Acta Oncologica 27 (1988) Fasc. 5

FROM THE INSTITUT JEAN-GODINOT, MEDICAL ONCOLOGY DEPARTMENT, F-51056 REIMS CEDEX, FRANCE.

RESULTS OF A FIVE-DRUG COMBINATION CHEMOTHERAPY IN NON-SMALL CELL LUNG CANCER

A phase II trial

F. MARECHAL, C. INCATASCIATO and A. CATTAN

Abstract

Twenty-six non-small lung cancer patients entered a phase II trial of a 5-drug combination chemotherapy. On day 1, patients received vinblastine, bleomycin, methotrexate, 5-FU, cisplantinum, leucovorin, and a similar sequence with an increased dosage was administered on day 6. Out of 22 fully evaluable patients we observed 1 CR and 7 PR. Hematological toxicity was significant, including 15 cases of neutropenia grade 4 and four grade 3, with one death during aplasia. Our results are disappointing but they are similar to most current reports on drug combinations in advanced non-small cell lung cancer. A better scheduling might improve the efficiency toxicity ratio.

Key words: Chemotherapy; non-small cell lung cancer, 5-drug combination, phase II study.

Numerous phase II trials of chemotherapy have been carried out in non-small cell lung cancer (NSCLC) and the response rate of present types of chemotherapy is about 30 to 40%. Cohen (2) showed that red blood cell deformability decreased in cancer patients and that chemotherapy was able to restore this parameter (3). By using a sequential chemotherapy based on the improvement of the red blood cell deformability, he obtained a major response rate of 85% including 15% with complete response among 20 patients with inoperable squamous cell lung cancer (4). We have followed his treatment schedule to a certain extent in a phase II trial in order to study its feasibility and efficacy.

Material and Methods

Twenty-six patients who met the following protocol eligibility requirements were treated: 1) biopsy proven non-small cell lung carcinoma previously untreated, 2) stage III disease according to the American Joint Committee for Cancer Staging Definitions (1), 3) at least one evaluable target other than brain metastases, 4) less than 75 years of age, Karnofsky index $\geq$50 and serum creatinine <130 mmol/l. Pretreatment screening included a complete history and physical examination, chest radiogram, fiber optic bronchoscopy, abdominal ultrasonography, bone scan, and brain CT scan in case of neurological symptoms. Follow-up studies included blood cell counts twice a week. Chest radiograms were taken at each course, bronchoscopy and abdominal ultrasonography after 2 or 3 courses.

Treatment schedule

On day 1 vinblastine 4 mg/m^2 and methotrexate 60 mg/m^2 were given by bolus injection into a freely running i.v. infusion. Bleomycin 15 mg/m^2 was injected i.m. Four hours later, 5-FU 450 mg/m^2 (by bolus injection) and cisplatinum 20 mg/m^2 were administered. Leucovorin was started 24 h after methotrexate and 4 doses were given orally. Fluid loading consisted of 5% dextrose in 0.45% saline with 20 mEq potassium chloride/1×2 l and 0.5 l 20% mannitol. A similar schedule was used on day 6 with a dosage modification of vinblastine (6 mg/m^2), 5-FU (600 mg/m^2) and cisplatinum (40 mg/m^2). Patients received acetaminophen 650 mg orally prior to chemotherapy and were maintained on 450 mg of oral magnesium daily throughout the treatment. Chemotherapy cycles were repeated on day 29.

No schedule for dosage reduction was planned in case of aplasia. Efficacy was evaluated after 2 or 3 cycles according to standard criteria and toxicity after each cycle

Presented at ECCO-4, Madrid, November 1–4, 1987.

Table

Patient characteristics

Patient No	Sex	Age (years)	Histology	Disease stage	Karnofsky index	Treatment response	Survival (months)	Polynuclear toxicity (WHO grade)
1	F	54	ADN	T2 N1 M1	50	Inevaluable	<1	4
2	M	51	EPI	T1 N2 M0	90	MR	27+	1
3	M	44	EPI	T1 N2 M0	80	CR	18	4
4	M	44	EPI	T3 N2 M1	70	PR	6	3
5	M	58	EPI	T2 N1 M1	70	Inevaluable	5	4
6	M	45	ADN	T3 N1 M0	100	SD	15.5	3
7	M	60	EPI	T2 N2 M1	90	SD	5	4
8	M	71	EPI	T2 N2 M1	90	PROG	4	4
9	M	62	EPI	T2 N1 M1	70	MR	14.5+	4
10	M	57	EPI	T3 N1 M0	70	MR	7.5	2
11	M	58	EPI	T1 N1 M1	80	PROG	6	4
12	M	56	EPI	T3 N0 M1	90	SD	8.5	2
13	M	73	EPI	T3 N2 M0	50	PR	27+	0
14	M	55	EPI	T3 N2 M1	60	SD	7.5	3
15	F	48	EPI	T3 N2 M1	70	PR	6	4
16	M	50	EPI	T3 N2 M0	60	PR	11.5+	4
17	M	71	LC	T1 N2 M1	70	MR	11.5	4
18	M	62	ADN	T3 N2 M1	80	PR	11	4
19	M	72	EPI	T2 N1 M1	70	Inevaluable	<1	Inevaluable
20	M	53	EPI	T3 N1 M0	70	MR	5.5	2
21	M	34	ADN	T3 N2 M1	70	PROG	3	4
22	M	69	EPI	T1 N0 M1	80	Inevaluable	<1	Inevaluable
23	M	64	EPI	T2 N1 M0	90	PR	10+	4
24	M	70	EPI	T2 N1 M1	80	MR	6.5	3
25	F	61	EPI	T3 N2 M0	90	MR	8.5+	4
26	M	47	ADN	T3 N2 M1	70	PR	8+	4

ADN = adenocarcinoma, EPI = epidermoid carcinoma, LC = large cell carcinoma, CR = complete response, PR = partial response, MR = minor response, SD = stable disease, PROG = progression.

according to the WHO scoring test (5). The Kaplan-Meier method was used for the survival curve. After completion of 2 or 3 courses of chemotherapy, a dose of 50–55 Gy was applied to the primary tumour and the mediastinal and supraclavicular lymph nodes in non-metastatic patients.

Results

Characteristics of the 26 study patients are shown in the Table.

One patient died prematurely from brain metastases and another from heart failure; accordingly it was impossible to evaluate the level of toxicity in these cases. In the remaining 24 patients who were fully evaluable, hematological toxicity was greater than expected: there were 15 cases of neutropenia grade 4 and four cases of grade 3. Subsequently 11 patients were placed in a sterile area, including 9 having received treatment with antibiotics. Unfortunately, the first patient died at home in aplasia. The dosage had to be modified in 3 cases and, in another 4 cases, the following cycle had to be delayed. However, there was no platelet toxicity and we found only one case of anemia (grade 1). Poor digestive tolerance was also noted: 4 patients suffered from grade 3 vomiting, 17 patients from grade 2 vomiting and 5 patients from grade 2 diarrhea. Neither renal nor pulmonary toxicity occurred. Alopecia was moderate, grade 3 in three cases and grade 2 in ten cases.

Four patients were not evaluable on account of premature death (n=2) or high toxicity level after the first treatment (n=2). We observed one complete response, 7 major responses, 11 cases of minor reponse or no change, and a progression in 3 cases. The major response rate was 31% in 26 patients with a 95% confidence limit interval of 14–52%. It reached 44% in 9 patients who did not have metastases and 24% in 17 patients who had metastases (but only 14 of them were fully evaluable). Fourteen patients underwent radiotherapy after which 4 were considered complete responders and 4 major responders. The median survival was 7.6 months. Seven patients were, at the time of writing, living with an average follow-up of 13 months (range: 8.5–27+ months) but only one was living disease-free with a follow-up of 27 months.

Discussion

Even if the hematological toxicity was significant, our schedule is manageable and the results in terms of re-

sponse rate and survival were similar to most reports concerning current chemotherapy combinations in stage III NSCLC. Comparison of our results with those of Cohen et al. (4) shows that we had lesser platelet and renal toxicity, clearly greater polynuclear toxicity and lower response rate. Our protocol differs from theirs in that we did not measure the modification of the red blood cell deformability during chemotherapy and therefore administered the second sequence on a fixed day. Our patient characteristics were also somewhat different and we had a greater proportion of metastatic (17/26) and low-Karnofsky index patients. We also included female patients and various histological types of NSCLC. However, none of the patient characteristics appeared to have an obvious effect on toxicity or response rate except for the extent of the disease. No definitive conclusions can be drawn from our trial because of its small size and various interfering factor.

However, drug scheduling based on red blood cell deformability might be important and we suggest that this factor is taken into account when new chemotherapy combinations are tested.

ACKNOWLEDGEMENTS

The authors are grateful to the Département Recherche et Développement des Laboratoires UPJOHN for their assistance in translation and to Mrs B. Fosset for typing the manuscript.

Request for reprints: Dr F. Marechal, Institut Jean-Godinot, Medical Oncology Department, B.P. 171, F-51056 Reims Cedex, France.

REFERENCES

1. American Joint Committee for Cancer Staging and End Reporting Results: Manual for staging cancer, p. 59. American Joint Committee, Chicago 1978.
2. Cohen M.: Impairment of red blood cell deformability by tumor growth. JNCI 63 (1979), 525.
3. — Cure of advanced L 1210 leukemia after correction of abnormal red blood cell deformability. Cancer Chemother. Pharmacol. 5 (1981), 175.
4. — Johnston-Early A., Citron M., Krasnow S. and Fossieck B.: An active chemotherapy regimen for squamous cell lung cancer. Cancer Treat. Rep. 68 (1984), 475.
5. Miller A., Hoogstraten B., Staquet M. and Winkler A.: Reporting results of cancer treatment. Cancer 47 (1981), 207.