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First-time-in-man and pharmacokinetic study of weekly oral perifosine in patients with solid tumours

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ABSTRACT

Aim: To identify the maximum-tolerated dose (MTD) and pharmacokinetics of oral perifosine.

Methods: Patients with solid tumours received perifosine at dosages ranging from 100–800 mg/week. Eligibility criteria included life expectancy > 12 weeks, WHO performance status ⩽ 2, normal blood, liver and renal functions and no recent anticancer treatment. Drug concentrations were analysed by HPLC–MS/MS.

Results: Thirty six patients were recruited (75% males, mean age 54.7 years, performance status 1 in 72.2%). Adverse events included nausea (69.4%), diarrhoea (55.6%), vomiting (52.8%) and abdominal pain (13.9%). Antiemetic regimens including glucocorticoids, dopamine antagonists and 5-HT3-antagonists were used as treatment and/or prophylaxis in 50% of the patients. Though MTD was formally not reached with 800 mg/week, the treatment discontinuation due to diarrhoea and vomiting likely related to perifosine in two cases led to the decision to stop further dose escalation. Pharmacokinetics after a single dose were median t_{max} = 8.0–24.2 h, median $t_{1/2}$ = 81.0–115.9 h and mean$_{geo}$ CL/f = 0.28–0.43 mL/min/kg. Urinary excretion was below 1%. Perifosine slightly accumulated and steady state was nearly reached after 2–3 weeks.

Conclusion: Oral perifosine was tolerable up to 600 mg/week in cancer patients when administered with meal and prophylactic antiemetics. Based on its half-life of about 4 days, a weekly regimen may be appropriate.

1. Introduction

Perifosine (AEZS-104, previously D-21266) is a synthetic phospholipid-like substance structurally related to the alkylphosphocholine miltefosine (Fig. 1), a drug approved for the topical treatment of cutaneous metastases of breast cancer[1] and for the oral treatment of leishmaniasis,[2] a parasitological tropical infectious disease. Oral use of miltefosine in cancer patients was limited by gastrointestinal side-effects,[3,4] and perifosine was selected for clinical development because

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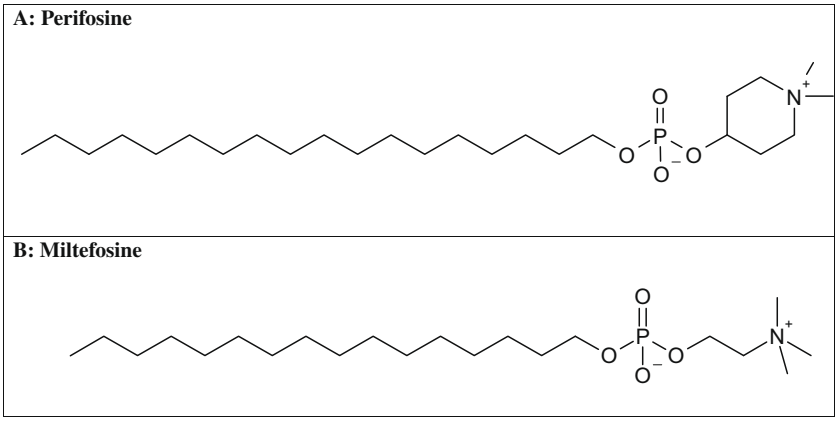

Fig. 1 – Chemical structures of perifosine (A) and miltefosine (B).

of its superior tolerability in pre-clinical tests.[5] In vitro, perifosine showed antineoplastic effects against melanoma, nervous system, lung, prostate, colon and breast cancers, similar to or stronger than miltefosine.[5] In human leukaemia cells, perifosine dose-dependently increased the rate of apoptosis. This effect was even stronger in combination with radiation, suggesting a favourable profile of perifosine in combination therapies.[6] In vivo studies using various models, including syngeneic murine tumours and human tumour xenografts, showed marked antineoplastic effects which could be further enhanced by a dose schedule combining a high loading dose with a lower maintenance dose.[5] Mode of action studies of perifosine revealed inhibition of the PI3-K/Akt pathway (reduction in phosphorylated Akt), inhibition of MAPK/ERK pathway and activation of SAPK/JNK pathway, which can act together in the induction of apoptotic cell death.[7–9] Perifosine induced, via inhibition of the PI3-K/Akt pathway, an up-regulation of the cyclin-dependent kinase inhibitor $p21^{waf}$ which was independent of p53 function.[10] Recently, in multiple myeloma cells perifosine was shown to down-regulate survivin and to prevent the bortezomib-induced up-regulation of survivin, suggesting a potential role in this haematological malignancy and for drug combinations.[11]

Herein, we report the results of a first-time-in-man study of orally administered perifosine in patients with advanced solid tumours. The objectives of this clinical Phase I study were to determine the maximum-tolerated dose (MTD) and pharmacokinetics of oral perifosine in a once weekly dosage regimen.

2. Patients and methods

2.1. *Patient population*

Female and male patients (age 18–75) were eligible if they had histologically/cytologically proven solid tumours for whom standard treatments were not or no longer available. Other inclusion criteria were: anticipated life expectancy > 12 weeks, WHO performance status of 0–2, platelets $\geqslant 150 \times 10^9$/L, white blood cells (WBC) $\geqslant 4 \times 10^9$/L, haemoglobin $\geqslant 1$ g/dL, ASAT/ALAT $\leqslant 2.5 \times$ upper limit of normal range ($\leqslant$5x if clearly related to liver metastases), bilirubin $\leqslant$ upper limit of normal range and serum creatinine $\leqslant 135$ μmol/L. The patients were not included if any of the following was present: ongoing or recent ($\leqslant$4 weeks prior to study entry) treatment of their malignant disease, concomitant or recent treatment with an investigational drug, history of haemolytic events, recent acute or chronic gastrointestinal conditions that might predispose to intolerability or poor drug absorption, non-compensated or uncontrolled non-malignant conditions, pre-existing retinal disease or pathologic baseline electro-oculogram, brain metastases or leptomeningeal disease, breast feeding, pregnancy or inadequate contraception in women of childbearing potential or men.

2.2. *Study design*

This study was designed as open-label, non-controlled, dose escalation study involving four centres. The protocol was approved by the Institutional Review Board of participating centres and informed consent was obtained from all patients prior to study entry.

Perifosine film-coated tablets (50 mg/tablet) were supplied by ASTA Medica AG (Frankfurt/Main, Germany) now Aeterna Zentaris GmbH. The starting dose level was 100 mg/week. The tablets were administered orally once weekly together with a meal and under supervision. This dosing regimen was based on pre-clinical data where the no-effect level of toxicity was below 2.15 mg/kg body weight and gastrointestinal toxicity was less marked in non-fasting rats.

Three to six patients were enrolled per dose level (3 patients in the absence of and up to 6 patients in the presence of significant or dose-limiting toxicity). The decision to proceed to the next higher dose level was based solely upon toxicity. The dose was escalated between patients only and no intrapatient dose escalation was performed. Dose escalation steps followed a modified Fibonacci scheme and consisted in 200, 350, 450, 600 and 800 mg/week. A treatment interruption of no more than 2 weeks was allowed. Prophylactic antiemesis was planned if >2/6 patients required 5-HT3-antagonist-type antiemetic treatment on the preceding dose level. Treatment was continued until progression of malignant disease or occurrence of significant or dose-limiting toxicity (ST/DLT). ST was defined as an adverse event likely

related to perifosine with an intensity of common toxicity criteria (CTC) grade 2 (non-haematological toxicity) or 3 (haematological toxicity) despite symptomatic/prophylactic treatment. DLT was defined as an adverse event likely related to perifosine with an intensity of CTC grade ⩾ 3 (non-haematological toxicity) or 4 (haematological toxicity) despite symptomatic/prophylactic treatment). MTD was defined as the dose where 2 or more patients experienced the same type of DLT.

Pre-treatment evaluation included a complete medical history and a complete physical examination. Indicator lesions were measured before start of treatment and repeatedly during the study. At baseline and weekly during treatment, blood chemistry and urine were checked. Ophthalmologic examinations, electrocardiograms and lung function assessments were conducted at baseline and at end of treatment. A global assessment of tolerability was provided by the investigator. Adverse events were graded according to CTC (NCI, version 2.0).

2.3. *Pharmacokinetic study*

Blood samplings (5 mL) were performed at pre-dose, 1 h post-dose, q 2 h up to 8 h afterwards and then q 24 h up to 120 h post-dose. Urine was collected in plastic containers and stored at room temperature in the dark over specific collection periods (pre-dose, 0–8, 8–24, 24–48, 48–72 h post-dose). At the end of each collection period, the urine volume was measured and 10 mL aliquots were retained. The samples were kept frozen at –20 °C or below until analysis.

Plasma and urine samples were analysed for perifosine by a validated HPLC-MS/MS method, as described previously.[12] The terminal mono-exponentially decreasing parts of the curves were subjected to curve fitting to estimate the terminal elimination rate constant (λ_z). λ_z was used for determination of $t_{1/2}$ and for extrapolation of the area under the curve (AUC) from the last measured data point to infinity. All pharmacokinetic calculations were performed with a validated Excel-based software 'FUNCALC', a collection of functions for non-compartmental pharmacokinetic evaluations. Descriptive statistics were used for plasma concentrations and pharmacokinetic analyses. A two-sided Wilcoxon rank test was applied to $AUC_{0\text{-tlast}}$ and C_{max} to explore gender effects after linear adjustment to the 100 mg/week dose in male and female patients. Regression analyses were performed on C_{max} and $AUC_{0\text{-tlast}}$ to establish dose linearity and dose proportionality, after normalisation to a body weight of 70 kg and to a body surface area of 1.73 m^2 to investigate the influence of these variables on the coefficients of determination.

3. Results

3.1. *Patients*

Thirty six patients were entered in the study. Most patients were male (75%), with a mean age of 54.7 years and a mean weight of 69.5 kg. All patients were Caucasian and 72.2% had a WHO performance status of 1. The most frequent types of cancer were lung ($n = 7$), melanoma ($n = 5$) and gastrointestinal ($n = 4$) cancer. The mean time since diagnosis was 27 months (range = 1–117 months). Overall, 32 patients (88.9%) had received prior chemotherapy (alone or in combination) and 25 patients (69.4%) had undergone surgery for their disease.

Treatment duration with perifosine (time between first and last administration) ranged from 1 week to 15.1 weeks. Overall, mean exposure time was 5.2 weeks, ranging from 2.6 weeks in the 800 mg/week dose group to 8.7 weeks in the 450 mg/week dose group. Four out of 36 patients (11.1%) received perifosine for 12 weeks. Disease progression was at least one reason for discontinuation of study treatment in 30 of 36 patients (83.3%). Three patients (one patient at 100 mg/week and 2 patients at 800 mg/week) discontinued treatment due to poor drug tolerability. No objective tumour response or partial remission was observed. Eight out of 36 patients (22.2%) had no change as best overall response, with time to progression ranging from 6 to 16 weeks.

3.2. *Toxicity*

Thirty-two out of 36 patients (88.9%) reported an adverse event (AE) possibly related to perifosine. AEs affected most commonly the gastrointestinal system, in 31 out of 36 patients (86.1%). The most common AEs were nausea (69.4%), diarrhoea (55.6%), vomiting (52.8%) and abdominal pain (13.9%) (Table 1). The following AEs occurred once in the high dose groups: coughing, dyspnoea and peripheral oedema at 450 mg/week; bradycardia, dysphonia and tongue discolouration at 600 mg/week; arthralgia, hypotension, myalgia, increased sputum and taste abnormal at 800 mg/week.

Antiemetics were used as symptomatic treatment in approximately 50% of the patients while they were given as prophylaxis, in approximately 55% of the patients, commonly as triple combination of including a glucocorticoid (dexamethasone), a dopamine antagonist (alizapride) and a 5-HT3-antagonist (tropisetrone). On the other hand, antidiarrhoea drugs were used as treatment in at least 37.5% of the patients in the dose group of 600 mg and 800 mg/week while they were given prophylactically in only one patient at 350 mg/week. Additionally, 6 patients out of 20 (30%) required further antiemetics despite initial prophylaxis. All these patients were in the higher dose groups (450, 600 and 800 mg/week).

The incidence of AE (including AEs of grade ⩾ 3 and serious AE) did not increase with increasing dose of perifosine. Though the MTD was formally not reached with a dose of 800 mg/week, the occurrence of two discontinuations judged as likely related to perifosine due to gastrointestinal intolerability led to the decision to stop dose escalation. A total of 6 patients out of 36 (16.7%) experienced an adverse event with grade ⩾ 3 judged possibly related to perifosine. The incidence of AE with grade ⩾ 3 related to perifosine did not increase with increasing dose of perifosine and ranged from 0% to 33.3%.

A total of 3 patients out of 36 (8.3%) experienced a serious AE. The events consisted of gastrointestinal symptoms (leading to discontinuation) in two patients (both at 100 mg/week) and syncope in one patient (at 200 mg/week). Overall, two patients presented a marked laboratory abnormality (defined as a treatment-emergent laboratory value of NCI CTC grade ⩾ 3):

Table 1 – Adverse event following weekly perifosine (reported in >1 patients).

Event	Perifosine dose (mg/week)						
	100 (n = 6)	200 (n = 6)	350 (n = 6)	450 (n = 3)	600 (n = 8)	800 (n = 7)	All (n = 36)
Nausea	4	4	3	3	6	5	25 (69.4%)
Grade ⩾ 3[a]	2	0	0	0	1	0	3 (8.3%)
Diarrhoea	2	3	2	1	8	4	20 (55.6%)
Grade ⩾ 3	0	0	0	0	1	1	2 (5.6%)
Vomiting	3	2	2	2	6	4	19 (52.8%)
Grade ⩾ 3	1	0	1	0	0	0	2 (5.6%)
Abdominal pain	1	0	0	0	3	1	5 (13.9%)
Grade ⩾ 3	0	0	0	0	1	0	1 (2.8%)
Sweating increased	0	0	1	0	2	1	4 (11.1%)
Fatigue	0	0	2	0	1	1	4 (11.1%)
Rash erythematous	1	0	0	2	0	0	3 (8.3%)
Gastritis	3	0	0	0	0	0	3 (8.3%)

a Data shown if Grade ⩾3 occured.

Table 2 – Pharmacokinetic parameters of perifosine after single dose.

Dose (mg/week)	C_{max}[a] (ng/mL)	t_{max}[b] (h)	$t_{1/2}$[b] (h)	$AUC_{0\text{-tlast}}$[a] (ng·h/mL)	$AUC_{0\text{-}\infty}$[a] (ng·h/mL)	CL/f[a] (mL/min/kg)	n
100	763 (430–1352)	16.0 (4.2–24.8)	100.3 (63.9–245.5)	62,623 (27,525–142,475)	98016 (32,554–295,110)	0.28 (0.10–0.78)	6
200	1496 (1083–2068)	8.0 (6.0–24.1)	94.4 (57.5–106.0)	129,444 (95,618–175,236)	174,322 (127,567–238,211)	0.28 (0.20–0.39)	6
350	2256 (1467–3468)	24.0 (8.0–24.1)	81.3 (66.3–155.6)	199,808 (135,284–295,106)	275,744 (160,607–473,422)	0.31 (0.16–0.59)	6
450	2523 (1847–3445)	24.0 (8.0–24.0)	97.6 (60.0–146.9)	214,362 (151,241–303,826)	306,194 (196,469–477,198)	0.33 (0.18–0.59)	3
600	2632 (1533–4518)	24.0 (8.0–25.9)	115.9 (37.2–299.5)	213,994 (126,186–362,905)	348,832 (159,196–764,363)	0.43 (0.21–0.86)	8
800	3691 (2668–5107)	24.2 (24.0–48.4)	81.0 (63.9–100.6)	302,768 (216,379–423,649)	398,084 (275,876–574,429)	0.43 (0.29–0.65)	7

a $Mean_{geo}$ (95% CI_{ln}, lower-upper limit).
b Median (min–max).

one patient at 100 mg/week (bilirubin, alkaline phosphatase) and another patient at 600 mg/week (anaemia and thrombocytopenia). In both cases, the investigator judged these abnormalities to be due to the underlying malignant disease. Electro-oculograms revealed a slight, dose-independent decrease in the median ARDEN ratio between screening and follow-up measurements (on- or post-treatment). However, the number of patients with increase and decrease in this sensitive indicator for retinal function was balanced and changes were not paralleled by changes in other parameters, worsening in visual function, or progression of pre-existing, age-dependent abnormalities. No significant toxicity judged as possibly related to perifosine was observed based on laboratory tests, vital signs, electrocardiogram and lung function.

3.3. *Pharmacokinetics*

Analyses of pharmacokinetic variables after the first dose revealed a rather slow absorption of perifosine after oral administration (median t_{max} 8.0–24.2 h) and a slow elimination from plasma (median $t_{1/2}$ 81.0–115.9 h). Apparent total clearance of perifosine was low ($mean_{geo}$ of CL/f: 0.28–0.43 mL/min/kg). High interindividual variability was observed (coefficient of variation of the logarithmic normal distribution ranged from 12.6% to 72.0% for C_{max} and from 14.1% to 92.0% for $AUC_{0\text{-tlast}}$). Urinary excretion of unchanged drug was below 1%. Table 2 summarises pharmacokinetic parameters. Median perifosine concentrations over time per dose group are shown in Fig. 2. $AUC_{0\text{-tlast}}$ and C_{max} after adjustment to the 100 mg/week dose group did not show any significant difference between male and female subjects (p = 0.898 and 0.571, respectively). Linear regression analysis indicated rough dose linearity for C_{max} and $AUC_{0\text{-tlast}}$ (r^2 = 0.3955 and 0.3994, respectively). Normalisation to a standard body weight or body surface area resulted in slightly better coefficients of determination for dose linearity of C_{max} and $AUC_{0\text{-tlast}}$ (r^2 = 0.4490 and 0.4570, respectively, after normalisation to body weight and 0.4391 and 0.4457, respectively, after normalisation to body surface area).

In order to investigate the accumulation of plasma concentrations following repeated administration of perifosine, median trough values were plotted versus the study time

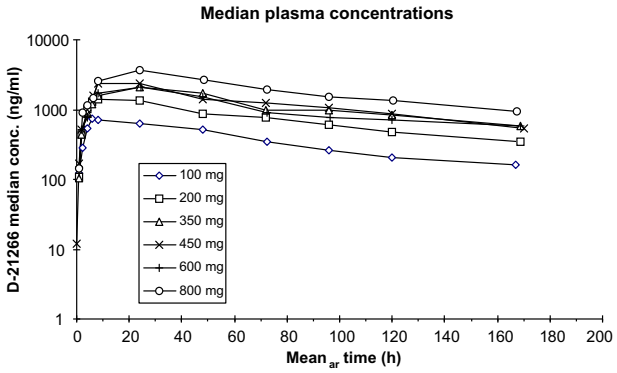

Fig. 2 – Median plasma concentrations of perifosine after administration of a single oral dose.

(Fig. 2). Perifosine slightly accumulated when administered once a week. The mean accumulation rate was 1.61 (range = 0.66–3.80). Steady state appeared to be reached after 2–3 weeks (see Fig. 3).

4. Discussion

Perifosine induced a similar pattern of gastrointestinal side-effects as was known from miltefosine. However, gastrointestinal reactions were more severe after miltefosine, which required the administration in multiple 50 mg doses over the day of treatment.[3] In contrast, the weekly dose of perifosine was administered in a single dose. Thus, the hypothesis derived from pre-clinical studies[5] that orally administered perifosine should be better tolerated than miltefosine could be verified, although some patients still required antiemetics or treatment for diarrhoea. In this study, perifosine administered orally as a film-coated tablet once weekly with a meal was tolerated up to a dose of 600 mg/week. Antiemetics, including glucocorticoids, dopamine antagonists and 5-HT3-antagonists, were efficiently used in combination for prophylaxis and/or individually post-dose, if needed as symptomatic treatment. At a dose of 800 mg/week, gastrointestinal symptoms were dose limiting. This is distinctly higher than the MTD of miltefosine when administered weekly (300 mg/week)[3] and higher than the MTD of perifosine when administered daily as 3-week cycles (100 mg/day).[13]

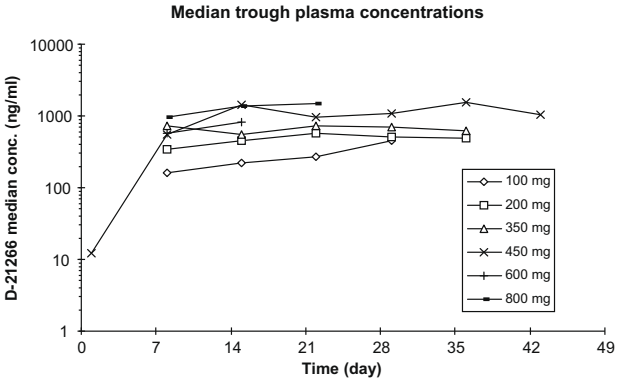

Fig. 3 – Median trough plasma concentrations of perifosine after weekly administration.

No increase in leucocytes or platelets was noticed after repeated weekly dosing of perifosine, in contrast to daily dosing of miltefosine.[15] This may be due to a different pharmacodynamic profile. On the other hand, a recent study confirmed the feasibility of perifosine 150 mg/day in combination with radiotherapy with no bone marrow toxicity.[16] The absence of influence on bone marrow function holds promises for future studies with perifosine to be combined with classic cytotoxic drugs or radiotherapy.

Perifosine slightly accumulated in plasma when administered once a week. The mean accumulation ratio was 1.61. Steady state was reached after 2–3 weeks of drug administration. Both findings were in accordance with the half-life determined in this study (81–116 h) and in the daily dosing study.[13]

The tolerability of high perifosine doses in the weekly dosing scheme served as basis for subsequent Phase I studies that resulted in loading dose regimens combining starting dosages of 150 mg and 300 mg (every 6 h) with maintenance dosages of 100 mg/day and 150 mg/day, respectively.[14] The loading dose regimens were investigated in various advanced solid tumours; prolonged courses of stable disease and tumour responses were reported for patients with advanced soft tissue and renal cell carcinoma.[17] Based on its novel mode of action as inhibitor of the PI3-K/Akt pathway and acceptable spectrum of treatment related adverse events, studies of perifosine have recently been extended to haematological malignancies like Waldenström's macroglobulinemia[18] and multiple myeloma, as well as combinations with agents targeting complementary signalling pathways (see http://www.clinicaltrials.gov).

Conflict of interest statement

Clemens Unger, Wolfgang Berdel, Axel-R Hanauske and Klaus Mross: no conflict of interest to declare.

Herbert Sindermann and Jürgen Engel: Employees of the trial sponsor (Aterna Zentaris, formerly ASTA Medica).

Role of the funding source

Aeterna Zentaris GmbH (formerly ASTA Medica) was the sponsor of the study which included supply of study medication, trial budget, drug level measurements, monitoring, statistical analysis and a draft of the publication manuscript.

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