose SHBI as a systemic treatment did not fulfil our expectations: to give better or even similar results to those obtained with chemotherapy and thus to be a real alternative in the treatment of SCLC. According to our findings, SHBI was less effective than the POCC–VAM combination and did not improve overall survival even compared with local radiotherapy in extensive disease patients. Similar results were obtained by Urtasun *et al.* [16], who could not show any advantage for SHBI, either.

Table 5. *Time spent in hospital in cases of systemic radiotherapy (A), chemotherapy (B) and local radiotherapy (C) for SCLC*

Treatment	Hospital days/percentage of overall survival	Days of hospitalization min–max
A	72/42%	44–194
B	83/26%	35–115
C	68/30%	26–219

Characteristic side-effects were modest and reversible in all treatment groups, except for one patient who died from myocardial infarction due to doxorubicin-induced cardiomyopathy. None of the treatment regimens we used should be abandoned because of intolerable toxicity.

On the whole, the results of the treatment of extensive stage SCLC are disappointingly bad. However, chemotherapy seems to remain the treatment of choice, because even combinations of chemotherapy and radiotherapy are not very promising. Median survival and overall response rates are identical for patients treated with chemotherapy alone or chemotherapy plus thoracic irradiation [17]. Moreover, combinations of chemotherapy and SHBI did not improve the efficacy of treatment but increased rapidly the acute toxicity, i.e. radiation pneumonitis [3, 17]. Further investigations have to show whether and under what conditions radiotherapy may be possibly more important for the treatment of limited disease SCLC in relation to extensive disease.

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