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Original Paper

Accelerated Split-course (Type B) Thoracic Radiation Therapy Plus Vinorelbine/Carboplatin Combination Chemotherapy in Stage III Inoperable Non-small Cell Lung Cancer

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43 patients with stage III NSCLC (non-small cell lung cancer) entered a phase II study aimed at evaluating the toxicity and the activity of a combined modality programme including an accelerated split-course schedule (type B) of thoracic radiation therapy and a combination chemotherapy with vinorelbine and carboplatin. An objective response was achieved in 18/42 evaluable patients (5 complete and 13 partial responses), for an overall response rate of 43% (95% confidence interval, 28–58%). Four complete responses had a duration which exceeded 16 months. Treatment was well tolerated; grade III myelotoxicity occurred in only 14% of patients and treatment was delayed in only 2 cases because of grade 3 oesophagitis. Both tolerability and efficacy data suggest that this regimen holds promise for the treatment of patients with stage III NSCLC.

Key words: non-small cell lung cancer, vinorelbine, carboplatin, accelerated split-course radiotherapy

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INTRODUCTION

LUNG CARCINOMA represents at present the leading cause of death from malignant disease in Western countries [1]. Non-small cell lung cancer (NSCLC) constitutes approximately 80% of primary malignant lung tumours and is inoperable at the time of presentation in 70% of patients because of either locally advanced disease or distant metastatic dissemination [2].

Although there has been a surge of interest in combined modality therapy for locally advanced NSCLC, the optimal treatment schedule is not clearly established; the addition of platinum compounds to thoracic irradiation provides therapeutic benefits since the chemotherapy decreases metastases while improving local control through its radiosensitising action. Variation of radiotherapy fractionation strategy toward a greater number of small size fractions given in a slightly decreased overall time with respect to conventional therapy has been widely used in recent years [3], with the aim of increasing the therapeutic differential, with late responding normal tissue having a greater capacity for repair of sublethal injury [4].

In advanced disease, the survival benefit offered by chemotherapy is limited, since very few single agents have been reported to yield a greater than 15% objective response rate. However, platinum-based chemotherapy regimens have been shown to result in survival benefits compared with supportive care [5–7], and are currently accepted as the most active chemotherapy.

More recently, the activity of the new vinca alkaloid vinorelbine against NSCLC has been investigated. Various clinical trials have shown that it is well tolerated and active

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either as single agent [8] or in combination with cisplatin [9, 10] in patients with advanced NSCLC.

In this trial, we investigated the activity of a combined modality programme including an accelerated split-course schedule (type B) [11] of radiotherapy and combination chemotherapy with vinorelbine and carboplatin in patients with stage III inoperable NSCLC; the therapeutic strategy was designed with the aim of administering the highest amount of active, non-cross-resistant, and possibly synergistic antiproliferative treatment as soon as possible in the course of the disease. Carboplatin was used instead of cisplatin because of its better toxicity profile.

PATIENTS AND METHODS

Eligibility requirements for study entry included histological or cytological confirmation of NSCLC, age less than or equal to 70 years, World Health Organization (WHO) performance status (PS) of 2 or lower, measurable or evaluable stage III A2 or IIIB disease according to the International Union Against Cancer classification; absence of any prior or concurrent malignant tumour except adequately controlled basal cell carcinoma of the skin, no prior chemotherapy, normal baseline organ functions (serum creatinine < 1.5 mg/dl, bilirubin < 11 g/dl, white blood cell count < 4000/μl, platelet count > 100,000/μl). Informed consent was obtained from each patient. Before treatment, all patients underwent the following investigations: complete clinical examination, complete blood cell count, biochemical survey, chest X-ray, fiberoptic bronchoscopy, computed tomography (CT) of the chest, bone scan, liver CT scan or ultrasonography; CT brain scan was performed only in case of clinical suspicion of brain metastases.

Our treatment plan consisted of a 160 cGy fraction size, given twice daily with a 6-h separation between fractions. The total dose was 3840 rads: it was followed within 14 days by one course of carboplatin at the dose of 250 mg/m^2 on day 1, and vinorelbine at the dose of 30 mg/m^2 on days 1 and 8; 12 more 160 cGy fractions given twice daily were administered for a total dose of 1920 cGy. At the completion of radiotherapeutic treatment, five courses of the aforementioned chemotherapy were administered. The treatment plan is detailed in Table 1.

The main end-points of the study were response and tolerance. A complete response (CR) was defined as the complete disappearance of all objective disease. A partial response (PR) was defined as a 50% or greater decrease in the sum of the products of the two longest perpendicular diameters of all measurable lesions. CR and PR had to be confirmed by a second evaluation 4 weeks later. Stable disease (SD) was defined as a less than 50% decrease or a less than 25% increase in the sum of the products of the two longest perpendicular diameters of all measurable lesions. Progressive disease (PD) was indicated by an increase of 25% or more in the sum of the products of the two longest perpendicular diameters of measurable lesions, or the appearance of new lesions. Toxic effects were evaluated according to WHO criteria [12]. Duration of response and survival were calculated from the beginning of treatment.

Table 1. Treatment plan

24 fractions of twice daily radiotherapy at the dose of 160 cGy for a total of 3840 cGy
+
(within 14 days)
1 course of carboplatin (250 mg/m^2) on day 1
and
vinorelbine (30 mg/m^2) on day 8
+
12 fractions of twice daily radiotherapy at the dose of 160 cGy for a total of 1920 cGy
+
5 courses of the above mentioned chemotherapy

Table 2. Patient characteristics

Characteristic	Number of patients
Total	43
Evaluable	42
Median age (years)	62
Range (years)	(43–70)
Sex	
Male	35
Female	8
Histology	
Squamous cell carcinoma	23
Adenocarcinoma	16
Large cell carcinoma	4
Stage	
III A N2	8
III B	35
Performance status	
0	16
1	22
2	5

RESULTS

43 patients with stage IIIA2-B NSCLC were entered on to the study from June 1992 until April 1995. Patient characteristics are detailed in Table 2; 8 patients (19%) had stage III A2 N2 inoperable disease, 35 patients (81%) had stage III B disease, and squamous cell carcinoma was the predominant histology (23 patients).

42 patients were evaluable for response and toxicity, after completing the whole treatment as planned; 1 patient with stage IIIB disease was lost to follow-up after enrolment and was therefore not evaluable. 18 patients (5 CRs and 13 PRs) achieved an objective response, for an overall response rate of 43% (95% confidence interval, 28–58%). 10 patients (24%) had stable disease and 14 (33%) had PD during treatment (Table 3).

Response to treatment by stage of disease is reported in Table 4. 1 CR lasted 5 months; the other 4 had durations of 16+, 17+, 20+, 27+ months, respectively. Duration of partial responses ranged from 4 to 26+ months. 11 patients

Table 3. Response to treatment

Response	Number (%)	
CR	5 (12)	18 (43)
PR	13 (31)	
SD	10 (24)	
PD	14 (33)	

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

Table 4. Response to treatment by stage of disease

Response	Number of patients	Stage III A	Stage III B
CR	5	3	2
PR	13	2	11
SD	10	2	8
PD	14	1	13

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

achieved an objective response after the first part of the treatment (radiotherapy plus one course of chemotherapy). 2 more patients obtained a tumour regression following the second radiotherapy course and in 5 patients an objective response was achieved during the last five courses of chemotherapy. Median survival of our patient population has not yet been reached.

The treatment was well tolerated. Neutropenia was experienced by 30 patients (71%), but reached grade III in only 6 cases (14%). Thrombocytopenia and anaemia were common, occurring in 16 patients each (38%), but never reached grade III–IV. Alopecia was nearly universal; grade I–II infections occurred in only 4 cases (10%); oesophagitis occurred in 21 patients (50%) and reached grade III in 2 patients during the first part of the split-course combined treatment; gastrointestinal and neurological toxicities were generally moderate. No cardiac, pulmonary, renal toxic effects were recorded. No treatment-related deaths occurred, since all patients were still alive within 2 months of starting treatment. Toxic effects are reported in Table 5.

DISCUSSION

Over 40% of patients with NSCLC have disease that is considered locally advanced, that is, limited to lung parenchyma and mediastinum. Although extensive literature has reported on the benefits of standard fractionated radiation therapy, this approach results in a 5-year disease-free survival not higher than 5% and in a median survival which does not exceed 10–12 months [13]. Type B accelerated fractionation with a twice a day schedule [11] involves the administration of a higher number of low-dose fractions achieving a modest decrease in overall treatment time without reduction of total dose by using a split-course technique. The rationale for such a strategy consists of an increased opportunity for tumour cell redistribution and reoxygenation between dose fractions, a possibly lower oxygen enhancement ratio with small incremental doses, and differential sparing of late reacting normal tissues with small dose fractions [4]. However, the high incidence of distant relapses in stage III NSCLC calls for systemic treatment [14]. The question of the benefit of chemotherapy over the best supportive care in advanced disease has been addressed by several randomised trials. Three important meta-analyses of these trials have been published [5–7] and have concluded that chemotherapy prolongs life by a few months and that quality of life is improved when chemotherapy is given, rather than supportive care. Although a number of new agents have shown some degree of activity in advanced NSCLC, current therapeutic regimens have necessarily to include platinum-derivatives. In one meta-analysis [15], cisplatin-based chemotherapy for NSCLC resulted in both a higher response rate and better survival than non-cisplatin-containing combinations. In another study [16], the use of cisplatin was an independent predictor of improved survival in stage IV disease.

Vinorelbine is a new vinca alkaloid which has demonstrated a high level of activity in preclinical studies compared with other vinca alkaloids [17]. In a phase II trial, vinorelbine achieved an impressive 29% overall objective response rate with promising results in terms of time to progression (median, 34 weeks) and survival (median, 33 weeks) [18]. Le Chevalier and colleagues [9] have reported the results of a large European multicentre study in which patients with advanced NSCLC were randomised to receive cisplatin + vinorelbine, cisplatin + vindesine, or vinorelbine alone. This trial has demonstrated that the combination cisplatin + vinorelbine yields a statistically significant higher response rate and longer survival duration with respect to the others, at the expense of acceptable toxicity and should therefore be considered as a reference regimen in patients with advanced NSCLC.

Our treatment plan included a combination of accelerated split-course (type B) radiotherapy and a chemotherapy programme with vinorelbine and carboplain, which was preferred to cisplatin because of its better toxicity profile. A phase I/II study combining carboplatin and vinorelbine in patients with advanced NSCLC has recently been published [19] and has shown that no additional toxicities than expected were observed. The response rate (29%) and preliminary survival data were quite promising and very similar

*Table 5. Toxicity**

	WHO grade 0	1	2	3	4	Total
Neutropenia	12	10	14	6	0	30
Anaemia	26	11	5	0	0	16
Thrombocytopenia	26	8	8	0	0	16
Alopecia	5	12	20	5	0	37
Nausea/vomiting	17	12	12	1	0	25
Oesophagitis	21	10	9	2	0	21
Infections	38	2	2	0	0	4
Stomatitis	19	13	10	0	0	23
Constipation	38	2	2	0	0	4
Paraesthesia	28	8	6	0	0	14

* Number of patients.

to those reported with the combination of vinorelbine and cisplatin.

In our study, we have used a combination of carboplatin and vinorelbine with a different schedule than that used in the aforementioned study at the aim of reducing myelotoxicity, which is likely to represent the most significant toxic effect. We supposed that the highest amount of active, non-cross-resistant and possibly synergistic antiproliferative treatment administered as intensively as possible could have a favourable impact on the outcome of the disease. The purpose of split-course treatment is to allow time between courses for the resolution of radiation-induced acute side-effects; tumour cell regrowth during treatment interval, however, could outweigh any possible advantage of improved patient tolerance. The administration of a single course of an effective chemotherapy regimen after the first phase of split-course radiotherapy could result in a strong cell-kill effect, given the recruitment of tumour resting cells possibly induced by radiation therapy [20]. The interaction between the two treatment modalities does not presume direct cellular interaction. In fact, platinum compounds seem to act preferentially against radiation resistant hypoxic cells [21].

Our treatment was very well tolerated. In 40 patients, the first part of the treatment (split course radiotherapy + one course of chemotherapy) was completed at full dosage in 2 months. Only 2 patients had a 2-week delay because of grade 3 oesphagitis; myelotoxicity, which was supposed to be the most relevant side-effect, was less frequent and severe than expected. The overall response rate was 43%; this result is quite promising, although comparable with that observed in other trials in which accelerated radiotherapy was administered alone [22]. Still a more interesting finding, is the duration of response, which exceeded 16 months in 4 patients.

The results of this study show that our treatment plan is active against stage III NSCLC and looks particularly promising because of the number of long-lasting complete responses. A parallel study of carboplatin and vinorelbine in stage IV NSCLC in currently ongoing. However, further investigations are to be performed to determine the optimal scheduling of these agents and whether the use of haematopoietic growth factors might allow further dose intensification and/or the addition of other active drugs to the regimen.

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