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A Phase II Trial of Peplomycin in Squamous Cell Carcinoma of the Lung

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Abstract—*A phase II trial has been performed in squamous cell carcinoma of the lung using peplomycin. This compound is a bleomycin analogue with less pulmonary toxicity and a broader antitumor effect than bleomycin in experimental animal systems. Twenty-one evaluable patients were treated using a dose schedule of* 5 mg/m^2 *twice weekly intravenously. None of the patients had previously received radiation or chemotherapy. The median dose of peplomycin received was* 160 mg *(range* 45–254*). One patient obtained a partial remission lasting* 3 months. *One out of* 21 *patients developed clinical symptoms and a decrease in the lung function test performed during treatment indicative of toxicity. Other manifestations of toxicity are comparable to those of bleomycin.*

INTRODUCTION

THE ANTITUMOR effect of bleomycin is well-defined in squamous cell carcinoma in experimental animal systems [1]. Since high concentrations of bleomycin can be obtained in the lungs, the drug was an obvious candidate for systemic treatment of squamous cell carcinoma of the lung. A significant activity of bleomycin was also reported in pilot studies, but in subsequent phase II trials the response rate was 8–27% with a duration of 2–3 months when bleomycin was given as a single agent [2].

The disappointing results of these trials combined with the dose-limiting pulmonary toxicity of bleomycin have stimulated the search for bleomycin analogues with a broader antitumor spectrum and with less pulmonary toxicity than that of bleomycin. Among more than 300 such analogues peplomycin was selected for clinical trials.

Peplomycin is, like bleomycin, a glycopeptide and its terminal moiety is 3-(*s*)-1-phenylethylaminopropylamine. In mice Matzuda *et al.* have shown that the pulmonary toxicity of peplomycin compared to bleomycin, evaluated by histopathologic changes, was reduced by approximately 75% when given in equitoxic doses [3]. They demonstrated also that the antitumor activity of peplomycin was equivalent to or higher than that of bleomycin in various experimental animal systems [2].

Similar observations have been made in the U.S.A. by Sikic *et al.* [4] who, using the Lewis lung carcinoma and B16 melanoma, have shown that the activity of peplomycin was equal to that of bleomycin. Furthermore, the former showed significantly less pulmonary toxicity, evaluated by measuring the amount of hydroxyproline in the lung tissue. The hydroxyproline levels were correlated to the collagen content and are thus indicative of the degree of interstitial pneumonitis.

In a phase I trial performed at the Finsen Institute the pulmonary toxicity of peplomycin at different dose schedules was evaluated by means of lung function tests [5]. The recommended dose for further phase II trials was determined as a 5 mg/m^2 twice weekly intravenously.

Accordingly, a trial was initiated in Copenhagen and Oslo to evaluate the effect of peplomycin in patients with squamous cell carcinoma of the lung.

MATERIALS AND METHODS

All patients included in this trial were outpatients with a performance status of more than 70 according to the Karnofsky scale. They all had histologically proven localized non-resectable squamous cell carcinoma of the lung (WHO I).

Further criteria for inclusion were measurable

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or evaluable disease and an expected survival of at least 3 months. Minimal hematologic requirements were a platelet count of more than 125,000/μl and a white blood cell count of more than 3500/μl. Liver enzyme tests and serum creatinine levels had to be normal, unless the abnormal values were due to the neoplastic disease.

Peplomycin was supplied by Lundbeck Ltd. in vials of 10 mg. The drug was dissolved in 100 ml of 0.9% saline and was given intravenously over a period of 10 min twice weekly.

During the trial forced vital capacity, forced expiratory volume in 0–1 sec, vital capacity, residual volume and total lung capacity were measured in all patients treated in Copenhagen. A helium dilution technique with single-breath in a Hewlett–Packard computing pulmonary system was used. Carbon monoxide diffusion capacity, DL_{CO}, was determined by the method of Ogilvie *et al.* [6] as modified by Mitchell and Renzetti [7].

All DL_{CO} values were normalized to blood hemoglobin concentration by the method of Dinakara *et al.* [8]. 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.

Clinical examinations and lung function tests were performed before initiation of therapy and every 2 weeks thereafter. Hematologic status and chest roentgenograms were also performed every 2 weeks, while tests for serum electrolytes, creatinine, alkaline phosphatase, lactate dehydrogenase, bilirubin and prothrombin time were performed every 4 weeks. The treatment was continued until progression of the disease.

If a patient developed toxic side effects, such as stomatitis or sclerosis of the skin with ulceration, the treatment was discontinued until these symptoms had disappeared. Treatment was thereupon resumed at the same doses. Short-term fever was treated with acetylsalicylates and did not lead to discontinuation of treatment with peplomycin in any of the patients. If a patient developed dyspnea and more than a 30% decrease in DL_{CO} without objective tumor progression the treatment was stopped.

In order to be evaluable for response the patients should be treated for at least four weeks. Objective remission and progression of the disease during therapy were evaluated according to the directions of WHO [9]. The occurrence of CNS metastases was not considered to be progression of the disease. All patients had given their informed consent with acception of the investigational character of the treatment.

RESULTS

Twenty-two patients with a median age of 56 yr (range 47–70) and a performance status according to the Karnofsky scale of more than 70 were included in the trial. Eighteen patients were treated in Copenhagen and 4 in Oslo.

None of these patients had previously received chemotherapy or irradiation to the chest. Six patients had had a resection of their tumor 6–8 months before treatment and they had all relapsed. One patient was not evaluable because of rapid tumor progression after initiation of therapy, leading to discontinuation of treatment within 14 days.

In 21 evaluable patients one partial remission was observed with a duration of 3 months.

The median cumulative dose of peplomycin received was 160 mg (range 45–254).

With regard to toxicity, hyperpigmentation, ulceration of the skin and stomatitis (WHO grade 3) were seen in all 11 patients receiving more than 150 mg of peplomycin.

The patients did not show evidence of myelosuppression, decreasing renal function or changes in the hepatic biochemical tests. None of the patients suffered total alopecia, but minor loss of hair was seen.

In 6 out of 21 patients fever was registered after infusion of peplomycin, but it subsided in about 6 hr. The fever attacks were less pronounced later on during the treatment with peplomycin.

One patient, who had received 140 mg of peplomycin, developed severe dyspnea and decreasing DL_{CO}. Chest X-rays showed a minor tumor regression, but there were no signs of interstitial pneumonitis. The treatment was discontinued and after 2 months without treatment, during which the lung function steadily decreased, the patient died. At autopsy minor fibrosis and evidence of disseminated carcinomatosis in the lung was found.

None of the remaining patients developed signs of decreasing lung function evaluated by chest X-rays or by lung function studies, which could not be explained by progression of the neoplastic disease.

DISCUSSION

The results of antineoplastic treatment of squamous cell carcinoma of the lung has hitherto been disappointing and development of new active compounds is needed.

In the search for new compounds the bleomycin derivatives have been the subject of special interest because bleomycin is known to be active in the treatment of squamous cell carcinoma. One of the analogs newly developed and tested in Japan is

peplomycin, which is reported to have less pulmonary toxicity than bleomycin.

After an exploratory phase I study had been performed the present study was initiated.

Among 21 treated patients only one patient achieved a partial remission of short duration. The results are disappointing, particularly considering that none of the patients had previously received irradiation or chemotherapy and that they all had an initial good performance status.

The results are in agreement with the experience of the EORTC Lung Cancer Cooperative Group, who used peplomycin in the treatment of squamous cell carcinoma of the lung [10]. Forty-seven evaluable patients received either 20 mg weekly or 10 mg twice weekly of peplomycin intramuscularly to a median cumulative dose of 160 mg (range 70–320). One previously untreated patient obtained a partial remission.

It can therefore be concluded with 95% probability that the antineoplastic activity of peplomycin in squamous cell carcinoma of the lung is less than 20% in the three dose schedules mentioned.

Concerning pulmonary toxicity, two previous reports have dealt with this subject in lung cancer. Oka *et al.* (unpublished data) and the EORTC Lung Cancer Cooperative Group [10] reported that 9 out of 34 and 7 out of 47 patients respectively developed X-ray changes ascribed to peplomycin treatment.

In our trial, with previously untreated patients, the changes in chest X-rays and the decreases in the lung function tests performed during the trial could all be explained by progression in the malignant disease, except for one patient who developed decreasing DL_{CO} in spite of a minor tumor regression at the chest X-ray during treatment. The dose level used in the two former trials were 20 mg weekly or 10 mg twice weekly. As the dose level used in our trial was 5 mg/m^2 twice weekly with a median dose of 8.5 mg twice weekly, the lack of pulmonary toxicity in the present trial is notable. No conclusive remarks concerning pulmonary toxicity can, however, be drawn because both radiation and chemotherapy have been given in the two former trials.

A bleomycin analogue with a clinically meaningful efficiency in the systemic treatment of squamous cell carcinoma of the lung still has to be found.

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