Clinical Phase I Pilot Study of the Alkyl Lysophospholipid Derivative ET-18-OCH_3[1]

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Sixteen patients suffering from widespread malignant disease, the majority pretreated and found in poor general health, were treated in a phase I pilot study with the alkyl lysophospholipid derivative 1-*O*-octadecyl-2-*O*-methyl-*rac*-glycero-3-phosphocholine (ET-18-OCH_3). Eleven patients were treated intravenously, and five were given oral therapy. Prolonged IV administration of 15-20 mg/kg/day at a concentration of 5 mg ET-18-OCH_3 per 1 ml 20% human serum albumin could be continued safely. The maximum-tolerated dose was either 50 mg/kg as a single injection or 20 mg/kg during daily dispensions. Grade 2-4 toxicity, as pulmonary edema and impairment of hepatic function, then occurred during daily treatment. Toxicity was reversible. Mitogen stimulation and mixed lymphocyte culture studies revealed possible immunosuppressive effects of higher doses of ET-18-OCH_3. There were no chromosomal changes in cytogenetic studies. Frequent post-mortem examinations revealed no further toxicity. IV and oral treatment showed few encouraging response data since there were two partial remissions in non-small cell lung cancers and a reduction of leukemic blasts to less than 10% in an acute myelomonocytic leukemia.
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Alkyl lysophospholipid (ALP) derivatives represent the first generation of ether lipids with antineoplastic properties in vitro and in vivo. A detailed review of this area of investigation has been published recently (1). Some of these compounds have substantial therapeutic efficacy in various rodent tumor systems. This activity has been interpreted to be mediated partially by cytotoxic effector cell populations, e.g. macrophages and direct effects of this material on tumor cells as cytotoxicity, induction of differentiation and anti invasiveness. After toxicologic investigations (1), which included studies with subhuman primates (Munder and Andreesen, personal communication), we have introduced 1-*O*-octadecyl-2-*O*-methyl-*rac*-glycero-3-phosphocholine (ET-18-OCH_3) into a first clinical phase I pilot trial (2,3).

MATERIALS AND METHODS

Sixteen patients with solid tumors (seven non-small cell lung cancers, one bowel carcinoma, one hypernephroid carcinoma, one urothelial carcinoma, one adrenal cortex carcinoma, one thyroid gland carcinoma, one glioblastoma) and leukemias (one acute myelomonocytic leukemia, two chronic myeloid leukemias/blast crisis) were treated in our institution from 1979-1982. There were 11 male and five female patients. The median age of those with solid tumors was 64 years (range: 19-85 years). The median age of the leukemic patients was 37 years (range: 17-39 years). With the exception of two patients with non-small cell lung cancers, all patients have been refractory to prior therapy as surgery, radiation or chemotherapy; ten patients had obtained multi-modality treatment before entering the study. All patients suffered from metastatic or widespread disease, and the performance score (Karnofsky index) before the study was below 50 for the majority of the patients. Written informed consent of the patients was obligatory.

The chemical structure of the ALP 1-*O*-octadecyl-2-O-methyl-*rac*-glycero-3-phosphocholine (ET-18-OCH_3) is given in Figure 1. The compound was synthesized according to methods modified from procedures previously published (4-6), stored in a desiccator at −20 C, dissolved aseptically in 20% human serum albumin (HSA) up to a concentration of 5 mg/ml and infused intravenously at 37 C. For oral treatment, the ET-18-OCH_3 was dissolved in milk (3.5% fat content) at various concentrations. Routine checks on purity (chromatography), sterility (microbiology) and pyrogen content (animal experiments) were performed on each batch.

The study was performed in accordance with German law. The study protocol has been reviewed and approved by an ethical board. Eleven patients were treated intravenously. For dose finding, we began with single applications of 2 mg/kg, which is 10% of the lowest dose that produces moderate toxicity in toxicologic studies with subhuman primates (Munder and Andreesen, personal communication). Single application doses then were increased by doubling the amount of ET-18-OCH_3 and beyond 10 mg/kg by adding smaller amounts. Some patients were treated by prolonged daily applications, beginning with 1 mg/kg/day and using the same dose escalation procedure. Five patients were treated orally, following a similar dose escalation but starting with daily applications. Since we faced a shortage of the noncommercial drug during this first pilot study, dose increases for individual patients were performed at due intervals to obtain a maximum of information.

Prior to treatment, the following studies were performed on every patient: a case history, A (chest x ray,

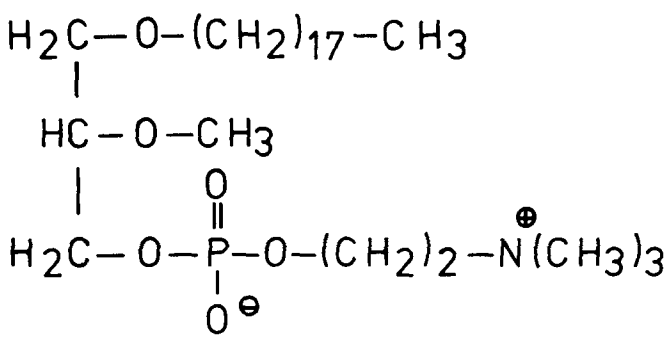

FIG. 1. Chemical structure of ET-18-OCH_3.

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electrocardiography, echocardiography, abdominal sonography, pulmonary function, tumor/leukemia staging with the necessary examinations, Coombs-tests, bone marrow) and B (physical examination, performance-status, weight, cellular blood count including erythrocyte morphology, reticulocytes, erythrocyte osmotic resistance, differential white blood count, thrombelastography, blood sedimentation rate, serum [blood urea nitrogen, creatinin, uric acid, electrolytes, bilirubin, glytamic oxaloacetic transaminase, glytamic pyruvic transaminase, γ-glutamyl transferase, alkaline phosphatase, cholinesterase, gamma-lactate dehydrogenase, lactate dehydrogenase, amylase, lipase, creatinin phosphokinase, β_2-microglobulin, haptoglobin, hemopexin, plasmatic coagulation, triglycerides, cholesterin, glucose, electrophoresis, immunoglobulins, complement C_3 and C_4 and antinuclear factors], creatinin-hippurane-clearance, urine-profile, urine-protein, urine-glucose and urine-electrolyes). A-values were repeated when necessary, at least once every month and at the end of the treatment. B-values were repeated at least once every week. Other examinations, such as thyroid hormones and chromosome analysis in peripheral blood cells, were done facultatively.

Toxicity was determined according to the Southeastern Cancer Study Group criteria with some minor modifications. Maximum-tolerated dose (MTD) was defined as the occurrence of grade 2 (moderate) toxicity after single or during daily applications and was evaluated for IV treatment.

For response evaluation partial remission (PR) has been defined as regression of all measurable tumor parameters of more than 50% with a remission duration for at least one month. Tumor regression of less than 50% for more than one month has been referred to as minor response (MR). Progressive disease (PD) was stated if one or more tumor parameters or white blood count in patients with leukemia developed progressively under therapy, paralleling a drop in performance status. No change (NC) or complete remissions (CR) have not been observed.

RESULTS AND DISCUSSION

Eleven patients were treated intravenously. Generally, toxicity was mild, i.e. grade 1 of the Southeastern group criteria. Two patients developed transient indurative erythema, which so far lacks a pathophysiological explanation on some parts of their skin. Six patients experienced gastrointestinal side effects of vomiting and diarrhea, which we found to be independent of dose level but correlated with the concentration of ET-18-OCH_3 in HSA and the infusion rate. Both side effects could be avoided by choosing an ET-18-OCH_3 concentration in 20% HSA, not exceeding 5 mg/ml, and by keeping the infusion rate below 20 ml per hr. Grade 1 liver toxicity was observed in three patients as an impairment of hepatic synthesis function monitored by a temporary drop in serum cholinesterase, and in one occasion as a drop of the Quick test. One patient showed grade 2 liver toxicity, as there was a cholestasis with increased alkaline phosphatase and bilirubin. Grade 1 renal toxicity was found in two patients with an elevation of serum creatinine and glucosuria, and proteinuria was found in one case. Life-threatening toxicity (grade 4) was observed in one patient, who developed an interstitial pulmonary edema, which correlated with a change of performance status. Similar pulmonary edema in a second patient reached only grade 2 toxicity because of prompt drug removal. Grade 1-2 toxicity was found to be reversible within a few days after removal of ET-18-OCH_3; it did not require any special treatment. Grade 4 pulmonary edema was found to be completely reversible under assisted ventilation and corticosteroids with the drug removed.

The MTD during single IV applications, given to five patients with weekly intervals, was 50 mg/kg infused within 24 hr. This dosage was reached in two patients, and the limiting factor was the infusion rate, since gastrointestinal toxicity occurred. MTD during daily applications was 20 mg/kg/day, reached by four patients. One patient could be treated with 20 mg/kg/day for 10 days without grade 2 toxicity. The other patients experienced either liver or lung toxicity reaching grade 2 or more (see Table 1). Additionally, after accidental extravasal infusion, there were two episodes of thrombophlebitis.

Five patients were treated orally. Grade 1 toxicity was concentrated on the gastrointestinal tract, hepatic function and renal function, and it had the same characteristics as those induced by IV treatment. Five mg/kg/day could be given safely to four of the patients for longer time intervals, 10 mg/kg/day produced life-threatening pulmonary edema after 10 days in one patient, which was completely reversible under short-term assisted ventilation and corticosteroids with the drug removed. However, oral MTD was not established in this pilot trial since better galenic formulations of this type of drug are under way.

Mitogen stimulation and mixed lymphocyte culture (MLC) studies in the blood lymphocytes of six patients were performed to reveal possible in vivo immunosuppression of higher doses of ET-18-OCH_3, which had been found in vitro (7). The results so far remain contradictory. However, since there was a significant decrease of mitogen stimulation and MLC reactivity in one patient, which showed reversibility after the end of the treatment, further studies in this direction should be performed.

Cytogenetic studies have been performed in lymphocytes of patients under treatment with negative results (8). Pathological and histological post-mortem examinations were performed in eight of the 16 patients who died of progressive disease after various time intervals. There were no further signs of toxic alterations exceeding the common findings in advanced neoplastic disease and death.

TABLE 1

Maximum-Tolerated Dose (MTD) and Limiting Toxicity for IV ET-18-OCH_3

• MTD for single infusion of ET-18-OCH_3 (20% HSA, 5 mg/ml): 50 mg/kg
Limiting toxicity: Gastrointestinal toxicity (nausea, diarrhea)
• MTD for daily infusions of ET-18-OCH_3 (20% HSA, 5 mg/ml): 20 mg/kg/day
Limiting toxicity: Lung, liver

Details of response and survival data are in previous reports (2,3,9). In summary, there were two PR in intravenously treated patients with non-small cell lung cancer, which were controlled by both x ray and bronchoscopy, and showed a remission duration for five and six months. Minor responses were found in one patient with a hypernephroid carcinoma and another patient with a thyroid gland carcinoma. In a patient with an acute myelomonocytic leukemia that was treated intravenously, we observed a ca. 1-log reduction of leukemic blasts in the peripheral blood ($78.7 \times 10^3/\mu l$ to $3.4 \times 10^3/\mu l$) within 15 days of treatment with a parallel recovery of granulopoiesis. However, this did not qualify for response since we could not obtain a second bone marrow examination from this patient. All other patients were found with progressive disease. However, all patients finally died from progressive disease; none of the patients survived longer than one year after study.

In summary, we have treated 16 patients suffering from widespread malignant disease; the majority has been refractory to previous treatments and was found to be in poor general performance. MTD for single IV administration of the drug was ca. 50 mg/kg with nausea and vomiting as the limiting toxicity. Prolonged daily IV applications of doses less than 20 mg/kg/day at 5 mg ET-18-OCH$_3$/1 ml 20% HSA seemed to be safe. Limiting toxicity occurred in liver and as interstitial pulmonary edema giving 20 mg/kg/day. The etiology of the pulmonary edema remains speculative. However, residual platelet-aggregating effects of the ET-18-OCH$_3$ similar to the chemically related platelet-activating factor (PAF) may play a role (10). Thus, it seems to be essential to look for antitumor ether lipids and derivatives for future clinical trials without PAF effects. On the other hand, typical side effects for antitumor cytotoxics as myelosuppression or alopecia were not found within the study; the drug also remained genetically inactive.

The purpose of this study performed with a limited amount of drug was only to obtain basic information on the applicability and possible value for further clinical testing of this material in cancer patients. Since we have partially characterized the tolerability of this first antineoplastic ether lipid have found some limited antitumor activity of the material, the information obtained from this pilot trial represents basis and justification for further clinical testing of related structures within a wider scope of phase I and II trials (see also Herrmann, D. et al., this issue).

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