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Original Paper

Early Alternating Chemotherapy and Radiotherapy Schedule in Limited Disease Stage Small Cell Lung Cancer

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44 patients with limited small cell lung cancer were treated with six cycles of chemotherapy (cisplatinum 60 mg/m² day 1, doxorubicin 40 mg/m² day 1, etoposide 100 mg/m² days 1–3) alternating with three courses of mediastinal irradiation, the first one starting 7 days after the first day of chemotherapy. A total dose of 55 Gy was delivered. Prophylactic cranial irradiation (30 Gy after the third cycle of chemotherapy) was left to the physician's discretion. 4 patients had radical surgery before combined modality treatment. 29 patients finished the scheduled program. The complete response rate (bronchoscopically confirmed) was 25.6% after two cycles of chemotherapy and 41% at the end of treatment. Median survival time was 17.2 months, with an estimated survival of 32% at 2 years. Main toxicity was haematological with one early toxic death and six premature interruptions of treatment. We conclude that this treatment modality is feasible and efficacious. Prospective studies comparing chemotherapy with alternating or concurrent early radiotherapy schedules in limited disease small cell lung cancer are needed to determine the best treatment modality.

Key words: combined treatment modality, small cell lung cancer, limited disease
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INTRODUCTION

CHEMOTHERAPY (CT) IS the cornerstone of the treatment of small cell lung cancer. However, despite a high initial response rate, relapses are frequent, especially at the site of the primary tumour in limited stage disease [1]. The issue of local control provides the rationale for adding thoracic radiation therapy (TRT) to systemic CT [2]. The first positive randomised trial comparing CT alone versus CT and TRT was published in 1984 [3]. By 1987, two more positive trials [4, 5] and three negative trials [6–8] had been published. The positive trials administered TRT concurrently or in an alternating schedule with CT whereas in the negative trials, TRT was administered on a sequential or split-course schedule. On the basis of these studies and of the very promising results of an alternating radiotherapy and chemotherapy schedule [9], we investigated the efficacy, toxicity and survival obtained in limited disease small cell lung cancer after an induction CT with cisplatinum, etoposide, doxorubicin administered in six courses alternating with three courses of TRT.

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PATIENTS AND METHODS

Patients with histologically or cytologically proven small cell lung cancer were included provided they fulfilled the following criteria of eligibility: age <75 years, Karnofsky performance status >60, and normal hepatic, renal and cardiac function. Radical surgery was the only previous treatment allowed.

Staging procedures included clinical examination, blood cell count and chemistry, chest X-ray, pulmonary tomograms or computed axial tomographic (CAT) scan of chest, bronchoscopy, abdominal ultrasound and/or CAT scan of upper abdomen, brain CAT scan, bone scan and bone marrow biopsy. Limited disease was defined as a disease confined to one hemithorax with or without mediastinal lymph nodes and/or ipsilateral supraclavicular lymph nodes [10].

Treatment

CT consisted of two cycles of cisplatinum [60 mg/m² intravenously (i.v.) on day 1], doxorubicin (40 mg/m² i.v. on day 1) and etoposide (100 mg/m² i.v. on days 1–3). From the third

to the sixth cycle a drug dosage reduction was applied for doxorubicin (30 mg/m^2 i.v. on day 1) and etoposide (80 mg/m^2 i.v. on days 1–3). CT was repeated every 28 days if the neutrophil count was >1500/mm^3 and the platelet count >100 000/mm^3; it was otherwise postponed until blood count recovery. Drug dosage reduction was applied from the second cycle in the case of grade 4 haematological toxicity after the first cycle.

TRT was delivered in three courses starting on days 8, 36 and 64. The first two courses consisted of 22 Gy administered in 10 fractions over 15 days. The third and last course consisted of 11 Gy in five fractions over 1 week. All TRT was administered via antero-posterior and postero-anterior portals. The volume treated was the tumour, the homolateral hilum and the mediastinum, including supraclavicular nodes.

Prophylactic cranial irradiation (PCI) was left to the physician's discretion in the case of a complete response. When appropriate it was performed on day 64 along with the third TRT course (30 Gy in 15 fractions over 3 weeks).

Evaluation of response

The first evaluation was performed before starting the third cycle of CT. Operated patients were considered as non-evaluable for response. Chest X-ray, tomograms or CAT scan of thorax and bronchoscopy were systematically repeated in the case of a complete radiological response. The second evaluation was performed 3 weeks after the last CT cycle. All the initial staging procedures were repeated except for bone marrow biopsy. A 3-monthly follow-up was performed after the end of treatment with clinical examination and chest X-ray. Thorax CAT scan, brain CAT scan, abdominal ultrasound and/or upper abdomen CAT scan were repeated every 6 months for a 2-year period.

A complete response was defined as complete disappearance of all tumour lesions including bronchoscopic abnormalities; a partial response was defined as a >50% reduction in the product of the two longest perpendicular diameters of the indicator lesions; progressive disease was defined as a >25% increase in the product of the two longest perpendicular diameters of the indicator lesions or appearance of any new lesions [11].

Toxic effects

Toxic effects were evaluated according to World Health Organization criteria [11].

Survival

Probability of survival was estimated according to the Kaplan–Meier method and survival was calculated from the first day of treatment. All survival data were updated to March 1994.

RESULTS

45 patients were included in the study between July 1987 and March 1992. One patient was ineligible because of the presence of adrenal gland metastasis in initial work-up. Among the eligible patients there were 40 males and 4 females. Average age was 56.3 years (range 37–74). 18 patients had a performance status (according to Karnofsky scale) of 70 or 80% and 26 patients of 90 or 100%. One patient was classified as stage I, 2 were stage II, 21 were stage IIIA and 20 stage IIIB. 4 patients underwent radical surgery before entering the study because of the lack of precise initial diagnosis: 2 had pneumonectomy (stage IIIA and II), 1 had bilobectomy (RML plus RLL) and was stage II, and 1 had a right lower lobectomy (stage II).

Table 1. Drug dosages received at first and second cycle

Drug	First cycle (mg/m^2 ± S.D.)	Second cycle (mg/m^2 ± S.D.)
Cisplatinum	59.2 ± 1.40	56.80 ± 6.18
Doxorubicin	39.1 ± 2.06	39.16 ± 5.43
Etoposide	98.6 ± 5.44	90.05 ± 14.9

42 patients (95%) received at least two cycles of CT, 2 had only one cycle of CT and no TRT (one early toxic death before any TRT due to neutropenia and multiple organ failure and one withdrawal after the first course of TRT due to neutropenia with septicaemia and diarrhoea). 29 patients (66%) completed the six chemotherapy cycles. Mean doses of CT received at cycles 1 and 2 are shown in Table 1. Complete TRT could be administered to 35 patients. Apart from the 2 patients already quoted above, 5 patients received only the first course of TRT (1 refusal, 4 severe neutropenia) and 2 received only the two first courses (1 because of failure and 1 because of grade 4 neutropenia after the first CT cycle, and grade 3 after the second cycle with reduced doses of CT). Finally, 29 patients (66%) completed the whole treatment as scheduled. 7 patients (16%) received prophylactic cranial irradiation.

40 patients were evaluable for haematological toxicity in the first cycle (4 patients did not have blood cell count controls between the first and second cycle).

The predominant toxicities associated with this combined modality were haematological (Table 2). There were three severe infectious events resulting in one early toxic death (first cycle), one withdrawal after septicaemia and diarrhoea (first cycle), one tumoral necrosis after the fifth cycle. Moderate oesophagitis was experienced by 7 patients. One more patient developed candidiasis of the upper digestive tract. Alopecia was observed in all patients and was grade 3.

Of the 42 patients who completed the first two cycles, 39 were evaluable for response (3 of the 4 operated patients remained disease free after the two cycles and are, therefore, inevaluable and 1 had progressive disease). There were 10 complete responders (25.6%), 24 partial responders (61.5%) and five non-responders. At the end of the treatment, 16 were complete

Table 2. Haematological toxicity

	WHO grade				
	0	1	2	3	4
Leucocytes					
First cycle†	—	1	10	23	6
Second cycle‡	—	2	4	22	11
Neutrophils					
First cycle†	—	1	4	9	26*
Second cycle‡	1	2	1	17	18
Platelets					
First cycle†	30	1	4	2	3
Second cycle‡	20	7	5	6	1

*One death due to septicaemia. †40 evaluable patients. ‡39 evaluable patients.

responders (41.0%) and seven partial responders out of the 39 (3 operated patients remained disease free). Of the 8 patients who had progressive disease during treatment, 4 had local failure, 3 metastatic and 1 local plus metastatic. Median survival of the 44 patients was 17.2 months. Per cent survival at 2 years was 32%. 10 patients survived at least 30 months and 8 are still alive at 33, 35, 38, 41, 57, 63, 71 and 77 months. Among them, 6 are disease free (including 2 of the 4 operated patients and 3 of the 7 patients who received PCI) and 2 have progressive disease.

DISCUSSION

Our study shows a 25.6% complete response rate at first evaluation and 41% complete response rate at the end of the treatment. Median survival time is 17.2 months and 22.7% survived longer than 30 months. TRT in limited disease stage has long been controversial but two recently published meta-analyses [12, 13] indicate a clear benefit on local control and a modest improvement in survival (with, on the other hand, an increase in treatment-related mortality rate). The only modest improvement of survival observed may be due to the fact that the sequencing of CT and TRT differs in the various studies, in some of them TRT being administered early and in others TRT being administered late. Early TRT may eradicate chemo-resistant clones before they spread outside the thorax and CT controls local and distant chemosensitive tumour cells; therefore, only early TRT may improve survival significantly [14]. At this time, however, the best modality of treatment combining CT with early TRT, either concurrent or alternating, is not defined. Survival of our population is very close to that observed in the IGR protocols on alternating TRT and CT in limited small cell lung cancer [15].

Among our 8 patients surviving more than 30 months, 3 had PCI and 2 were operated on. The role of PCI in small cell lung cancer is still controversial and under investigation and until now no survival benefit could be demonstrated [16]. The real place of surgery is also difficult to assess in small cell lung cancer as most of the operated patients were so because of unknown diagnosis, as in our study. The only randomised study comparing CT + TRT plus surgery versus CT + TRT alone is negative [17].

Acute toxicity was mainly haematological as in other studies [15] and was the cause of one early death and six premature interruptions of treatment in our series. Whether the use of granulocyte growth factor would allow a better fit to the scheduled dose intensity of both CT and TRT remains to be proven [18]. Non-haematologic toxicity was mild and this may be a potential benefit of alternating CT and TRT.

In conclusion, our results are in the range of those of the authors using early TRT combined with CT. Randomised studies comparing early TRT, either concurrent or alternating with CT, should be performed in order to determine the best modality. There is no need for more studies on late TRT as it is established that there is no survival benefit from this modality.

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