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Short Communication

Concurrent radiation and weekly cisplatin for non-small-cell lung cancer – a phase I/II study

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Summary. A total of 20 patients with loco-regional non-small-cell lung carcinoma were entered into a study of irradiation (3.0 Gy × 15 doses to a total dose of 45 Gy given in 4 fractions per week on days 1, 2, 4 and 5 of each week) and cisplatin given at a dose of 40 mg/m^2 on day 3 of each week for a total of three infusions. One patient who had stage 1 disease showed a complete response to therapy and is alive and clear of disease at 35 months. In 19 patients with stage 3 disease, the complete response rate was 16% and the partial response rate was 42%. The rate of 1-year survival was 42% and the rate of 2-year survival was 11%; the median survival of these patients was 11 months. Relapse occurred, mostly at metastatic sites, in 10 of the 11 patients who responded to therapy. Acute toxicity was modest and tolerable by our patients. No severe late toxicity was encountered, and none of the patients developed grade 3 dyspnoea (an inability to walk 100 yards because of breathlessness) while clear of recurrent disease. Changes in lung function observed at follow-up examinations were similar to those seen after irradiation alone. Weekly administration of cisplatin is therefore feasible in patients receiving a continuous course of irradiation. The high relapse rate observed in responding patients indicates the need for evaluation of the efficacy of combination chemotherapy in the adjuvant or neo-adjuvant setting.

Introduction

The present study was undertaken to evaluate the use of weekly infusions of cisplatin together with a course of continuous irradiation for the treatment of loco-regional non-small-cell lung cancer. We hoped to obtain a therapeutic advantage by giving the agents 24 h apart on the basis that the repair of either cisplatin- or radiation-induced damage might be slower in tumours than in normal tissues.

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Patients and methods

The study was approved by the local ethical committee for a total of 20 patients. Informed consent was obtained from all patients. In all, 20 individuals with loco-regional non-small-cell lung carcinoma who exhibited a WHO-Zubrod [9] performance status of 0–2 were entered in this study between April 1988 and May 1990; 17 of the patients were from Groote Schuur Hospital and 3 were from allied departments in Port Elizabeth and East London. All were staged by means of a chest radiograph, a computed tomographic (CT) chest scan and serum chemistry. Further screening investigations (bone scan or liver ultrasound) were done if clinically indicated. The patients showed a glomerular filtration rate of more than 60 ml/min as calculated by the Cockroft-Gault formula [5].

Responses and acute toxicity were monitored according to the WHO scale [9]. CT scans were used to assess response in patients showing no bidimensional disease on chest radiographs and to document complete responses. The dyspnoea score [8] (see Table 1) and lung functions were measured in patients at presentation, and these determinations were repeated in individuals showing no evidence of progressive carcinoma at 6 and 12 months. The minimal follow-up period for surviving patients was 2 years.

The median age of the patients was 53 years (range, 37–66 years). There were 17 (85%) men and 3 (15%) women. The histology was squamous in 9 patients (45%), large-cell carcinoma in 3 individuals (20%), undifferentiated in 4 subjects (20%) and adenocarcinoma in 3 patients (15%). In all, 1 patient had stage 1 disease (declined surgery) and 19 had inoperable stage 3 disease. The performance status (PS) was 0 in 1 patient (5%), 1 in 12 subjects (60%) and 2 in 7 patients (35%). The dyspnoea score (DS) was 1 in 5 patients (25%) and 2 in 15 subjects (75%).

The radiotherapy schedule consisted of 3.0 Gy × 15 doses to a total dose of 45 Gy given in 4 fractions per week on days 1, 2, 4 and 5 of each week. The field included the tumour along with a 2-cm margin and the adjacent mediastinum, with extension of the portal 3–5 cm above radiological adenopathy. The dose to the spinal cord was limited to 36 Gy, and this was achieved either by posterior shielding of the cord or by the use of planned fields. Cisplatin was given at a dose of 40 mg/m^2 on day 3 of each week for a total of three infusions. Cisplatin was given on an out-patient basis; patients received 1 l intravenous hydration prior to and

Table 1. Modified MRC dyspnoea scale

0	Not troubled with breathlessness
1	Breathless when hurrying on a level surface or walking up a slight hill
2	Walks slower than people of the same age because of breathlessness
3	Stops for breath after walking less than 100 yards on a level surface
4	Too breathless to leave the house

Table 2. Acute toxicity encountered, with WHO grading

Oesophagitis, grade 3 (ability to swallow liquids only)	15%
Nausea, grade 3 (persistent vomiting)	10%
Renal toxicity, grade 1[a]	5%
Acute symptomatic pneumonitis	5%

[a] Serum creatinine values 1.25–2.5 times normal

Table 3. Changes in lung function observed in patients on follow-up examination

	Group 1[a]		Group 2[b]	
	Presentation	6 months	Presentation	12 months
FEV_1 (ml)	2130	2090	2350	2050
FEV_1 SD	780	735	910	595
TLCO (ml/min/mm Hg)	18.9	18.3	17.8	15.4
TLCO SD	4.4	4.5	3.2	2.3

[a] Cohort of 10 patients showing no evidence of active carcinoma at 6 months

[b] Cohort of 5 patients showing no evidence of active carcinoma at 12 months

FEV_1, Forced expiratory volume in 1 s; TLCO, single-breath carbon monoxide transfer factor

following the cisplatin infusion and were instructed to drink at least eight glasses of water over the subsequent 24 h.

Results

In all, 19 patients had inoperable stage 3 disease. The complete response rate in these patients was 16% (3 of 19) and the partial response rate was 42% (8 of 19), for an overall response rate of 58%. The rate of 1-year survival was 42% and the rate of 2-year survival was 11% (life-table method). The median survival of these patients was 11 months.

Relapse occurred in 10 of the 11 patients with stage 3 disease who responded to therapy. The median time to relapse in responding patients was 7 months (range, 4–20 months). The recurrence manifested as local disease in 2 subjects, nodal disease in 2 individuals and metastatic disease in 6 patients. The median time to progression in patients who failed to respond was 5 months (range, 1–9 months). The site of progression involved local disease in 1 patient, nodal disease in 1 subject and metastatic disease in 6 individuals. The patient who had stage 1 disease showed a complete response and is well and free of disease at 35 months.

Toxicity was evaluated in all 20 patients together. Mild acute toxicity consisting of oesophagitis and nausea was common (Table 2). No grade 2 haematological toxicity occurred. Other types of toxicity encountered are described in Table 2.

None of the patients who showed no evidence of active carcinoma had grade 3 dyspnoea at follow-up examinations performed at 6 months (10 patients), 12 months (5 subjects) or 24 months (2 patients). The changes in lung function observed in the cohort of patients who showed no sign of active carcinoma at the 6- and 12-month follow-up examinations are described in Table 3.

Discussion

The interaction between radiation and cisplatin is complex. Cisplatin is a weak sensitiser of radiation, and the more important ways in which it may enhance the effect of irradiation include impairment of repair processes, depletion of thiols and inhibition of cell proliferation [2, 3, 6, 7]. A differential effect between tumours and normal tissues is required for the combined modalities to be of therapeutic benefit. One possible difference between normal tissues and tumours involves the kinetics of repair.

In studies on experimental mice, Tanabe et al. [11] obtained the highest and most consistent therapeutic gain factor (ratio of the effect on the tumour to the effect on normal tissue) when cisplatin was given either 24 h prior to a course of fractionated radiation or simultaneously with irradiation as compared with other regimens. Bartelink et al. [2] found that the optimal treatment involved the administration of cisplatin once a week at 24 h prior to daily fractionated doses of radiation. In the present clinical trial, we elected to separate the two modalities by 24 h.

Schaake-Koning et al. [10] conducted a randomised study in patients with non-small-cell lung cancer who had no distant metastases. These investigators used a split-dose regimen of irradiation alone (5 fractions per week) or together with weekly (30 mg/m^2) or daily (6 mg/m^2) administration of cisplatin. The rates of 1- and 2-year survival obtained using these regimens were 46% and 13%, respectively, for irradiation alone; 44% and 19%, respectively, for the weekly cisplatin regimen; and 54% and 26%, respectively, for the daily cisplatin regimen. Severe nausea and vomiting was experienced by 26% and 28% of the patients, respectively.

Boven et al. [4] have reported the results of daily administration of cisplatin at 6 mg/m^2 in patients with inoperable non-small-cell lung cancer. In addition, 3-Gy radiation doses were given four times per week at 2-week intervals to a total dose of 48 Gy. Toxicity was mild and the median survival was 10.5 months. Tobias et al. [12] used cisplatin daily at 10 mg absolute over 6 weeks together with irradiation to a total dose of 60 Gy given in 30 fractions; they

found the regimen to be poorly tolerated by patients and to be nephrotoxic.

The toxicity encountered in the present study was tolerable and modest. There was no indication of severe late lung toxicity as measured by the dyspnoea score. The observed changes in lung function were similar to those that might be expected following radiation treatment alone [1]. Weekly administration of cisplatin is therefore feasible in combination with this continuous fractionated radiation schedule.

The rates of response and survival of patients with inoperable disease in this phase I/II study were similar to those obtained using irradiation alone. However, a high relapse rate was seen in responding patients with inoperable non-small-cell carcinoma. Radiation remains the cornerstone of therapy for symptomatic inoperable non-small-cell lung carcinoma. A continuous course of irradiation is preferable to the delivery of radiation in split-dose regimens. We believe that an improvement in the survival of patients with inoperable non-small-cell lung cancer in the absence of undue toxicity is more likely to be obtained by the use of effective combination chemotherapy in the adjuvant or neo-adjuvant setting.

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