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Phase I Evaluation of Peplomycin with Special Reference to Pulmonary Toxicity*

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Abstract—*In the search for bleomycin analogues with less pulmonary toxicity than bleomycin itself, peplomycin was selected for a phase I clinical trial, based on experimental animal data. Eighteen patients received peplomycin at three exploratory levels. Six patients were treated at a level of* 5 mg/m², *8 patients at* 10 mg/m² *and* 4 *patients at* 15 mg/m² *of peplomycin, each dosage being given twice weekly intravenously. Pulmonary function tests were performed prior to treatment and serially thereafter. Pulmonary toxicity was encountered when the administered total dose of peplomycin was in the range* 190–350 mg *in patients who had received either* 10 *or* 15 mg/m² *twice weekly. Pulmonary toxicity was not observed when the dosage of peplomycin was restricted to* 5 mg/m² *twice weekly. During the trial no haematological, hepatic or renal changes induced by the drug were observed. Skin changes, stomatitis and fever were observed with increasing frequency the higher the cumulative dose of peplomycin, and these effects were similar to those seen with bleomycin. Two of fifteen patients with cervical cancer obtained a partial response, lasting* 1 *and* 2 months *respectively. Although peplomycin is free from pulmonary toxicity at a dose of* 5 mg/m² *twice weekly, the maximum tolerated cumulative dose has still to be defined.*

INTRODUCTION

TODAY bleomycin plays a major role in the management of patients with testicular cancer [1], malignant lymphoma [2, 3] and carcinoma of the head and neck [4].

The limiting toxic effect of bleomycin is interstitial pneumonitis, which is reported to occur in 5–20% of all patients receiving bleomycin to a cumulative total dose of more than 350 mg [5].

In order to find a new bleomycin analogue with reduced pulmonary toxicity and a greater and broader antitumour activity, Matzuda and co-workers selected peplomycin among 300 new bleomycin analogues for clinical evaluation [6].

Peplomycin is, like bleomycin, a glycopeptide, and its terminal moiety is 3-((*S*)-1-phenylethyl-amino)-propylamine. Matzuda *et al.* have shown that in mice the pulmonary toxicity of peplomycin was reduced by approximately 75% compared to that of bleomycin, based on an evaluation of histopathologic changes in lung tissue [6].

In addition, it was demonstrated that the antitumour activity of peplomycin was equivalent to or greater than that of bleomycin in various experimental animal systems [6]. Similar observations have been made by Sikic *et al.* [7], who found that the activity of peplomycin was equal to that of bleomycin using the Lewis lung carcinoma and B16 melanoma as models. In the same studies peplomycin showed significantly less pulmonary toxicity than bleomycin, evaluated by the lung collagen content, as estimated by hydroxyproline levels in the lung tissue. However, peplomycin was more lethal, with a 50 and 100% mortality rate at doses which produced a mortality rate of 0 and 19% respectively, in mice treated with bleomycin.

The LD_{50} of peplomycin in mice after intraperitoneal administration was about 82 mg/kg compared to 257 mg/kg for bleomycin, while the LD_{50} of peplomycin in rats was

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155 mg/kg compared to 168 mg/kg for bleomycin. The explanation for this species difference in LD_{50} for peplomycin is uncertain. Apparently it does not relate exclusively to pulmonary toxicity as the mice also experienced greater hepatic and renal toxicity.

Clinical investigations of peplomycin have been performed primarily in Japan. In an interim report from the National Cancer Institute, Bethesda, MD, U.S.A. and a subsequent publication, Oka reported on phase II trials being performed in Japan involving 329 patients [8; unpublished data]. Peplomycin was given intravenously, intramuscularly or intra-arterially in a dose of 10 mg twice or three times weekly up to a cumulative total dose of 200 mg. In 264 patients with neoplastic disease outside the lungs only 3 cases of pulmonary toxicity were observed. In 34 lung cancer patients pulmonary toxicity was seen in 9 patients, but no detailed information was given.

Based on this information clinical trials were initiated in Europe. The present article describes our experience with peplomycin in a phase I trial.

MATERIALS AND METHODS

Peplomycin was supplied as drug powder in vials of 10 mg* and dissolved in 200 ml of 0.9% saline given intravenously over a period of 10 min.

The study was planned with dose escalation, exploring the dose schedules of 5, 10 and 15 mg/m^2, each twice weekly.

The first 4 patients received 5 mg/m^2, and if no toxicity was observed the next 4 patients received 10 mg/m^2 and so on. If unacceptable toxicity occurred, the dose level was abandoned and the study was resumed at the subjacent dose level.

Minimal haematological requirements for inclusion in the study were a platelet count of $>100{,}000/mm^3$ and a white blood cell count of $\geqslant 3500/mm^3$.

Hepatic biochemical tests and serum creatinine levels had to be normal.

Clinical examination was performed before the start of therapy and every two weeks thereafter. Complete blood cell counts, serum electrolytes, serum creatinine, serum alkaline phosphatase, serum lactate dehydrogenase, serum bilirubin, prothrombin time and chest X-rays were performed every two weeks.

Objective remission and progression of the disease during therapy were evaluated according to the recommendations of WHO [9].

Forced vital capacity and forced expiratory volume in 0–1 sec were measured by standard spirometric techniques. Vital capacity, residual volume and total lung capacity were measured with a dilution technique together with single-breath carbon monoxide diffusion capacity, DL_{CO}. The tests were performed on a Hewlett-Packard computing pulmonary system 47 80 4 S.

DL_{CO} was determined by the method of Ogilvie *et al.* [10] as modified by Mitchell and Renzetti [11]. All DL_{CO} values were corrected according to the haemoglobin concentrations by the method of Dinakara *et al.* [12].

DL_{CO} measurements were performed in duplicate. Determinations were required to agree within 2 ml/min/mm Hg. If the first two determinations did not meet this requirement, further measurements were made until two such values were obtained.

Baseline pulmonary function tests were performed prior to therapy and repeated serially after each incremental increase of 75 mg in peplomycin dosage.

If stomatitis, skin ulceration or sclerosis was observed, treatment with peplomycin was discontinued until all signs of toxicity had resolved. Thereupon the treatment was resumed at the same dose level. Short-term fever was treated with salicylates and did not lead to discontinuation of peplomycin. The treatment was stopped if the patient developed dyspnoea or if significant radiographic changes became apparent in serial chest X-rays.

Changes in pulmonary function tests alone, without changes on the chest X-rays and without clinical symptoms of lung dysfunction, were not used in the decision to discontinue peplomycin therapy.

Statistical analyses were performed using Student's *t* test for paired samples and linear regression analyses.

RESULTS

Eighteen patients, all women, with a median age of 55 yr (range 41–69 yr), whose diseases were progressive and resistant to conventional therapy, were admitted. The diagnoses included cervical cancer (15 patients), ovarian cancer (1), renal cancer (1) and breast cancer (1). Informed consent was obtained from all patients prior to treatment, which in all cases was given on an outpatient basis. None of the patients had previously received bleomycin or had undergone previous chest surgery. None of the patients suffered from chest disease and all had normal lung function studies prior to treatment. The patient with breast cancer had previously received high-voltage irradiation to the chest wall *ad modum* McWirther.

*By courtesy of H. Lundbeck Ltd., Ottilliavej 7–9, 2500 Valby, Copenhagen, Denmark.

Five patients had minimal pleural changes on chest X-rays and one had a lung metastasis which had been stable for 1 yr. The remaining patients had normal chest X-rays.

Six patients received 5 mg/m² of peplomycin twice weekly to a cumulative total dose which ranged from 120 to 280 mg. No significant changes were seen in serial lung function studies or in serial chest X-rays during treatment (Fig. 1). None of the patients developed dyspnoea, tachypnoea, non-productive cough or fine rales on auscultation of the lungs. All the patients died of their malignant disease in other institutions and no special histological examination of the lungs was performed.

At the second dose level eight patients received 10 mg/m² of peplomycin twice weekly to a cumulative total ranging from 112 to 315 mg. In two of these patients (Nos 10 and 11) values for both DL_{CO} and forced vital capacity (FVC) showed a progressive fall with increasing doses of peplomycin (Fig. 2, Table 1).

After having received 195 and 250 mg of peplomycin respectively, they developed dyspnoea, non-productive cough and fine rales on auscultation of the lungs, with the simultaneous

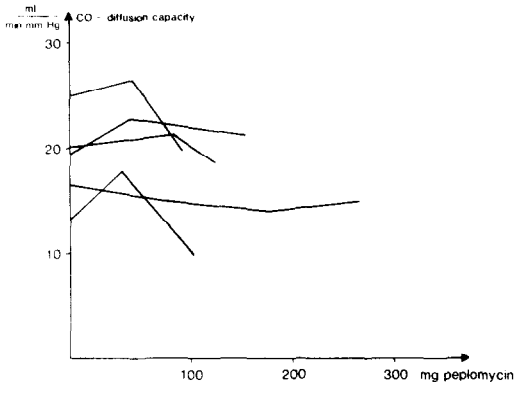

Fig. 1. Changes of DL_{CO} in patients during treatment with peplomycin 5 mg/m² intravenously twice weekly.

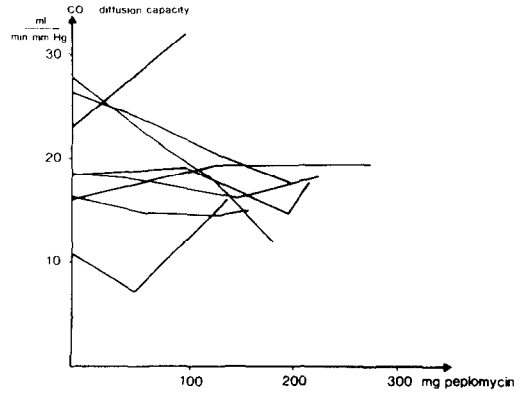

Fig. 2. Changes of DL_{CO} in patients during treatment with peplomycin 10 mg/m² intravenously twice weekly.

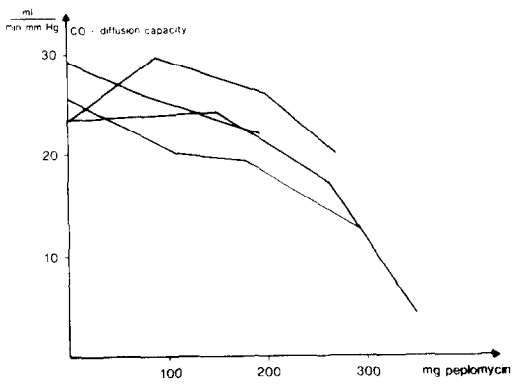

Fig. 3. Changes of DL_{CO} in patients during treatment with peplomycin 15 mg/m² intravenously twice weekly.

appearance of diffuse infiltrative changes on the chest X-rays.

In spite of discontinuation of treatment and initiation of steroid therapy using a dosage of prednisone 50 mg t.i.d., both patients developed respiratory insufficiency and expired. At autopsy no malignant changes were found in the lungs, but histologic signs of fibrosis were observed.

Another patient in this group (No. 12) died with radiographic evidence of diffuse pulmonary infiltration, but without alteration in lung function tests and without pulmonary symptoms. At autopsy multiple metastases were found in the lungs.

At the third dose level four patients received 15 mg/m² of peplomycin twice weekly to a cumulative total ranging from 190 to 350 mg. In all patients there was a decrease in DL_{CO} and FVC (Fig. 3, Table 1), but this was not statistically significant ($P > 0.05$).

Two patients (Nos 15, 18) developed dyspnoea and non-productive cough and diffuse infiltrative changes on chest X-rays after receiving 300 and 350 mg of peplomycin respectively. Despite discontinuation of treatment and initiation of steroid treatment with prednisone 50 mg t.i.d., one of the patients died from severe pulmonary insufficiency. Following autopsy, histological examination of the lungs revealed severe pulmonary fibrosis but no evidence of tumour.

The last patient died from her primary malignant disease, and at autopsy the patient had both lung metastases and fibrosis.

Other toxicities (Table 2)

With regard to other toxic manifestations, hyperpigmentation, skin ulceration and stomatitis were increasingly observed at all three dose levels with increasing cumulative total dose of peplomycin. The changes vanished within 14 days after discontinuation of treatment.

Table 1. Patient characteristics

Patient No.	Age	Performance	Dose/total	HB		DL_{CO}		FVC		PF	
				Before	After	Before	After	Before	After	Before	After
1	43	3	5/180	6.9	7.1	25.60	20.60	2.37	1.27	4.12	3.14
2	56	3	5/200	7.1	6.4	19.79	21.27	3.12	3.04	6.92	4.00
3	48	3	5/120	9.4	8.0	13.21	9.70	2.22	1.84	4.53	4.08
4	48	3	5/280	8.5	8.0	16.58	15.10	2.61	3.00	5.58	4.61
5	50	3	5/140	8.3	8.0	25.60	22.50	2.42	2.32	4.11	3.36
6	58	3	5/160	8.2	7.5	20.30	19.30	2.82	2.55	4.67	4.23
7	42	3	10/112	7.4	6.9	23.20	32.20	3.33	3.10	5.45	5.76
8	69	3	10/165	8.3	7.4	17.10	15.30	2.11	1.56	2.82	1.70
9	59	3	10/230	8.1	8.4	18.60	17.90	2.08	2.34	3.97	3.76
10	66	3	10/195	9.1	9.0	27.60	12.00	2.51	2.16	5.91	5.71
11	65	3	10/250	8.3	8.2	25.70	12.40	2.90	1.61	4.79	4.05
12	62	3	10/290	6.9	6.2	16.00	19.60	2.12	2.19	3.55	2.58
13	43	3	10/290	8.7	8.3	18.60	18.60	2.76	2.50	7.87	6.05
14	69	3	10/315	7.9	8.0	11.69	16.05	2.05	1.85	4.48	3.26
15	64	3	15/350	7.6	7.3	23.38	4.10	2.32	1.30	4.03	2.94
16	41	3	15/310	5.6	5.1	23.30	20.70	3.16	3.60	6.03	6.18
17	60	3	15/190	7.3	6.4	29.12	23.10	3.29	2.97	5.47	3.47
18	41	3	15/290	6.6	7.3	25.40	12.60	3.21	1.85	5.48	3.97

Table 2. Toxicity of peplomycin in 18 patients

	5 mg/m²	10 mg/m²	15 mg/m²
Hyperpigmentation of the skin	5/6	4/8	4/4
Ulceration	4/6	6/8	3/4
Stomatitis	2/6	4/8	2/4
Nausea and vomiting	4/6	5/8	3/4
Anorexia	3/6	6/8	3/4
Fever	2/6	6/8	2/4
Haematologic suppression	0/6	0/8	0/4
Hepatologic changes	0/6	0/8	0/4
Renal changes	0/6	0/8	0/4
Pulmonary X-ray changes	0/6	3/8	2/4
Total doses (mg)	180,200 120,140 280,160	230,112 315,290 250,200 165,290	350,310 140,290

Haematologic suppression or changes in hepatic biochemical tests were not seen during treatment with peplomycin. In one patient with cervical cancer, receiving 15 mg/m² of peplomycin, declining renal function was seen during treatment, but at autopsy this could have been accounted for by bilateral ureteric compression secondary to progression of the malignant disease.

Total alopecia was not observed at any dose level, but minor hair loss was evident at all dose levels.

In all patients fever was common after the first infusion of peplomycin with a maximum of 39°C, but it subsided in about 6 hr. Febrile episodes were less pronounced with subsequent infusions.

At all dose levels anorexia and nausea were observed during treatment.

Of the 15 patients with advanced cervical cancer, two patients had histologically proven malignant disease outside the irradiation field. Partial responses were obtained in both patients, lasting 1 and 2 months respectively.

DISCUSSION

As the effectiveness of cytotoxic therapy for malignant disease has improved, the toxicity of the compounds in use has become more and more important. The side-effects of various antineoplastic drugs are often the limiting factor in today's treatment of a variety of malignancies, but they are usually reversible, as is the case with haematologic toxicity. However, the dose-limiting factor with bleomycin is its pulmonary toxicity, which can be life-threatening and is often irreversible.

Various lung function tests have been performed in order to determine the pulmonary toxicity of bleomycin. Pasqual *et al.* [13] have shown that forced vital capacity and carbon monoxide diffusion capacity decrease during treatment with bleomycin. In their study it was impossible to define a correlation between doses and decrements in the pulmonary function tests performed because lung metastases were present. Samuels *et al.* [14] have also shown that the forced vital capacity is a reliable indicator of the pulmonary toxicity induced by bleomycin in a similar group of patients.

In a study of previously healthy young men with germ cell tumors Comis *et al.* [15] performed serial pulmonary function tests with measurement of FVC and DL_{CO}. They showed that the latter was the most sensitive indicator of subclinical bleomycin toxicity.

In the present trial both FVC and DL_{CO} were selected to desribe the pulmonary changes during treatment.

The design of the study was planned with dose escalation in order to avoid severe toxic effects.

In the first two groups, each of 4 patients, treated with peplomycin in doses of 5 mg/m² and 10 mg/m² twice weekly respectively, none of the classical symptoms of interstitial pneumonitis such as non-productive cough or dyspnoea were seen during treatment. No changes were observed in serial pulmonary function tests and chest films. In all cases treatment was discontinued because of progression of malignant disease.

In the next group, receiving 15 mg/m² i.v., two severe cases of pulmonary toxicity were observed. As a consequence no additional patients were included at this dose level. The study was resumed at the lower dose level of 10 mg/m² twice weekly.

At this dose level the maximum tolerated dose was explored. Out of 8 treated patients the last 2 patients developed interstitial pneumonitis, and the dose level was accordingly abandoned.

A constant fall in DL_{CO} with increasing cumulative doses of peplomycin was observed in six patients. Of these, four patients developed interstitial pneumonitis. Declining values for both DL_{CO} and FVC were seen, but the reduction in DL_{CO} was more pronounced than the change in FVC (Fig. 4).

Questions concerning the relationship between pulmonary toxicity, the size of individual doses and the cumulative dose of peplomycin cannot be answered in this trial because the trends in the lung function tests performed at the two toxic dose levels are contradictory.

In the trial reported by Oka [8; unpublished data] 269 patients with disease outside the lungs were treated with peplomycin 10 mg i.v., i.m. or i.a. twice or three times weekly up to a total dose of 200 mg. Only 3 patients suffered from pulmonary

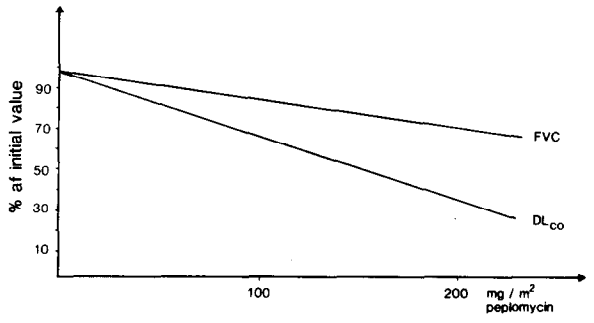

Fig. 4. Linear regression analysis of DL_{CO} *and FVC as a percentage of the initial value related to the total dose of peplomycin administered in the four patients who developed interstitial pneumonitis.* DL_{CO}, $y = -0.31x + 100$, $r = 0.84$, $P < 0.01$; *FVC*, $y = -0.14x + 102$, $r = 0.36$, $P < 0.05$.

toxicity. Pulmonary toxicity was observed in 9 out of the 34 patients with lung cancer in this study.

The EORTC Lung Cancer Cooperative Group has performed a phase II trial with peplomycin in squamous cell lung cancer [16] and found 7 cases of pulmonary toxicity at two different schedules, 20 mg i.m. weekly and 10 mg i.m. twice weekly, with a median cumulative dose of 160 mg (range 70–320 mg).

The details concerning pulmonary toxicity in this latter study are not yet published. The frequency of pulmonary toxicity seen in our phase I trial is in striking contrast to that encountered by Oka in patients without pulmonary disease.

Compared to the pulmonary toxicity of bleomycin given in the same way (i.e. twice weekly intravenously) and at the same dose schedule (i.e. 10–15 mg per dose), the pulmonary toxicity of peplomycin appears to be more pronounced. However, only direct comparative trials can with certainty elucidate a possible difference.

The other side-effects of peplomycin are, as with bleomycin, stomatitis, pigmentation and ulceration of the skin, anorexia, nausea and fever.

In summary, this trial has demonstrated that peplomycin in a dose of 10 mg/m² or more given intravenously twice weekly has a moderate to life-threatening pulmonary toxicity.

At a dose level of 5 mg/m² in 200 ml of saline given intravenously over a period of 10 min twice weekly, peplomycin has not shown any significant pulmonary toxicity, but the maximum tolerated cumulative dose has still to be defined.

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