Eur J Cancer Clin Oncol, Vol. 20, No. 7, pp. 911–914, 1984.
Printed in Great Britain.

0277-5379/84$3.00+0.00

Phase II Randomized Trial of Radiotherapy Alone vs the Sequential Use of Chemotherapy and Radiotherapy in Stage III Non-small Cell Lung Cancer. Phase II Trial of Chemotherapy Alone in Stage IV Non-small Cell Lung Cancer

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Abstract—*In order to clarify if the sequential combination of chemotherapy and radiotherapy offered any advantage over radiotherapy alone in stage III non-small cell lung cancer, 33 patients were randomized between radiotherapy alone or chemotherapy followed by radiotherapy, then chemotherapy again. Chemotherapy consisted of a combination of* cisplatinum, *VP-16 and adriamycin. Twenty-four patients with stage IV disease received the same chemotherapy regimen alone for six cycles. Median survival for stage III patients receiving radiotherapy alone was* 5 months. *For patients receiving the sequential combination of chemotherapy and radiotherapy median survival was* 11 months (*log-rank test,* $P = 0.025$). *Median survival for stage IV patient receiving chemotherapy alone was* 15 months. *It is concluded that the sequential combination of chemotherapy and radiotherapy is significantly superior to radiotherapy alone in patients with stage III non-small cell lung cancer.*

INTRODUCTION

NON-SMALL cell lung cancer (NSLC) is generally considered as relatively refractory to chemotherapy. In stage III NSLC (TNM classification, UICC, Genova, 1978) radiotherapy is considered by many physicians as the treatment of choice. During recent years high response rates have been reported in NSLC using combination chemotherapy with *cis*platinum and vindesine or VP-16 [1, 2]. Regimens containing adriamycin without vindesine or VP-16, however, have also produced a significant percentage of response [3]. In an earlier study we have demonstrated the feasibility of giving sequential chemotherapy and radiotherapy in stage III patients [4]. In 1979 a randomized study was started comparing radiotherapy alone vs sequential chemotherapy and radiotherapy in stage III patients with NSLC. The study was designed as a randomized phase II trial to be analysed with a relatively small number of patients (15 patients foreseen in each treatment arm) after a minimum median follow-up of 18 months. Based upon the results of that first analysis, a decision would be made on how to proceed. At the same time a phase II trial was conducted also using the same chemotherapy regimen in patients with stage IV disease. We now report our first analysis after a median follow-up of 20 months.

Accepted 20 January 1984.

MATERIALS AND METHODS

Between July 1979 and May 1983, 57 patients were diagnosed as having inoperable NSLC. Thirty-three patients had stage III disease according to the TNM classification, which means $T_{1-3}N_2M_0$ tumours. Twenty-four patients had distant metastases (stage IV). In Table 1 the patient eligibility criteria are shown. Table 2 shows the patient characteristics. There was no imbalance between the randomized groups in factors which may be of prognostic value, such as weight loss and histologic cell type. Stage IV patients had a significantly higher incidence of

adenocarcinoma. This type of NSLC has been reported to be more often diagnosed at an already advanced stage [1].

Irradiation was given by linear accelerators (photons of 5 MV). Initially the target volume encompassed the tumour and areas of lymph node drainage, including the supraclavicular regions. In 2.5-Gy daily fractions, 4 times a week, AP and PA portals, a total target dose was given of 45.0 Gy. The second part of the treatment consisted of an additional 15.0 Gy, under the same scheme, to a total dose of 60.0 Gy on a smaller target volume, encompassing the primary and the adjacent part of the mediastinum but keeping the spinal cord out of the treatment field. The patients who were treated with cytostatic drugs received the same treatment policy, but the total target dose in the initial plan was reduced to 40.0 Gy and the additional dose in the second part of the treatment to 10.0 Gy. The treatment plan was always designed by a computer-assisted planning system.

Chemotherapy consisted of *cis*platinum 60 mg/m^2 i.v. day 1, adriamycin 40 mg/m^2 i.v. day 1 and VP-16 200 mg i.v. day 1 and 200 mg orally days 3 and 5. Cycles were repeated every 4 weeks. In patients who received the combination of chemotherapy and radiotherapy, two cycles of chemotherapy were given before radiotherapy and four cycles afterwards. The time interval between chemotherapy and radiotherapy was 4 weeks. Complete response was defined as total disappearance of all evidence of tumour. Since lesions on chest X-rays are often only evaluable but not exactly measurable, especially after radiotherapy, a partial remission was defined as a clear decrease of the lesions seen on X-rays agreed upon by two investigators. It has been shown that the clinical outcome in patients with measurable or evaluable disease is the same [2, 5]. Progression was defined as a 25% or more estimated increase in tumour volume or the appearance of new lesions.

Table 1. Eligibility criteria

Histologically proven non-small cell lung cancer	
Age:	≤70 yr
Karnofsky index:	≥70
No previous treatment with chemotherapy or radiotherapy	

RESULTS

In Tables 3 and 4 a summary of the results is given. Of the 57 eligible patients five were considered to be not evaluable because of early death within 4 weeks of starting treatment. One of these was a toxic death. The patient had stage IV disease with extensive bone marrow metastases. In the radiotherapy arm seven out of 13 patients showed a partial response, median duration of response, however, being only 5 months and median survival for all patients 5 months. In the chemotherapy plus radiotherapy arm 14 out of 17 patients showed a response (three complete responses), median duration of response being 14 months and median overall survival 11 months. The difference between the survival curves of these two groups of patients is very significant (log-rank test, $P = 0.025$). This difference remains significant even when the early deaths are included in the survival analysis. On the basis of this first analysis, it was decided to drop the

Table 2. Patient characteristics

	Radiotherapy	Chemotherapy + radiotherapy	Chemotherapy
Entered	14	19	24
Not evaluable	1	2	2
No. of evaluable patients	13	17	22
Stage	III	III	IV
Age (yr)	59 (48–70)	60 (43–70)	57 (31–68)
Karnofsky index	80 (70–100)	80 (70–100)	80 (70–100)
Weight loss (percentage of previous body weight)	5 (0–10)	5 (0–10)	6 (0–12)
Histology			
Squamous	11/13	12/17	7/22
Adenocarcinoma	1/13	2/17	11/22 ($P<0.005$)
Large cell anaplastic	1/13	3/17	4/22

Table 3. Results for patients with stage III disease

	Radiotherapy	Chemotherapy + radiotherapy
CR	0/13	3/17
PR	7/13	11/17
CR + PR	7/13	14/17 ($P = 0.08$*)
Median duration of response (months)	5	14
Median survival of all patients (months)	5	11 ($P = 0.025$)

*Fisher's exact test.

Table 4. Reults for patients with stage IV disease

CR	2/22
PR	11/22
Median duration of response (months)	13
Median survival of all patients (months)	15

radiotherapy arm and to treat all further stage III patients with the sequential combination of chemotherapy and radiotherapy. In stage IV patients 13 out of 22 responded (two complete responses), with a median duration of response of 13 months and a median overall survival of 15 months.

Figure 1 shows the survival curves for all patients with stage III disease. In Fig. 2 the survival curve for the patients with stage IV is shown.

The toxicity of the chemotherapy schedule was considerable, gastrointestinal disturbances and

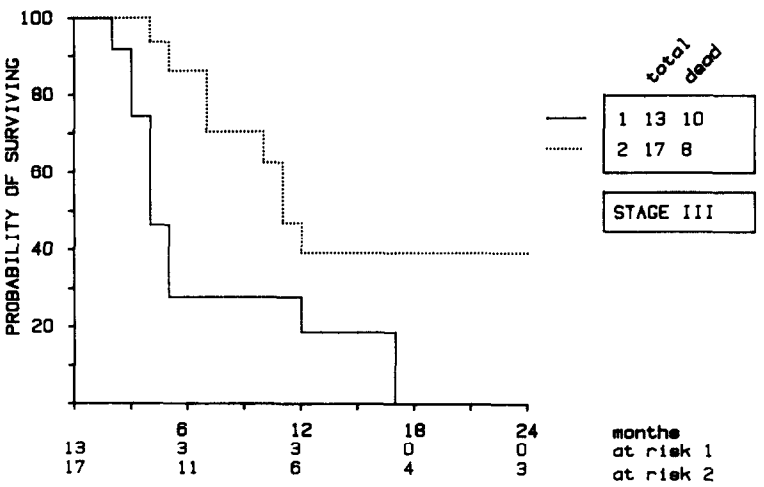

Fig. 1. Survival curves (Kaplan-Meier) for patients with stage III disease. 1 = Radiotherapy alone; 2 = radiotherapy and chemotherapy.

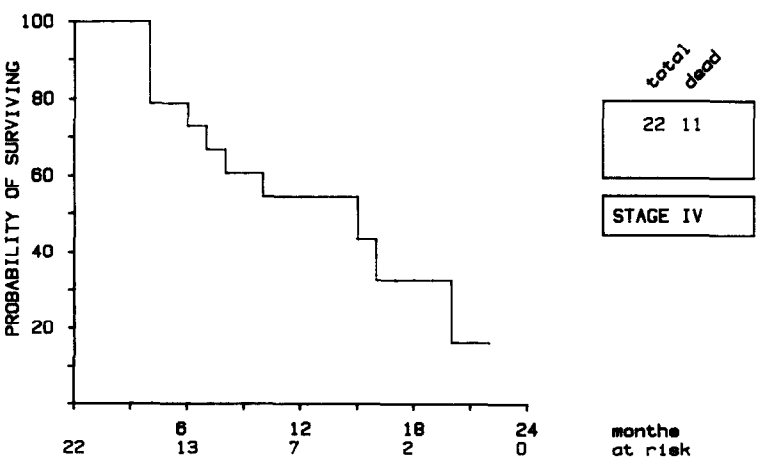

Fig. 2. Survival curve (Kaplan-Meier) for patients with stage IV disease.

alopecia being almost universal. Haematological problems were minor, anaemia being the most frequent; packed cells were given if the haemoglobin concentration fell to less than 6.0 mmol/l. Dose reductions according to the nadir of the leucocytes were not made. Only very few patients had leucocyte nadirs of less than 1.0×10^9/l; all had full recovery upon the next scheduled course. Apart from the one toxic death already mentioned, no granulocytopenic sepsis was seen. There was no clinical renal toxicity.

The radiotherapy, even in the patients with combined modality treatment, was well tolerated and no major complications of the myelum, heart and lungs were observed.

DISCUSSION

Our results show that for stage III NSLC the sequential combination of chemotherapy and radiotherapy is significantly better than radiotherapy alone, looking at median survival and especially at the relatively high number of long-term survivors. For stage IV patients chemotherapy with *cis*platinum and VP-16 or vindesine has been reported to give a relatively high incidence of remission and probably some impact on survival, which is confirmed by the results of our study. It has been suggested that the addition of a third drug, such as adriamycin, as used in this study, does not enhance therapeutic results [6]. Data on the activity of adriamycin used in combination regimens in NSLC are conflicting [3, 4, 7].

It is general practice in oncology to compare responders with non-responders, and mostly a survival benefit is found for responders which is then easily interpreted as the treatment itself prolonging survival. The finding of a longer survival in responders, however, must be cautiously interpreted. It may well be that patients respond and have a longer survival because of unknown biological factors, the fact that they respond merely showing the better prognosis. The only way to show that treatment itself prolongs survival is to compare the overall survival of a treated group of patients with a matched control group, ideally in a randomized trial. Therefore response rate in NSLC must not be overemphasized, overall survival being the most important treatment parameter. In conclusion, this study has shown that for stage III patients with NSLC in a relatively good condition the sequential use of chemotherapy and radiotherapy is better than radiotherapy alone. The overall median survival of 15 months obtained in stage IV patients suggests therapeutic benefit of the chemotherapy schedule used in this study. Results of other studies, however, may indicate that the inclusion of adriamycin may not be necessary. Further studies are needed to define the optimal chemotherapy regimen for NSLC.

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