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Phase I studies of darinaparsin in patients with relapsed or refractory peripheral T-cell lymphoma: a pooled analysis of two phase I studies conducted in Japan and Korea

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Abstract

Objective: Two phase I studies of darinaparsin including Japanese and Korean patients with relapsed/refractory peripheral T-cell lymphoma were performed to evaluate its safety (primary purpose), efficacy and pharmacokinetic profile (ClinicalTrials.gov: NCT01435863 and NCT01689220).
Methods: Patients received intravenous darinaparsin for 5 consecutive days at 200 mg/m^2/day in 4-week cycles, 300 mg/m^2/day in 4-week cycles or 300 mg/m^2/day in 3-week cycles.
Results: Seventeen Japanese and 6 Korean patients were enrolled and treated. Drug-related adverse events developed in 18 patients (78%). Dose-limiting toxicity, grade 3 hepatic dysfunction, was reported on Day 15 of cycle 1 in 1 Japanese patient who received 300 mg/m^2/day. The most common drug-related, grade $\geq$ 3 adverse events were lymphopenia (9%), neutropenia (9%) and thrombocytopenia (9%). No deaths occurred. In 14 evaluable patients, 1 and 3 patients had complete response and partial response, respectively. The plasma concentration-time profiles of arsenic, a surrogate marker for darinaparsin, were similar between Japanese and Korean patients. No significant difference was found in its pharmacokinetic profile.
Conclusions: These data indicate the good tolerability and potential efficacy of darinaparsin in patients with relapsed/refractory peripheral T-cell lymphoma. Darinaparsin 300 mg/m^2/day for 5 consecutive days in 3-week cycles is the recommended regimen for phase II study.

Key words: Asia, darinaparsin, peripheral T-cell lymphoma, pharmacokinetics, phase I

Introduction

Peripheral T-cell lymphomas (PTCLs) represent a large, biologically heterogeneous group of rare, clinically aggressive, non-Hodgkin lymphomas (NHLs) resulting from the clonal proliferation of mature post-thymic lymphocytes, T-cells and natural killer cells; patients with PTCL have a worse prognosis than patients with their B-cell lymphoma counterparts (1,2). In a global clinicopathological study of newly diagnosed patients from 22 institutions, the 5-year overall survival (OS) of patients with PTCL not otherwise specified (PTCL-NOS) was 32% (3,4). Following relapse or progressive disease (PD) after chemotherapy, the median OS in patients with PTCL was only 6.5 months, with a 3-year OS of 7% (5).

Due to the disappointing clinical outcomes of patients with relapsed/refractory PTCLs after standard care with CHOP (cyclophosphamide, doxorubicin, vincristine and prednisolone) as first-line treatment, there is an urgent need for new therapeutic modalities specifically for PTCLs (2). In recent years, various new drugs with different mechanisms of action have been approved in different countries: mogamulizumab, a humanized anti-CCR4 monoclonal antibody indicated for the treatment of relapsed or refractory CCR4-positive PTCL (6); brentuximab vedotin, a CD30-directed conjugate indicated for the treatment of CD30-positive PTCL (7,8); romidepsin and belinostat, histone deacetylase inhibitors (9,10); pralatrexate, an antifolate (11); and forodesine, a purine nucleoside phosphorylase inhibitor (12). All of these drugs have shown potential efficacy in the pivotal studies of monotherapy, but no options for further treatment are available to non-responders to these drugs. Furthermore, unmet needs still remain for drugs with new mechanisms of action and high safety that can be added to novel combination therapies.

Darinaparsin, a novel organic arsenical compound consisting of dimethylated arsenic conjugated to glutathione, has anti-tumor activity. Darinaparsin provokes cell cycle arrest at the G2/M phase, apoptosis and antiangiogenesis through the following proposed mechanisms of action: (i) disruption of mitochondrial functions; (ii) increased production of reactive oxygen species and (iii) modulation of signal transduction pathways (13,14). Arsenic trioxide (ATO), an inorganic arsenic compound, is approved for the treatment of relapsed acute promyelocytic leukemia. However, the use of ATO is limited due to its narrow range of pharmacological activity and its systemic toxicity, most notably cardiovascular toxicity (15–17). In mice, darinaparsin has a maximum tolerated dose that is 50-fold higher than ATO. Darinaparsin may be more effective than ATO, especially in neoplasms having MRP1/ABCC1 efflux pump expression, because it is not a substrate for the pump (13). The safety, tolerability, pharmacokinetics (PKs) and efficacy of darinaparsin have been examined in patients with refractory solid tumors (18), advanced/progressive multiple myeloma (19) and advanced hepatocellular carcinoma (20). In a study of relapsed/refractory Hodgkin lymphoma and NHL, darinaparsin was safe and showed preliminary activity in a heavily pretreated population of relapsed/refractory lymphoma patients, and PTCL in particular (21).

In this paper, the results of a pooled analysis of the phase I studies of darinaparsin in Japanese and Korean patients with relapsed/refractory PTCL are reported. The primary purpose of the present two studies was to evaluate safety, as assessed by dose-limiting toxicity (DLT), adverse events (AEs) and changes in the QT interval corrected by Fridericia's formula (QTcF) on electrocardiography (ECG) from the time-matched baseline (ΔQTcF), as well as to evaluate the PK profile of darinaparsin and tumor response in Japanese and Korean patients with relapsed/refractory PTCL.

To facilitate further investigation of darinaparsin for the treatment of relapsed/refractory PTCLs in the Asian region, the results of a pooled analysis of these two studies conducted in Japan and Korea, respectively, are presented.

Materials and methods

Study design

The phase I study in Japan was a multi-center, open-label, dose-escalation study to evaluate the safety, PK and preliminary efficacy of darinaparsin (Solasia Pharma K.K., Tokyo, Japan) and was conducted at 4 institutions. Two dosage regimens, darinaparsin 200 mg/m^2/day for 5 consecutive days followed by a 23-day rest in 4-week cycles (dose-schedule 1) to confirm the safety of darinaparsin in Japanese patients at a lower dose of darinaparsin, and 300 mg/m^2/day for 5 consecutive days followed by a 23-day rest in 4-week cycles (dose-schedule 2) were planned and escalated from dose-schedule 1 to 2 according to the standard '3 + 3' design. Subsequently, the study protocol was revised to add one more dosage regimen, 300 mg/m^2/day for 5 consecutive days followed by a 16-day rest in 3-week cycles (dose-schedule 3).

The Korean phase I study was a single-center, open-label study to investigate the safety, PK and preliminary efficacy of darinaparsin, with the same study design (e.g. eligibility criteria of patients, dosage and administration of investigational drugs, schedules for tests and examinations and methods of assessment) as the phase I study in Japan. This Korean phase I study was started from dose-schedule 2, because the study in Korea started later than the study in Japan, and the safety of darinaparsin in dose-schedule 1 had been confirmed in Japanese patients.

Darinaparsin was administered intravenously over ∼1 hour, and treatment was continued until disease progression or intolerable toxicities. Two studies with the same study design were conducted in each of Japan and Korea. The pooled analysis of the two studies was determined in advance in the protocols of both studies.

Patient populations

Patients aged ≥20 years, with an Eastern Cooperative Oncology Group performance status of 0–2, histopathologically diagnosed PTCLs according to the 2008 World Health Organization classification (22), including PTCL-NOS, angioimmunoblastic T-cell lymphoma (AITL) or anaplastic lymphoma kinase-positive/negative anaplastic large cell lymphoma (ALK-positive/negative ALCL), were eligible. Furthermore, patients who relapsed after or were refractory to at least 1 systemic chemotherapy regimen and had an evaluable lesion were eligible.

The key exclusion criteria were: major organ dysfunction; QT prolongation (QTcF ≥ 450 ms) and prior treatments (chemotherapy, cancer immunotherapy, radiation, autologous hematopoietic stem cell transplantation within 4 weeks before study enrolment, and allogeneic hematopoietic stem cell transplantation).

All patients provided written, informed consent. The protocol was approved by the institutional review board at each institution, and the studies were conducted in accordance with the Declaration of Helsinki.

Safety assessments

AEs were assessed after the first dosing on Day 1 of cycle 1 until the end of a 4-week follow-up and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0 (23). DLTs were assessed in cycle 1. The following drug-related AEs observed in cycle 1 were considered DLTs: grade ≥ 3 nonhematologic AEs; grade 4 neutropenia and grade ≥ 3 thrombocytopenia. Physical examination findings, vital signs, standard 12-lead ECG, arterial oxygen saturation and laboratory tests (hematology, blood chemistry, coagulation test and urinalysis) were also evaluated. ECG records were obtained at the following time points in cycle 1: −20, −22, −23 and −24 hours before the planned start time of dosing, time-matched baseline; 0, 1, 2 and 4 hours on Day 1; 0 hours on Day 2; 0, 1, 2 and 4 hours on Day 5 and 0 hours on Day 6.

Efficacy assessments

The efficacy endpoint was tumor response assessed by ^{18}F-fluorodeoxyglucose positron emission tomography and enhanced computed tomography at the ends of cycles 2 and 4 and of every 3 cycles thereafter. Response to therapy was defined according to the Revised Response Criteria for Malignant Lymphoma (24).

PK assessments

A validated assay for darinaparsin and its metabolites was not available; therefore, plasma arsenic concentrations were used as a surrogate for drug PK. The PK parameters [time to maximum concentration in plasma (T_{max}), maximum concentration in plasma (C_{max}), area under the concentration-time curve (AUC) and half-life in plasma ($t_{1/2}$)] were examined at the following time points for blood sampling in cycle 1: 0, 0.5, 1, 2, 4, 6 and 8 hours on Day 1; 0 hours on Days 2, 3 and 4; 0, 0.5, 1, 2, 4, 6 and 8 hours on Day 5 and 0 hours on Days 6, 8 and 15.

Statistical analyses

The protocols of both studies specified the pooled analysis of two studies with three analysis sets: safety analysis set, patients who received at least 1 dose of darinaparsin and were assessed for safety; efficacy analysis set, patients who underwent at least 2 cycles of darinaparsin therapy and in whom tumor response was assessed at least once for efficacy; and PK analysis set, patients who received at least 1 intravenous dose of darinaparsin, had at least 1 measured plasma drug concentration and were assessed for PK. The primary purpose of these studies was to evaluate the safety, including DLTs, during 1 cycle of treatment with darinaparsin. Treatment beyond 1 cycle was permitted as an option. On the other hand, the preliminary efficacy endpoint was the tumor response in patients who underwent at least 2 cycles of darinaparsin therapy. Therefore, the efficacy analysis set was determined in patients who underwent at least 2 cycles of darinaparsin therapy.

To confirm that the foreign clinical data obtained from Caucasian patients can be used to support the clinical dose in Asian patients, data from 6 patients in a phase I clinical study in patients with refractory solid tumors in the USA (18) were integrated into the analysis, and whether there were any obvious ethnic differences in the PK profiles between Asian (Japanese and Korean) patients and Caucasian patients was examined.

Descriptive statistics were calculated for the analysis of safety and PK. Analysis of variance with Tukey's multiple comparison test was used to examine whether there were any significant differences in the PK parameters of darinaparsin (C_{max} and AUC_{0-24}).

Results

Patients' characteristics

Seventeen patients (3 in dose-schedule 1, and 7 each in dose-schedules 2 and 3) were enrolled in the Japanese study. Six patients (3 in dose-schedule 2, and 3 in dose-schedule 3) were enrolled in the Korean study.

A total of 23 patients, with a median age of 63 (range, 22–83) years, were enrolled and treated in the studies (3 in dose-schedule 1, 10 in dose-schedule 2, and 10 in dose-schedule 3). The male/female ratio was 14/9. The most common PTCL subtype was PTCL-NOS (n = 16, 70%), followed by AITL (n = 6, 26%) and ALK-negative ALCL (n = 1, 4%). The patients' baseline characteristics are shown in Table 1.

Treatment

All 23 patients received at least 1 intravenous dose of darinaparsin: 15 of them underwent 2 or more cycles, and 8 patients (2 each in dose-schedules 1 and 2, and 4 in dose-schedule 3) discontinued treatment in cycle 1. The median number of cycles delivered to the study populations was 2 (range, 1–9). The median numbers of cycles delivered to dose-schedules 1, 2 and 3 were 1 (range, 1–3), 2.5 (range, 1–7) and 2 (range, 1–9), respectively. One patient in dose-schedule 3 underwent 9 cycles.

Safety

The safety analysis set consisted of 23 treated patients: 3, 7 and 7 Japanese patients in dose-schedules 1, 2 and 3, respectively; and 3 Korean patients each in dose-schedules 2 and 3. DLT (grade 3 hepatic dysfunction) was reported in 1 Japanese patient (4%) in dose-schedule 3 on Day 15 of cycle 1. AEs developed in all 23 treated patients (3, 10 and 10 patients in dose-schedules 1, 2 and 3, respectively). No deaths occurred during the study period.

Drug-related AEs developed in 18 patients (78%: 3, 7 and 8 patients in dose-schedules 1, 2 and 3, respectively), and those in 2 or more patients were as follows: for hematologic AEs, lymphopenia (3 patients, 13%), thrombocytopenia (3 patients, 13%), leukocytopenia (2 patients, 9%) and neutropenia (2 patients, 9%); and for nonhematologic AEs, constipation (4 patients, 17%), malaise (4 patients, 17%), pyrexia (4 patients, 17%), increased alanine aminotransferase (4 patients, 17%), increased aspartate aminotransferase (4 patients, 17%), nausea (4 patients, 17%), prolonged activated partial thromboplastin time (aPTT; 4 patients, 17%), decreased appetite (3 patients, 13%), somnolence (3 patients, 13%), herpes zoster (2 patients, 9%), hallucinations (2 patients, 9%), increased C-reactive protein (2 patients, 9%) and increased alkaline phosphatase (2 patients, 9%).

Grade 3/4 AEs developed in 13 patients (57%: 3, 4 and 6 patients in dose-schedules 1, 2 and 3, respectively): 3 (13%: 0, 1 and 2 patients in dose-schedules 1, 2 and 3, respectively) of whom experienced drug-related AEs. Drug-related, grade 3/4 AEs developed as follows: for hematologic AEs, lymphopenia, thrombocytopenia and neutropenia in 2 patients each (9%), as well as leukocytopenia, anemia and febrile neutropenia in 1 patient each (4%); and for non-hematologic AEs, nausea, prolonged aPTT and hepatic dysfunction in 1 patient each (4%) (Table 2). Serious AEs developed in 9 patients (39%: 2, 4 and

Table 1. Patients' demographic characteristics

Characteristic	Dose schedule			All (N = 23)
	1: 200 mg/m^2/day for 4 weeks (n = 3)	2: 300 mg/m^2/day for 4 weeks (n = 10)	3: 300 mg/m^2/day for 3 weeks (n = 10)	
Median age, y (range)	43 (33–70)	67 (22–83)	62.5 (34–79)	63 (22–83)
Sex, n (%)				
Male	0	7 (70)	7 (70)	14 (61)
Female	3 (100)	3 (30)	3 (30)	9 (39)
Ethnicity, n (%)				
Japanese	3 (100)	7 (70)	7 (70)	17 (74)
Korean	0	3 (30)	3 (30)	6 (26)
Number of prior treatments				
Median	3	1.5	2	2
Range	2–3	1–4	1–3	1–4
ECOG performance status, n (%)				
0	2 (67)	9 (90)	6 (60)	17 (74)
1	1 (33)	1 (10)	4 (40)	6 (26)
2	0	0	0	0
Histopathology of lymphomas, n (%)				
PTCL-NOS	2 (67)	5 (50)	9 (90)	16 (70)
AITL	1 (33)	4 (40)	1 (10)	6 (26)
ALCL, ALK-negative	0	1 (10)	0	1 (4)
ALCL, ALK-positive	0	0	0	0
Clinical stage by Ann Arbor classification, n (%)				
Stage I	0	0	0	0
Stage II	1 (33)	1 (10)	3 (30)	5 (22)
Stage III	1 (33)	6 (60)	1 (10)	8 (35)
Stage IV	1 (33)	3 (30)	6 (60)	10 (43)

ECOG, Eastern Cooperative Oncology Group; PTCL-NOS, peripheral T-cell lymphoma-not otherwise specified; AITL, angioimmunoblastic T-cell lymphoma; ALCL, anaplastic large cell lymphoma; ALK, anaplastic lymphoma kinase.

3 patients in dose-schedules 1, 2 and 3, respectively): 2 (9%) of whom experienced 2 episodes of drug-related serious AEs (1 episode each of grade 1 pyrexia and grade 2 hallucinations in dose-schedules 1 and 3, respectively).

Darinaparsin caused no obvious changes in electrocardiographic parameters (heart rate, RR interval, QRS interval, PR interval, QT interval and QTcF) from baseline. Four patients (1 patient received 200 mg/m^2/day and 3 patients received 300 mg/m^2/day) had at least 1 episode of ΔQTcF >30 ms. A prolonged QT interval with a QTcF >500 ms or a ΔQTcF >60 ms was not seen. QTcF at post-dose steady state was 3.5 $\pm$ 13.7 ms. No dose- or treatment duration-dependent effect of arsenic on QTcF was identified (Fig. 1). No association between plasma arsenic concentration and ΔQTcF was found (Fig. 2). No clinically relevant changes in vital signs, hematology, blood chemistry, coagulation testing and urinalysis were observed.

One Japanese patient, who had been diagnosed with AITL, was enrolled in dose-schedule 2 and then developed grade 4, drug-related, diffuse large B-cell lymphoma (DLBCL) as a secondary malignancy. Rash, which was observed at the time of enrolment, was exacerbated after the administration of darinaparsin. Repeated biopsies of palpable erythema in the neck showed that the patient had Epstein–Barr virus-positive DLBCL. The investigator reported this AE as related to the investigational drug. However, the Efficacy and Safety Assessment Committee decided that the palpable erythema was not associated with darinaparsin because of its development as early as Day 17 of cycle 1 (12 days after the completion of administration).

Efficacy

Of a total of 23 treated patients, 9 were excluded from the efficacy assessment according to the predefined terms of the protocol because they did not receive 2 or more cycles of darinaparsin therapy or were not evaluated for tumor response. Consequently, the efficacy analysis set consisted of 14 patients: 1, 5 and 4 Japanese patients in dose-schedules 1, 2 and 3, respectively; and 3 and 1 Korean patients in dose-schedules 2 and 3, respectively.

All responses, including 1 complete response (CR) and 3 partial responses (PRs), were obtained in patients with relapsed/refractory PTCL-NOS. The results of the assessments of tumor responses are shown in Table 3. The maximum tumor shrinkage rates are shown in the form of waterfall plots (Fig. 3), with the highest rate of 89.5%, and 10 of 14 patients showed tumor shrinkage. In 5 of 6 patients with stable disease (SD), tumor reduction was observed.

Pharmacokinetics

The PK analysis set consisted of 23 treated patients: 3 Japanese patients received darinaparsin 200 mg/m^2/day and 14 Japanese patients and 6 Korean patients received darinaparsin 300 mg/m^2/day.

The C_{max} was reached within 1 hour after the completion of the ~1-hour intravenous infusion of darinaparsin. Subsequently, plasma arsenic concentrations decreased exponentially, with a half-life of 15.3–22.0 hours and 20.6–25.3 hours in Japanese and Korean patients, respectively (Table 4). Furthermore, time-course changes

Table 2. Drug-related hematologic and nonhematologic adverse events, grades 1–2 (≥2 cases) and ≥grade 3 (≥1 case)

	Dose schedule									Total (N = 23)		
	1: 200 mg/m^2/day for 4 weeks (n = 3)			2: 300 mg/m^2/day for 4 weeks (n = 10)			3: 300 mg/m^2/day for 3 weeks (n = 10)					
Grade	1–2	3	4	1–2	3	4	1–2	3	4	1–2	3	4
Hematologic												
Lymphopenia	1	0	0	0	0	1	0	1	0	1 (4%)	1 (4%)	1 (4%)
Thrombocytopenia	0	0	0	1	0	0	0	1	1	1 (4%)	1 (4%)	1 (4%)
Leukocytopenia	0	0	0	0	0	0	1	0	1	1 (4%)	0	1 (4%)
Neutropenia	0	0	0	0	0	0	0	1	1	0	1 (4%)	1 (4%)
Anemia	0	0	0	0	0	0	0	1	0	0	1 (4%)	0
Febrile neutropenia	0	0	0	0	0	0	0	1	0	0	1 (4%)	0
Nonhematologic												
Constipation	0	0	0	3	0	0	1	0	0	4 (17%)	0	0
Malaise	2	0	0	1	0	0	1	0	0	4 (17%)	0	0
Pyrexia	2	0	0	1	0	0	1	0	0	4 (17%)	0	0
Increased ALT	0	0	0	2	0	0	2	0	0	4 (17%)	0	0
Increased AST	0	0	0	2	0	0	2	0	0	4 (17%)	0	0
Nausea	0	0	0	2	0	0	1	1	0	3 (13%)	1 (4%)	0
Prolonged aPTT	0	0	0	1	0	0	2	1	0	3 (13%)	1 (4%)	0
Decreased appetite	0	0	0	3	0	0	0	0	0	3 (13%)	0	0
Somnolence	2	0	0	1	0	0	0	0	0	3 (13%)	0	0
Herpes zoster	1	0	0	1	0	0	0	0	0	2 (9%)	0	0
Hallucinations	0	0	0	1	0	0	1	0	0	2 (9%)	0	0
Increased CRP	1	0	0	1	0	0	0	0	0	2 (9%)	0	0
Increased ALP	0	0	0	1	0	0	1	0	0	2 (9%)	0	0
Hepatic dysfunction	0	0	0	0	0	0	0	1	0	0	1 (4%)	0

ALT, alanine aminotransferase; AST, aspartate aminotransferase; aPTT, activated partial thromboplastin time; CRP, C-reactive protein; ALP, alkaline phosphatase.

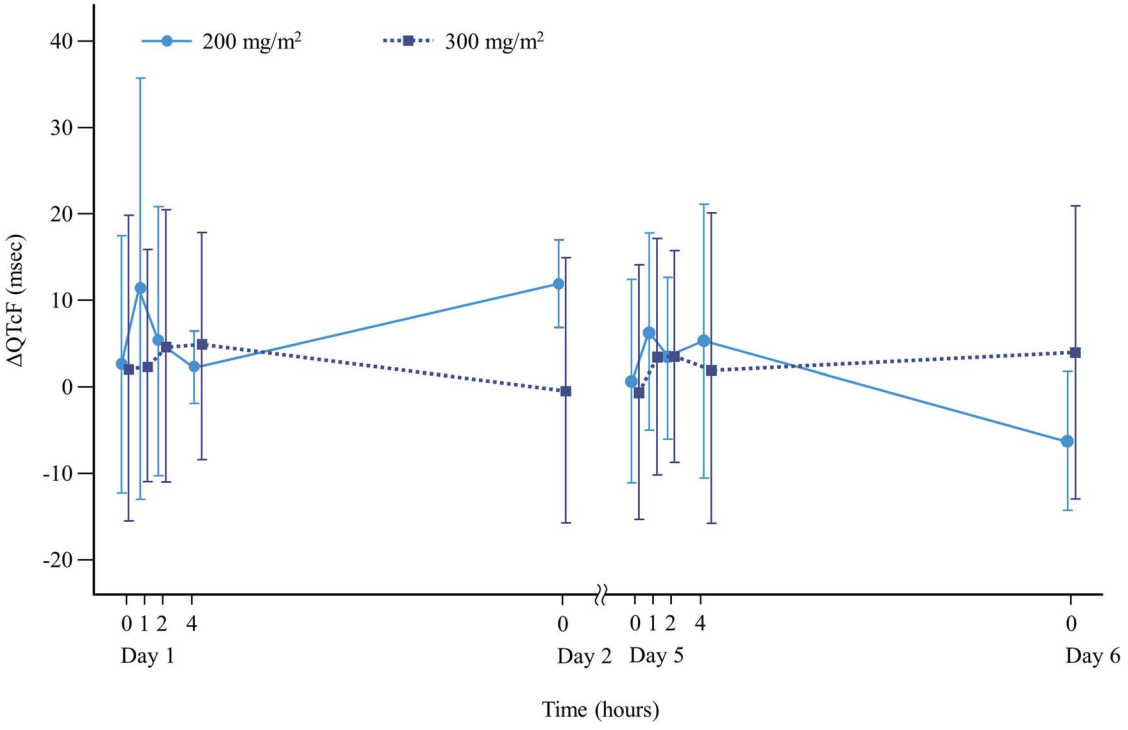

Figure 1. Time-course changes in mean ΔQTcF from the time-matched baseline after the intravenous administration of darinaparsin. Bars represent means ± standard deviation.

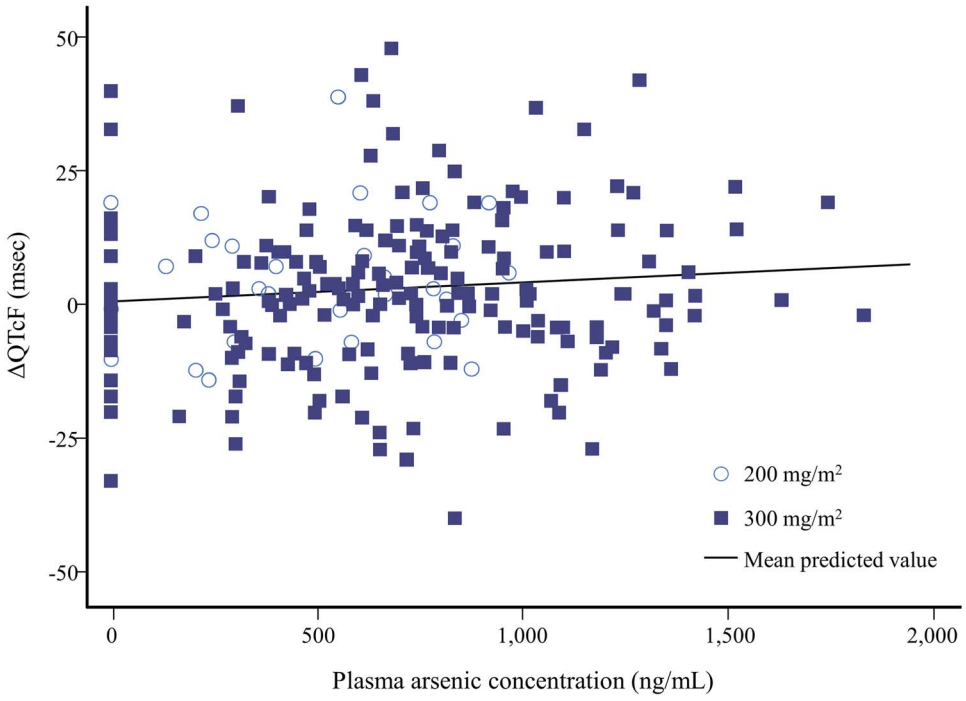

Figure 2. Scatter diagram of ΔQTcF versus plasma darinaparsin concentration.

Table 3. Tumor response

Dose-schedule	Histological subtype of tumor	Tumor response						Best tumor response
		Cycle 2	Cycle 3	Cycle 4	Cycle 6	Cycle 7	Cycle 9	
1: 200 mg/m²/day for 4 weeks	AITL	SD	PD					SD
2: 300 mg/m²/day for 4 weeks	PTCL-NOS	SD		PR	CR			CR
	PTCL-NOS	PR		SD				PR
	PTCL-NOS	SD						SD
	PTCL-NOS	SD		SD		SD		SD
	PTCL-NOS	SD	PD					SD
	ALCL ALK-negative	SD						SD
	AITL	PD						PD
	AITL	PD						PD
3: 300 mg/m²/day for 3 weeks	PTCL-NOS	SD		PR		SD		PR
	PTCL-NOS	PR		PR		PR	PR	PR
	PTCL-NOS	SD		SD	PD			SD
	PTCL-NOS	PD						PD
	PTCL-NOS	PD						PD

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

in plasma trough concentrations of arsenic suggested that plasma arsenic concentrations reached steady-state around Day 4. The mean C_{max} and the mean AUC_{0-24} in Japanese and Korean patients on Day 5 were 1.3- to 1.7-fold and ~1.5-fold higher than those on Day 1, respectively. Therefore, this suggested that darinaparsin accumulated slightly during 5-day consecutive administration. However, darinaparsin was considered not to accumulate as extensively as to be carried over into the next cycle, because plasma arsenic concentrations decreased to less than the detection limit (50 ng/ml) in all patients on Day 15 (data not shown).

Discussion

To date, a phase I study of darinaparsin in patients with refractory solid tumors (18), a phase I/II study in patients with advanced/progressive multiple myeloma (19), a phase II study in patients with advanced hepatocellular carcinoma (20) and a phase II study in patients with relapsed/refractory Hodgkin lymphoma and NHL (21) have been reported in western countries. In the study of relapsed/refractory Hodgkin lymphoma and NHL, encouraging responses were seen in PTCL (21). The present study is the first clinical study to limit the target population to patients with PTCL.

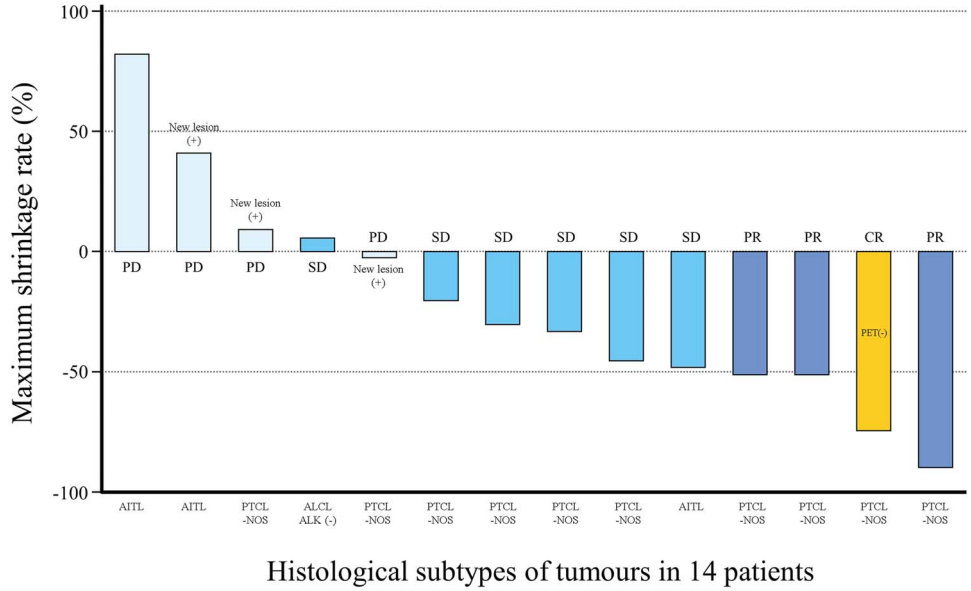

Figure 3. Maximum tumor shrinkage rates from baseline in 14 evaluable patients with PTCL. AITL, angioimmunoblastic T-cell lymphoma; PTCL-NOS, peripheral T-cell lymphoma-not otherwise specified; ALCL ALK (−), anaplastic lymphoma kinase-negative anaplastic large cell lymphoma.

Table 4. Plasma pharmacokinetic parameters on Days 1 and 5 during the 5-day consecutive, intravenous infusion of darinaparsin to Japanese and Korean patients with PTCL

	Japanese patients with PTCL		Korean patients with PTCL
	200 mg/m^2/day (n = 3)	300 mg/m^2/day (n = 14)	300 mg/m^2/day (n = 6)
Day 1			
C_{max} (ng/ml)	688 ± 116	838 ± 180	708 ± 81
T_{max} (h)	1 (1, 4)	1 (1, 6)	2 (1, 2)
$t_{1/2}$ (h)	15.3 ± 2.6	19.5 ± 6.3	20.6 ± 2.8
$AUC_{0–24}$ (ng·h/ml)	8728 ± 1893	12759 ± 3419	11282 ± 905
$AUC_{0–\infty}$ (ng·h/ml)	13237 ± 3719	22493 ± 8073	20381 ± 2878
Day 5			
C_{max} (ng/ml)	884 ± 74	1314 ± 333	1063 ± 166
T_{max} (h)	2 (1, 2)	1 (1, 4)	1 (1, 2)
$t_{1/2}$ (h)	15.8 ± 1.9	22.0 ± 6.0	25.3 ± 9.2
$AUC_{0–24}$ (ng·h/ml)	13130 ± 2575	21236 ± 6004	17591 ± 3695
C_{max} ratio (day 5/day 1)	1.3 ± 0.1	1.6 ± 0.2	1.5 ± 0.2
$AUC_{0–24}$ ratio (day 5/day 1)	1.5 ± 0.1	1.7 ± 0.2	1.5 ± 0.2

Mean ± standard deviation for C_{max}, AUC and $t_{1/2}$; median (min, max) for T_{max}.

C_{max}, observed maximum plasma concentration; T_{max}, time at which C_{max} was observed; $AUC_{0–24}$, area under the concentration-time curve over the once daily dosing interval of 0–24 hours; $AUC_{0–\infty}$, area under the concentration-time curve from time 0 to infinity; $t_{1/2}$, apparent terminal elimination half-life.

In a phase II study reported by Hosein et al. (21), 29 heavily pretreated patients with malignant lymphomas (7 with Hodgkin lymphoma and 22 with NHL) received intravenous darinaparsin 300 mg/m^2/day for 5 consecutive days every 4 weeks, with a median follow-up of 6.4 months (range, 0.9–35.7 months); the overall response rate (ORR) was 17.2% (95% CI: 5.9–35.8%), with 1 CR, 1 unconfirmed CR (CRu) and 3 PRs. In 7 patients with PTCL, there were 1 CR, 1 CRu and 2 SD, giving an ORR of 28.6%. In this study, the ORR of 28.6%, including 1 CR and 3 PRs, in heavily pretreated relapsed/refractory PTCL demonstrated efficacy in PTCL patients similar to that in a phase II study in the USA.

With a study design to confirm the safety and preliminary activity of darinaparsin 300 mg/m^2/day, the clinically recommended dose in the USA (21), two phase I studies were conducted in Asian countries (Japan and Korea) to examine the safety, efficacy and PK of darinaparsin in patients with relapsed/refractory PTCL. Given a potential racial difference in the safety and/or PK of darinaparsin compared with a clinical study in the USA, however, the phase I study was conducted in Japan, in which the starting dose (the dose level for dose-schedule 1) was set for the Japanese patient population at 200 mg/m^2 to ensure patients' safety.

The safety profile of darinaparsin in the present study was similar to that described in previous clinical studies in western countries (18–21). Neuropsychiatric disorders (e.g. delirium, insomnia and hallucinations) were DLTs in those studies. In the present study, no grade 3 or higher neuropsychiatric disorders were observed, but

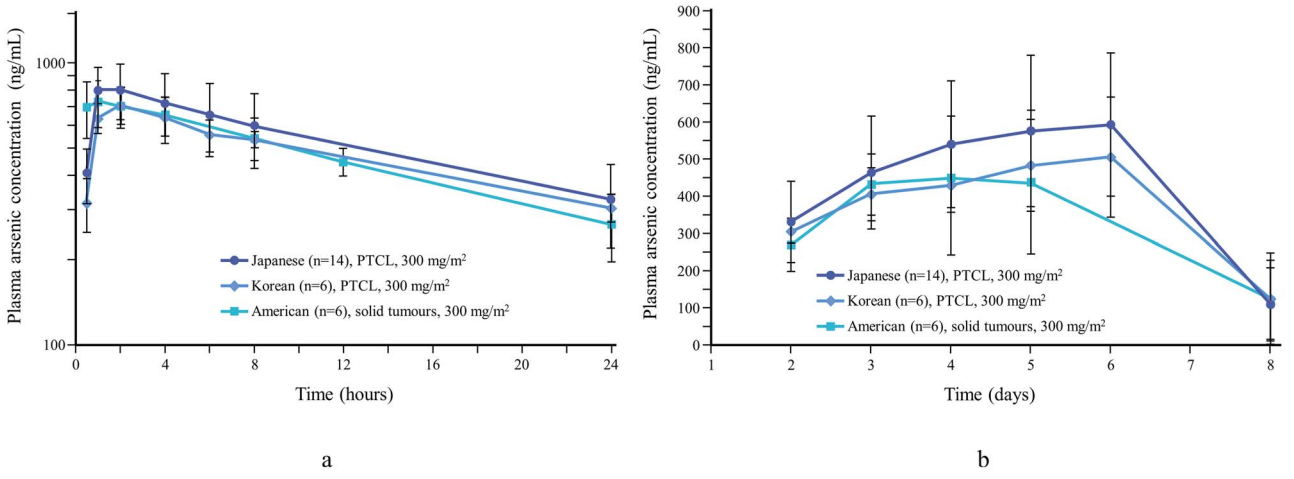

Figure 4. (a) Time-course changes in plasma arsenic concentrations on Day 1 during the 5-day consecutive, intravenous infusion of darinaparsin 300 mg/m^2/day to Japanese, Korean and Caucasian patients with PTCL. (b) Time-course changes in plasma trough concentrations of arsenic during 8 days after the onset of administration. Bars represent means ± standard deviation.

hallucination was reported in 2 patients (9%, 1 each at grade 1 and 2), delirium in 1 patient (4%, grade 2) and insomnia in 1 patient (4%, grade 1). All of these resolved without any medication. Under the dosage and dose schedule examined in the present study, it is thought that severe neuropsychiatric disorders can be avoided and that moderate and mild neuropsychiatric disorders can be controlled by dose skip or dose reduction, or by symptomatic treatment where necessary.

Epstein–Barr virus-positive DLBCL was seen in one Japanese AITL patient and was reported by the investigator as related to darinaparsin, but because of the short period (17 days) from the first dose of darinaparsin to onset, the Efficacy and Safety Assessment Committee deemed this event to be unrelated to darinaparsin. In Epstein–Barr virus-associated malignant lymphoma, it is thought that immunosuppression leads to the reactivation of the Epstein–Barr virus and failure of cytotoxic T lymphocytes to function, and B cells infected with the virus undergo abnormal proliferation and become cancerous. Furthermore, among PTCLs, secondary onset of Epstein–Barr virus-related malignant lymphoma is known to occur in AITL (25–27). In the present study, grade 3 or higher lymphopenia was seen in 2 patients (9%), and the following adverse reactions were suspected to be opportunistic infections: herpes zoster in 2 patients (9%, 1 each at grades 1 and 2), pneumonia in 1 patient (4%, grade 2) and nasopharyngitis in 1 patient (4%, grade 1). From these results, it is thought unlikely that darinaparsin causes immunosuppression, but Epstein–Barr virus-related malignant lymphoma should continue to be carefully monitored as an important AE in future clinical studies.

QT prolongation has frequently been observed with treatment with an inorganic ATO (28,29), with a mean ± standard deviation steady-state prolongation of 47 ± 5 ms (30). In the present study using an organic arsenic compound, darinaparsin, ECG records were examined carefully and in detail, and neither obvious treatment-related changes in ECG records nor any correlation between plasma arsenic concentration and ΔQTcF was found. Furthermore, the QT interval at steady state was prolonged by up to 3.5 ± 13.7 ms.

Arsenical compounds are known to cause necrosis. In cycle 1, 23 patients received darinaparsin via the central vein; 20 of these 23 patients did so throughout the study, but the route of administration was changed from the central to a peripheral vein in 3. However, in 2 of these 3 patients, the route was again changed from the peripheral vein to a central vein due to grade 2 injection site pain and grade 2 vasculitis, respectively. There were no safety issues with central venous administration of darinaparsin. These outcomes suggest the use of the central vein to ensure the safe administration of darinaparsin.

The ethnic differences in PKs between Asian (Japanese and Korean) patients and Caucasian patients were investigated. Time-course changes in plasma arsenic concentrations on Day 1 after the intravenous infusion of darinaparsin 300 mg/m^2/day nearly overlapped, indicating comparable systemic exposures to darinaparsin in Japanese and Korean patients with PTCL and Caucasian patients with solid tumors (Fig. 4a). On the other hand, the mean plasma trough concentrations of arsenic was higher in Japanese patients with PTCL than in their Korean and Caucasian counterparts. However, no significant difference was found due to the great variations among patients. Time-course changes in plasma trough concentrations of arsenic also overlapped (Fig. 4b).

In conclusion, darinaparsin showed high safety, as demonstrated by 1 case (4%) each of grade 3 and/or 4 hematologic toxicities, by 1 case each of grade 3 nonhematologic toxicities (nausea, hepatic dysfunction and prolonged aPTT) and by the absence of grade 4 AEs. Therefore, the present study demonstrated that darinaparsin was well tolerated and provided preliminary evidence of its efficacy in relapsed/refractory PTCL. At the dose levels examined, there were no significant differences in the plasma-time concentration profiles of Japanese and Korean patients, and no significant ethnic differences were found between these Asian patients and Caucasian patients. The recommended dosing schedule of darinaparsin for subsequent clinical studies is 300 mg/m^2/day for 5 consecutive days in 3-week cycles. Based on the encouraging results of these phase I studies, a multicenter, phase II, clinical study is ongoing in Asian patients with relapsed/refractory PTCL.

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Conflict of interest statement

Michinori Ogura has received personal fees from Celgene, Celltrion, Chugai Pharmaceutical, Denovo Biopharma, Eisai, Meiji Seika Pharma, Mundipharma, SymBio Pharmaceuticals, Teva Takeda Pharma and Verastem. Won-Seog Kim has received research funds from Celltrion, Johnson & Johnson, Kyowa Kirin, Mundipharma, Pfizer, Roche and Takeda Pharmaceutical. Toshiki Uchida has received personal fees from Bristol-Myers Squibb, Celgene, Chugai Pharmaceutical, Eisai, Janssen Pharmaceutical, Kyowa Kirin, Mundipharma, Nippon Shinyaku, Novartis Pharma, Ono Pharmaceutical, Otsuka Pharmaceutical, Pfizer and Takeda Pharmaceutical. Kenichi Ishizawa has received personal fees from Astellas Pharma, Celgene, Chugai Pharmaceutical, Eisai, Janssen Pharmaceutical and MSD; research funds from AbbVie, Otsuka Pharmaceutical, Pfizer and Sanofi; and grants from Kyowa Kirin and Takeda Pharmaceutical. Hirokazu Nagai has received personal fees and research funds from Celgene, Chugai Pharmaceutical and Takeda Pharmaceutical; personal fees from Eisai and research funds from AstraZeneca, Bayer Yakuhin, Mundipharma, SymBio Pharmaceuticals and Zenyaku Kogyo. Kensei Tobinai has received personal fees and research funds from Celgene, Chugai Pharmaceutical, Eisai, Janssen Pharmaceutical, Kyowa Kirin, Mundipharma, Ono Pharmaceutical and Takeda Pharmaceutical; personal fees from HUYA Bioscience International and Zenyaku Kogyo; and research funds from AbbVie, GlaxoSmithKline and Servier. Fumiko Nagahama and Yusuke Sonehara are employees of Solasia Pharma. The other authors declare that they have no conflict of interest.

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