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Short communication

Phase II study of 4′-iodo-4′-deoxydoxorubicin in non-resectable non-small-cell lung cancer

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Abstract. A total of 44 patients with previously untreated, non-resectable non-small-cell lung cancer (NSCLC) were treated with 4′-iodo-4′-deoxydoxorubicin (IDX), which is an analogue of doxorubicin with less cardiotoxicity. Patients received 80 mg/m^2 i.v. every 3 weeks. Dose reductions were carried out for haematological toxicity. Response was assessed prior to each treatment according to WHO criteria. Among the 43 evaluable patients, 1 (2%; 95% confidence limits, 0–8%) achieved a partial response. Leucocytopenia of WHO grade 3 or 4 occurred in 64% of patients and corresponding thrombocytopenia grade 3 or 4 occurred in 30%. Of the 26 patients who were evaluated by measurements of the left ventricular ejection fraction (LVEF), 4 had a decline in LVEF of more than 15%, and 2 patients developed congestive heart failure. Myocardial biopsies were not done. In conclusion, IDX is not active in NSCLC at the applied dose and on the schedule used. Moreover, it does not seem possible to increase the dose intensity further due to the observed toxicity.

Introduction

Non-small-cell lung cancer (NSCLC) is rather chemoresistant, and only a few cytotoxic drugs have shown activity in this disease [18]. More effective treatment is needed, and several investigative groups have in recent years evaluated new cytostatic agents in NSCLC patients [17]. The anthracycline analogue 4′-iodo-4′-deoxydoxorubicin (IDX) is such a new cytostatic agent, being a doxorubicin analogue with an iodine atom in the position 4′. The drug is highly cytotoxic to murine and human cell lines in vitro, including cell lines resistant to doxorubicin [2]. In addition, IDX is less cardiotoxic than doxorubicin when tested in rodent models [2]. The results of two phase I trials indicate that the major toxicity is myelosuppression, especially leucopenia, whereas other toxic effects are not pronounced [1, 8]. The maximum tolerated dose in these studies ranged from 70 [1] to 80 mg/m^2 [8] given i.v. every 3 weeks.

In a recent European Organization for Research and Treatment of Cancer (EORTC) study showing a response rate of 6% among 17 evaluable NSCLC patients, a dose of 70 mg/m^2 was given i.v. every 3 weeks [15]. Patients with breast cancer were included in the study and, interestingly, a 3-fold difference in objective response rates to IDX were observed between the EORTC trial and another breast cancer trial employing an IDX dose of 80 mg/m^2 [9]. Thus, the difference in response rates observed among breast cancer patients as well as the low activity noted in NSCLC may be due to differences in dose intensity, and a higher activity might be achievable in patients with NSCLC if the dose intensity were increased to 80 mg/m^2 every 3 weeks. The present study represents a further phase II assessment of IDX in patients with previously untreated NSCLC using a dose of 80 mg/m^2.

Patients and methods

Patients with histologically confirmed NSCLC who had not previously undergone chemotherapy were recruited into the study. All patients were required to have inoperable disease that was either measurable (bidimensionally measurable) or evaluable (unidimensionally measurable), to be 75 years of age or younger and to exhibit both a performance status of 50 or better on the Karnofsky Performance Status scale and adequate pretreatment cardiac function as determined by measurement of the left ventricular ejection fraction (LVEF), renal function (serum creatinine, <130 μmol/l), liver function (bilirubin, <20 μmol/l) and haematological parameters (WBC, $>3 \times 10^9$/l; platelet count, $>100 \times 10^9$/l). Patients were excluded if they had central nervous system metastases, a history of any other previous malignancy (other than basal-cell skin carcinoma or in situ cervical cancer), active infection, congestive heart failure or significant arrythmia.

The treatment schedule consisted of IDX given at 80 mg/m^2 by i.v. bolus infusion every 3 weeks. Haematological dose modifications were based on WBC and platelet counts, and the dose was either increased or

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Table 1. Patients' characteristics

Characteristics	Number of patients
Total number included	44
Evaluable patients	43
Sex:	
M	22
F	21
Performance status (Karnofsky scale):	
90–100	20
70–80	19
50–60	4
Histolog:	
Squamous-cell carcinoma	10
Adenocarcinoma	24
Large-cell carcinoma	7
Adenosquamous carcinoma	2
Stage[a]:	
IIIa	10
IIIb	24
IV	9
Measurability of tumour:	
Bidimensionally measurable	27
Unidimensionally measurable	16

[a] Staging according to Mountain [10]

Table 2. Percentage of patients developing toxicity[a]

Toxicity	WHO grade				
	0	1	2	3	4
Leucocytopenia	5	19	12	32	32
Thrombocytopenia	56	14	0	16	14
Nausea and vomiting	48	19	9	12	2
Mucositis	82	9	2	7	0
Alopecia	93	7	0	0	0
Drug-related infection	72	7	12	7	2

[a] The worst WHO-grade toxicity observed during any treatment cycle

decreased so as to achieve a WBC nadir or WHO grade 3 (WBC, $1.0-1.9\times10^9$/l). The LVEF was evaluated by multiple ECG-gated radionuclide cineangio-cardiography (MUGA) or by echocardiography after cumulative IDX doses of 250 and 400 mg/m^2 and then before each treatment course. Treatment was discontinued in patients who had a decline in LVEF of 15% in absolute values or a decline to 10% below the normal lower limit (LVEF, 0.50) during the study.

Patients were reviewed weekly for toxicity during the first two courses and then every 3 weeks, whereas the response was evaluated every 3 weeks throughout the study. Treatment was discontinued when objective evidence of disease progression or severe toxicity was observed. Non-responding patients had the treatment stopped after six courses of treatment, whereas in the case of a response the treatment was continued for a maximum of 1 year or until disease progression.

WHO criteria [19] were used in response assessment and evaluation of toxicity. The duration of response was calculated from the date of the first observation of a response until disease progression or death. In unidimensionally measurable lesions, a partial remission was defined as a definite decrease in the size of the lesions of at least 50% as evaluated by two observes and with a duration of at least 4 weeks. Informed consent was obtained and the study was approved by the regional ethics committee. Confidence intervals were calculated according to the method of Simon [16].

Results

From January 1990 to April 1991, a total of 44 patients fulfilled the inclusion criteria and were entered into the study. The pre-treatment characteristics of the patients are listed in Table 1. As 1 patient died of a pulmonary embolism on day 1 of the first treatment course, 43 patients were evaluable for response and toxicity. A total of 188 courses of IDX were given (median, 4 courses/patient; range, 2–10 courses/patient). The median cumulative IDX dose was 304 mg/m^2 (range, 137–816 mg/m^2).

Response

Of the 43 patients evaluated for response, 1 achieved a partial response (2%; 95% confidence limits, 0–8%) that lasted 8 weeks. No patient had a complete response, 29 showed no change (35%) and 13 developed progressive disease (63%). The median survival was 21 weeks (range, 5–131 weeks), and all patients were dead at the time of data retrieval. No patient was lost to follow-up.

Toxicity

Table 2 shows the worst toxicity encountered during the treatment according to WHO grade. The most common toxicity was leucocytopenia, with 95% of patients experiencing grade 1–4 toxicity at some point of their treatment and 64% experiencing grade 3–4 toxicity. There were 5 cases of infection during leucocytopenia, but no septic death occurred. Four patients developed bleeding during thrombocytopenia, and in three cases treatment was stopped due to prolonged thrombocytopenia after three courses and a cumulative IDX dose of 222 mg/m^2, four courses and a cumulative dose of 313 mg/m^2 and six courses and a total dose of 484 mg/m^2, respectively. Nausea or vomiting occurred in 52% of the patients and was moderate to severe in 33% of cases. Mucositis was less frequent (18% of the patients) and alopecia was rare, with minimal hair loss occurring in 7% of our patients.

Cardiac toxicity was evaluated by repeated measurements of LVEF, and the results are shown in Table 3. Measurement of LVEF after IDX treatment was not done in seven patients because of a low performance status due to progression of the malignant disease without clinical signs of heart failure. Among the 26 patients in whom the evaluation of LVEF was possible, 38% had no decrease at all, 46% had a minor decrease (from 0 to 15% decline from the initial value) and 16% (4) of the patients had a major drop in LVEF corresponding to a decline of more than 15% from the baseline value. The drop in LVEF in these 4 patients occurred after a median of 5 courses of treatment (range, 3–8 courses) and a median cumulative IDX dose of 364 mg/m^2 (range, 270–614 mg/m^2). In two of these patients, treatment was discontinued due to the decrease in LVEF, whereas the two other patients had previously had their treatment interrupted and were detected at follow-up. The LVEF fell below the lower normal limit (LVEF, 0.50)

Table 3. Cardiac toxicity occurring during IDX treatment

Cardiac evaluation	Number of patients (%)
Congestive heart failure	2 (5%)
LVEF:	
No decrease	10 (38%)[a]
0–5% decrease	7 (27%)[a]
6–10% decrease	2 (8%)
11–15% decrease	3 (12%)[a]
>15% decrease	4 (15%)[a]
Not done	17

[a] Percentage of patients among the group evaluated for LVEF

in six cases (median, 0.45; range, 0.41–0.49). After the cessation of IDX treatment, two patients developed congestive heart failure which in both cases responded well to diuretic treatment. The presence of extensive lymphangitis carcinomatosis and tumour irradiation including the mediastinum, respectively, may have contributed to the heart failure in these two patients. Myocardial biopsies were not obtained in any of these patients.

In all, 15 of 44 patients (34%) received IDX at a reduced dose at some point during the treatment period due to toxicity. In 20 of 188 courses (11%) the dose was reduced from that originally intended.

Discussion

The activity of IDX against NSCLC in this study is low and confirms in a larger group of patients the observations previously made by Sessa et al. [15]. The use of a stipulated dose of 80 mg/m^2 and treatment for six courses in the absence of progressive disease made the present therapy more intensive than that in the former study,which employed 70 mg/m^2 for three courses. This was reflected in the median number of treatment courses and the median cumulative IDX dose, which were four courses and 304 mg/m^2 in the present study and two courses and 140 mg/m^2 in the study by Sessa et al. [15]. The higher IDX dose did not result in a higher anti-tumour activity, but the toxicity was somewhat increased. The proportion of patients experiencing leucocytopenia of WHO grade 3 or 4 was nearly doubled, being 39% and 64%, respectively, in the two studies. Also, the occurrence of thrombocytopenia of WHO grade 3 or 4 in 30% of the patients suggests that it is not possible to increase the dose intensity further.

The occurrence of possible cardiac toxicity in 6 of 27 patients (22%), who in 2 cases developed congestive heart failure, was also somewhat higher than that encountered in the EORTC trial, in which only 1 of 61 patients experienced a significant decrease in LVEF [15]. However, a more detailed evaluation of the acute and chronic cardiac toxicity of IDX was not possible, as myocardial biopsies were not performed because the primary purpose of the regular assessment of LVEF was to protect the patients against potential cardiomyopathia.

Although the anthracyclines are one of the most active classes of chemotherapy drugs [5], doxorubicin has been shown to have only limited activity in NSCLC when given as a single agent, with the overall response rate being 12% (95% confidence limits, 9%–16%) in trials including 296 evaluable patients [4, 14]. In an attempt to increase this activity, several analogues of doxorubicin have in recent years been evaluated in patients with NSCLC. Pirarubicin is a semisynthetic 4′-*O*-tetrahydropyranyldoxorubicin, which is more lipophilic than the parent compound doxorubicin. Its activity has been found to be similar to that of doxorubicin, with the overall response rate being 13% (95% confidence limits, 6%–23%) among 75 previously untreated NSCLC patients treated in 2 studies [3, 7].

Another analogue of doxorubicin that is pharmacologically close to IDX is 4′-deoxydoxorubicin (DXDX). Like IDX, this compound lacks the hydroxyl group on the 4′-carbon of the aminosugar and is also of clinical interest because of its lower cardiotoxicity as compared with the parent compound. However, its anti-neoplastic activity has been scarce, with a cumulative response rate of 5% (95% confidence limits 2%–10%) being obtained among 146 previously untreated NSCLC patients in 3 studies [6, 12, 13].

Epirubicin, which is structurally different from the parent compound doxorubicin only in the epimerization of the hydroxyl group at the 4′ position of the daunosamine moiety, has yielded in 9 studies a response rate of 6% (95% confidence limits, 4%–9%) among 296 patients, of whom 183 were previously untreated [11]. Some of these studies suggest that epirubicin and doxorubicin are equally active when given in equitoxic doses [11].

Thus, to date it has not been possible to enhance substantially the limited anti-neoplastic activity of doxorubicin in NSCLC by semisynthetic modulation of the original compound as shown in the clinical results obtained using epirubicin, pirarubicin, DXDX or IDX. In conclusion, IDX has minimal activity in NSCLC and considerable haematological toxicity that precludes further dose escalation without the use of haemapoetic growth factors. In addition, the data obtained in this study suggest that the administration of IDX is limited by some cardiotoxic effects. These findings render IDX unsuitable for further investigation in NSCLC patients using the present dose and schedule.

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References

1. Alakl M, Orlandi F, Robert J, Fragu P, Munck JN, Carde P, Hurteloup P, Armand JP (1990) Phase I trial and pharmacokinetic (PK) study of 4′-iodo-4′-deoxydoxorubicin (IDOX) in i.v. bolus every 3 weeks (abstract). Ann Oncol 1 [Suppl]: 38
2. Barbieri B, Giuliani FC, Bordoni T, Casazza AM, Geroni C, Bellini O, Suarato A, Gioia B, Penco S, Arcamone F (1987) Chemical and biological characterization of 4′-iodo-4′-deoxydoxorubicin. Cancer Res 47: 4001
3. Berthaud P, LeChevalier T, Berille J, Herait P, Baldeyrou P, Tursz T, Arriagada R, Spielmann M, Hayat M (1989) Phase II study of pirarubicin in advanced non-small cell lung cancer. Eur J Cancer Clin Oncol 25: 1337
4. Blum RH (1975) An overview of studies with Adriamycin in the United States. Cancer Chemother Rep 6: 247

5. Chabner BA, Myers CE (1985) Clinical pharmacology of cancer therapy. In: DeVito T, Hellman S, Rosenberg SA (eds) Cancer: principles and practice of oncology. J. B. Lippincott, Philadelphia, p 311
6. Conley BA, Hornedo J, Abrams J, Eisenberger M, Hiponia D, Aisner J, Van Echo DA (1987) Phase II trial of 4′-deoxydoxorubicin in advanced non-small cell lung cancer. Cancer Treat Rep 71: 861
7. Drings P, Günther IU, Gatzemeier U, Berdel W, Stahl M, Salewski E, Edler L (1990) Pirarubicin in advanced non-small cell lung cancer. A trial of the phase I/II study group of the Association for Medical Oncology of the German Cancer Society. Onkologie 13: 183
8. Gianni L, Vigano L, Surbone A, Ballinari D, Casali P, Tarella C, Collins J, Bonadonna G (1990) Pharmacology and clinical toxicity of 4′-iodo-4′-deoxydoxorubicin: an example of successfull application of pharmacokinetics to dose escalation in phase I trials. J Natl Cancer Inst 82: 469
9. Gianni L, Capri G, Greco M, Villani F, Brambilla C, Luini A, Crippa F, Bonadonna G (1991) Activity and toxicity of 4′-iodo-4′-deoxydoxorubicin in patients with advanced breast cancer. Ann Oncol 2: 719
10. Mountain CF (1986) A new international staging system for lung cancer. Chest 89 [Suppl 4]: 225
11. Mouridsen HT, Alfthan C, Bastholt L, Bergh J, Dalmark M, Eksberg S, Hellsten S, Kjaer M, Peterson C, Skovsgård T, Sørensen JB, Tropé C, Aabo K (1990) Current status of epirubicin (Farmorubicin) in the treatment of solid tumours. Acta Oncol 29: 257
12. Ringenberg QS, Perry MC, Propert KJ, Modeas C, Hirsch V, Weiss RB, Richards F, Graziano S, Green M (1988) Phase II trial of 4′-deoxydoxorubicin (DXDX) in non-small cell lung cancer: a Cancer and Leukemia Group B trial. Med Pediatr Oncol 16: 27
13. Rose C, Lad TE, Kilton LJ, Schir J, Rosen ST, Rossof AH, Blough RR, Johnson CM (1990) Phase II trial of 4′-deoxydoxorubicin (DXDX) for unresectable non-small cell bronchogenic carcinoma. Invest New Drugs 8: 97
14. Rozencweig M, Kenis Y (1975) European studies with Adriamycin in lung cancer. Cancer Chemother Rep 6: 343
15. Sessa C, Calabresi F, Cavalli F, Cerny T, Liati P, Skovsgaard T, Sorio R, Kaye SB (1991) Phase II studies of 4′-iodo-4′-deoxydoxorubicin in advanced non-small cell lung, colon and breast cancers. Ann Oncol 2: 727
16. Simon R (1986) Confidence intervals for reporting results of clinical trials. Ann Intern Med 105: 429
17. Sørensen JB (1993) Treatment in non small cell lung cancer: new cytostatic agents. Lung Cancer (in press)
18. Splinter TAW (1990) Chemotherapy in advanced non-small cell lung cancer. Eur J Cancer 26: 1093
19. World Health Organization (1979) Handbook for reporting results of cancer treatment. Offset publication 42. WHO, Geneva