Multicenter phase II study of plitidepsin in patients with relapsed/refractory non-Hodgkin's lymphoma

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ABSTRACT

This phase II clinical trial evaluated the efficacy, safety and pharmacokinetics of plitidepsin 3.2 mg/m^2 administered as a 1-hour intravenous infusion weekly on days 1, 8 and 15 every 4 weeks in 67 adult patients with relapsed/refractory aggressive non-Hodgkin's lymphoma. Patients were divided into two cohorts: those with non-cutaneous peripheral T-cell lymphoma (n=34) and those with other lymphomas (n=33). Efficacy was evaluated using the International Working Group criteria (1999). Of the 29 evaluable patients with non-cutaneous peripheral T-cell lymphoma, six had a response (overall response rate 20.7%; 95% confidence interval, 8.0%-39.7%), including two complete responses and four partial responses. No responses occurred in the 30 evaluable patients with other lymphomas (including 27 B-cell lymphomas). The most common plitidepsin-related adverse events were nausea, fatigue and myalgia (grade 3 in <10% of cases). Severe laboratory abnormalities (lymphopenia, anemia, thrombocytopenia, and increased levels of transaminase and creatine phosphokinase) were transient and easily managed by plitidepsin dose adjustments. The pharmacokinetic profile did not differ from that previously reported in patients with solid tumors. In conclusion, plitidepsin monotherapy has clinical activity in relapsed/refractory T-cell lymphomas. Combinations of plitidepsin with other chemotherapeutic drugs deserve further evaluation in patients with non-cutaneous peripheral T-cell lymphoma. *(clinicaltrials.gov identifier: NCT00884286)*

Introduction

Non-Hodgkin's lymphomas (NHL) are a group of lymphoid neoplasms that rank among the ten most common types of cancer. There were an estimated 65,540 newly diagnosed cases and ~19,500 deaths from this malignancy in the United States in 2010.[1] In the European Union, about 74,000 new cases were diagnosed and ~31,000 patients died due to the disease in 2008.[2] Most NHL (85-90%) are precursor or mature B-cell lymphomas, whereas the remaining 10-15% are precursor or mature T-cell lymphomas. Over the last decade, there have been improvements in the outcome and survival of patients with B-cell NHL, as a result of increasing the doses of active cytotoxic drugs and adding the anti-CD20 monoclonal antibody rituximab to chemotherapy.[3] In contrast, peripheral T-cell lymphomas (PTCL) are still associated with poorer response rates and prognosis compared to B-cell lymphoma.[4,5] The median overall survival of PTCL patients after anthracycline-based chemotherapy ranges between 20 and 34 months, with a 4- to 5-year overall survival rate between 28% and 38%.[6-8] Hence, new compounds for treating relapsed aggressive NHL, especially PTCL, constitute a truly unmet medical need.

Plitidepsin is a cyclic depsipeptide originally isolated from the Mediterranean tunicate *Aplidium albicans* and currently produced by chemical synthesis. Plitidepsin has shown activity against several human malignant cell lines, including leukemias[9,10] and lymphoma.[11] Previous phase I studies showed that a plitidepsin schedule of 1-hour intravenous (i.v.) infusions given weekly on days 1, 8 and 15 every 4 weeks was the most convenient for patients with NHL. In addition, 3.2 mg/m^2 was defined as the recommended dose for phase II studies with this schedule.[12] The objective of this phase II clinical trial was to evaluate the efficacy, safety and pharmacokinetics (PK) of plitidepsin given at this dose and schedule to adult patients with relapsed or refractory aggressive NHL.

Design and Methods

Patients were recruited at 14 investigational sites in Spain (n=6), France (n=4), Italy (n=2), Switzerland (n=1) and Peru (n=1). The study protocol was approved by the Institutional Review Board of each center and was conducted in accordance with the Declaration of Helsinki, Good Clinical Practice guidelines, and local regulations. Signed informed consent was obtained from all patients prior to any study-specific procedure.

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Eligibility criteria

Eligibility criteria included: relapsed or refractory, histologically confirmed aggressive NHL, with measurable disease (a bidimensional lesion >2 cm in its longer diameter or >5x10^9/L lymphoma cells circulating in the peripheral blood); recovery from any non-hematologic toxicities derived from previous therapies; Eastern Cooperative Oncology Group performance status score of 0-2; normal left ventricular ejection fraction; and adequate hematologic, renal, and hepatic function.

Exclusion criteria included: acute lymphoblastic leukemia; central nervous system lymphoma; human immunodeficiency virus-associated lymphoma; concomitant treatment with any anti-proliferative drug; prior doxorubicin at cumulative doses >400 mg/m^2, gene therapy with viral vectors, and/or mediastinal radiotherapy; more than three previous lines of systemic biological agents or chemotherapies; radiation, radionuclide therapy, surgery or immunosuppressive therapy within 4 weeks; nitrosoureas, high-dose chemotherapy or extensive beam radiation therapy within 6 weeks; other chemotherapies or biological agents within 3 weeks; other investigational product within 30 days; history of neoplastic disease (except for non-melanoma skin cancer, carcinoma *in situ*, or any other cancer curatively treated and with no evidence of disease for >10 years); history of significant neurological or psychiatric disorders; and other relevant diseases and medical conditions (e.g., unstable angina, myocardial infarction, valvular heart disease or congestive heart failure, symptomatic arrhythmia, uncontrolled arterial hypertension despite optimal therapy, abnormal electrocardiogram, active infection, significant non-neoplastic liver disease, and uncontrolled endocrine disease). Patients also had to use appropriate contraceptive measures.

Study treatment

Plitidepsin (PharmaMar, Colmenar Viejo, Madrid, Spain) was administered through a central or peripheral venous line as a 1-hour infusion at a dose of 3.2 mg/m^2 weekly on days 1, 8 and 15 every 4 weeks. Prophylactic premedication consisted of glucocorticoids (dexamethasone 8 mg i.v.), 5-HT3 antagonists (ondansetron or equivalent), an H_1-receptor antagonist (diphenhydramine hydrochloride 25 mg i.v. or equivalent) and an H_2-receptor antagonist (ranitidine 50 mg i.v.). Therapeutic use of hematopoietic colony-stimulating factors was allowed. No other antineoplastic therapy was permitted (except for pain management, imminent bone fractures or spinal cord compression). Plitidepsin was administered until progressive disease, clinical deterioration, or unacceptable toxicity.

Two dose reductions, at most, were allowed for the following adverse events: febrile neutropenia; grade 4 neutropenia lasting >5 days; grade 3/4 thrombocytopenia; grade 3/4 nausea/vomiting despite adequate prophylaxis; grade ≥2 increase in bilirubin; grade 3/4 increase in alanine aminotransferase (ALT) or aspartate aminotransferase (AST); grade 3/4 increase in alkaline phosphatase; grade ≥2 muscular toxicity [creatine phosphokinase (CPK) increase, myalgia and/or muscular weakness]; or any other grade 3/4 non-hematologic toxicity.

Efficacy assessment

Efficacy was assessed every 8 weeks using magnetic resonance imaging or computed tomography. Treated patients who had at least one disease assessment were considered evaluable for efficacy. The primary efficacy endpoint was the best overall response rate, defined as the combined rate of complete response, unconfirmed complete response and partial response according to the International Working Group criteria for NHL.[13] Time-to-event endpoints were secondary efficacy endpoints.

Safety assessment

All patients who received at least part of one plitidepsin infusion were considered evaluable for safety. Adverse events were graded according to the National Cancer Institute-Common Toxicity Criteria (NCI-CTC), v. 3.0. Safety was evaluated throughout the study and for up to 30 days after administration of the last dose of plitidepsin, and all patients were followed until recovery from any drug-related adverse events.

Statistical methods

Sample size was based on the primary endpoint (overall response rate). A Simon's two-stage design[14] was adopted to test the null hypothesis that P≤0.10 *versus* the alternative that P≥0.25. The expected sample size was 40 patients. Sixteen patients were to be enrolled in the first stage, regardless of their type of lymphoma. The study was to be terminated due to lack of efficacy if no responses occurred in this stage. If at least one response occurred, the study was to continue until the expected total of 40 evaluable patients had been accrued.

After the accrual of 42 evaluable patients with relapsed/refractory lymphoma of any type (including 12 PTCL without cutaneous lymphoma), an extension cohort of 16 patients with non-cutaneous PTCL was recruited. Hence, expected accrual was 58 evaluable patients, 28 of whom with non-cutaneous PTCL. If ≥7 of these 28 patients were responders, the hypothesis that P≥0.350 for non-cutaneous PTCL was to be rejected (β=0.182) and this schedule would no longer be evaluated in this setting. Otherwise, if ≥8 non-cutaneous PTCL patients were responders (i.e., an overall response rate of 28.6%), the null hypothesis *P*≥0.150 would be rejected (α=0.049) and the plitidepsin schedule would be considered promising in this indication.

Statistical analyses

Both efficacy and safety analyses were conducted separately for the cohort of patients with non-cutaneous PTCL and for the cohort of patients treated for other lymphomas. The primary endpoint (overall response rate) was calculated using descriptive statistics (95% confidence interval and range). Time to progression, time to subsequent chemotherapy, progression-free survival and overall survival were analyzed by the Kaplan-Meier method. Time to response onset and duration of response were analyzed by calculating the median and range of values.

Pharmacokinetic analyses

Blood samples (5 mL) for PK evaluation were collected at predefined times at the first plitidepsin infusions (0, 0.5-0.83, 1.42-2, 3-4, 5.5-8.5, 20-33 and 168 hours after the start of the infusion) from patients recruited into the second stage of the study (i.e., excluding the 16 patients recruited into the first stage, regardless of lymphoma type). Blood samples were taken from the arm not receiving the infusion. A 3-mL aliquot of whole blood was stored at -20°C. Whole blood concentrations of plitidepsin were determined using a validated high performance liquid chromatography system coupled with electrospray ionization tandem mass spectrometry (HPLC-MS/MS) method.[15] Complete concentration-time profiles of plitidepsin were analyzed by standard non-compartmental methods.

Results

Patients' characteristics

Non-cutaneous peripheral T-cell lymphomas

Thirty-four patients were enrolled (Table 1). Twenty-

three (67.6%) had stage III-IV disease at diagnosis. All had refractory (n=18, 52.9%) or relapsed (n=16, 47.1%) disease at baseline, 16 (47.1%) had extranodal disease and seven (20.6%) had bone marrow involvement. All patients had received prior systemic therapy, with a median of two lines (range, 1-5 lines) per patient. Other prior therapies comprised radiotherapy (n=8, 23.5%) and stem cell transplantation (n=9, 26.5%).

Other lymphomas

Thirty-three patients were included in this cohort (Table 1). Twenty-four (72.7%) had stage III-IV disease at diagnosis. Most (n=24, 72.7%) had refractory disease at baseline, while the other nine (27.3%) had relapsed disease. Eighteen (54.5%) had extranodal disease and seven (21.2%) had bone marrow involvement. Prior systemic therapy was given to all patients, with a median of three lines (range, 1-10 lines) per patient. In addition, prior radiotherapy was given to 11 patients (33.3%) and seven underwent stem cell transplantation (21.2%).

Treatment and dosing

Non-cutaneous peripheral T-cell lymphomas

A total of 77 plitidepsin cycles were administered, with a median of two cycles per patient (range, 1-8 cycles). The median relative dose intensity was 87.4%. Most patients (n=21; 65.6%) discontinued the study treatment due to disease progression (Figure 1).

Other lymphomas

A total of 57 plitidepsin cycles were administered, with a median of 1.5 cycles per patient (range, 1-4 cycles). The median relative dose intensity was 94.6%. Most patients (n=28; 87.5%) discontinued the study treatment due to disease progression (Figure 1).

Efficacy

Three patients with non-cutaneous PTCL and two with other lymphomas were excluded from the efficacy analysis (Figure 1). The reasons for exclusion were no tumor evaluations during treatment (n=2); lesions not measurable according to International Working Group criteria; having an active infection at study entry; and wrong diagnosis (lung carcinoma instead of aggressive NHL) (n=1 each). Figure 2 shows a waterfall chart of the changes in tumor size that occurred in 32 patients with bidimensional measurements taken from the same lesions at baseline and during treatment with plitidepsin: 16 with non-cutaneous PTCL and 16 with other lymphomas.

Non-cutaneous peripheral T-cell lymphomas

Six patients showed an objective response to plitidepsin (two complete responses and four partial responses; overall response rate = 20.7%, 95% CI, 8.0%-39.7%) (Table 2). The histologies of the six responding patients comprised angioimmunoblastic T-cell lymphoma (n=3, including both patients with complete responses) and PTCL (n=3). Both patients who achieved a complete response had previously received high-dose therapy and stem cell transplantation: one received eight cycles and achieved long-term remission (lasting for 27.9 months), and the other one showed a bone marrow complete morphological remission for 2.8 months. The median duration of response was 2.2 months (range, 0-27.9 months), with the response lasting for >14 weeks in two patients (6.9%); one patient with partial response developed septic shock unrelated to treatment shortly after a response had been documented and was withdrawn from the study. In addition, six patients had disease stabilization. The median time to progression was 1.6 months (95% CI, 1.1-3.0 months), the median progression-free survival was 1.6 months (95% CI, 1.1-2.7 months), and the median overall survival was 10.2 months (95% CI, 4.4-24.3 months). The time to progression was ≥3 months in six patients.

Other lymphomas

None of these patients responded to plitidepsin (Table 2). The median time to progression/progression-free sur-

Table 1. Demographic and baseline characteristics of the patients.

Characteristic	Non-cutaneous PTCL (n=34)		Other lymphomas (n=33)	
	N.	%	N.	%
Age (years) (median, range)	58 (22-80)		63 (17-79)	
Gender				
Male	24	70.6	22	66.7
Female	10	29.4	11	33.3
ECOG PS				
0-1	27	79.4	24	72.7
2	7	20.6	9	27.3
Type of lymphoma				
Mature B-cell neoplasms				
Diffuse large B-cell lymphoma	-	-	20	60.6
Mantle-cell lymphoma	-	-	5	15.2
Follicular lymphoma	-	-	3	9.1
Burkitt's lymphoma	-	-	1	3.0
Mature T-cell neoplasms				
Peripheral T-cell lymphoma NOS	17	50.0	-	-
Angioimmunoblastic T-cell lymphoma		9	26.5	- -
Anaplastic large-cell lymphoma, primary systemic type	5	14.7	-	-
Anaplastic large-cell lymphoma, primary cutaneous type	-	-	2	6.1
Extranodal NK/T-cell lymphoma	3	8.8	-	-
Precursor T-cell neoplasms				
Precursor T-lymphoblastic lymphoma	-	-	2	6.1
Ann Arbor Lymphoma Staging at diagnosis				
I	4	11.8	2	6.1
II	7	20.6	6	18.2
III	10	29.4	2	6.1
IV	13	38.2	22	66.7
UK	-	-	1	3.0
Disease at baseline				
Refractory	18	52.9	24	72.7
Relapsed	16	47.1	9	27.3
Sites of disease at baseline				
Lymph nodes	30	88.2	27	81.8
Extranodal	16	47.1	18	54.5
Bone marrow	7	20.6	7	21.2
Previous therapy				
Radiotherapy	8	23.5	11	33.3
Stem cell transplantation	9	26.5	7	21.2
Systemic therapy	34	100	33	100
Number of previous systemic therapy lines (median, range)	2 (1-5)		3 (1-10)	

PTCL: peripheral T-cell lymphoma; ECOG PS: Eastern Cooperative Oncology Group performance status; NOS: not otherwise specified; UK: unknown.

vival was 1.3 months (95% CI, 0.8-1.6 months), and the median overall survival was 4.5 months (95% CI, 2.7-6.4 months).

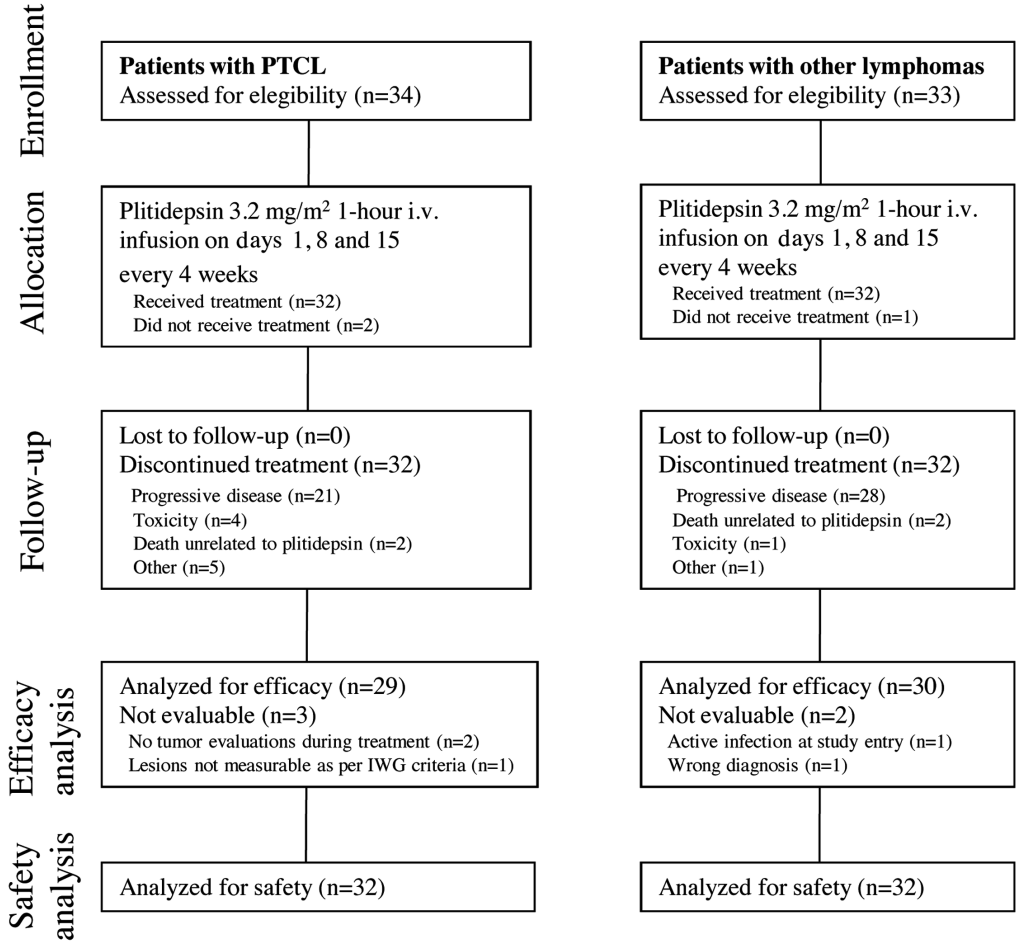
Safety

Most treatment-related adverse events were mild/moderate (Table 3). The most common were nausea, fatigue and myalgia. Seven patients had grade 3/4 treatment-related adverse events. These comprised muscle weakness (n=2), Guillain-Barré syndrome, increased cardiac troponin I, decreased ejection fraction (all three with an unknown relationship to treatment), prolonged QTc interval on an electrocardiogram, supraventricular arrhythmia, tachycardia, myalgia, back pain, injection site reaction, fatigue and edema (n=1 each).

The most common severe hematologic abnormalities were grade 3 anemia and grade 3/4 lymphopenia (Table 3). All patients with severe anemia and most of those with severe neutropenia or thrombocytopenia already had these abnormalities at baseline. No cases of febrile neutropenia were found. Most severe biochemical abnormalities did not reach grade 4. The most common were grade 3 increases in ALT/AST and grade 3/4 increases in CPK; all these abnormalities were transient and were managed with dose delays, omissions or reductions, and none resulted in treatment discontinuation. Other severe biochemical abnormalities were less common and had no effects on treatment. Of note, three patients with ALT/AST increases and all those with severe increases in alkaline phosphatase or bilirubin levels while on plitidepsin already showed these abnormalities at baseline. Five patients were withdrawn from the study due to treatment-related adverse events: grade 2 CPK increase (n=2); maculo-papular rash; a combination of hypotension, rigors, injection site reaction and back pain; and asthenia concomitant with muscular toxicity (n=1 each).

Pharmacokinetics

A total of 23 patients had evaluable PK profiles, and 19 of them had a complete profile (with samples up to 168 hours) after the start of the first plitidepsin infusion. The PK profile of plitidepsin in NHL patients was characterized by a mean clearance of 7.45 L/h, a mean volume of distribution at steady state (V_{ss}) of 355 L and a mean terminal half-life of 36.5 h. A population PK model consisting of an open, three-compartment model with linear elimination and distribution from the central compartment was appropriate to describe the time course of i.v. plitidepsin whole blood concentrations in NHL patients. Univariate analyses found statistically significant direct relationships



IWG, International Working Group; PTCL, perìpheral T-cell lymphoma.

Figure 1. Study flow chart.

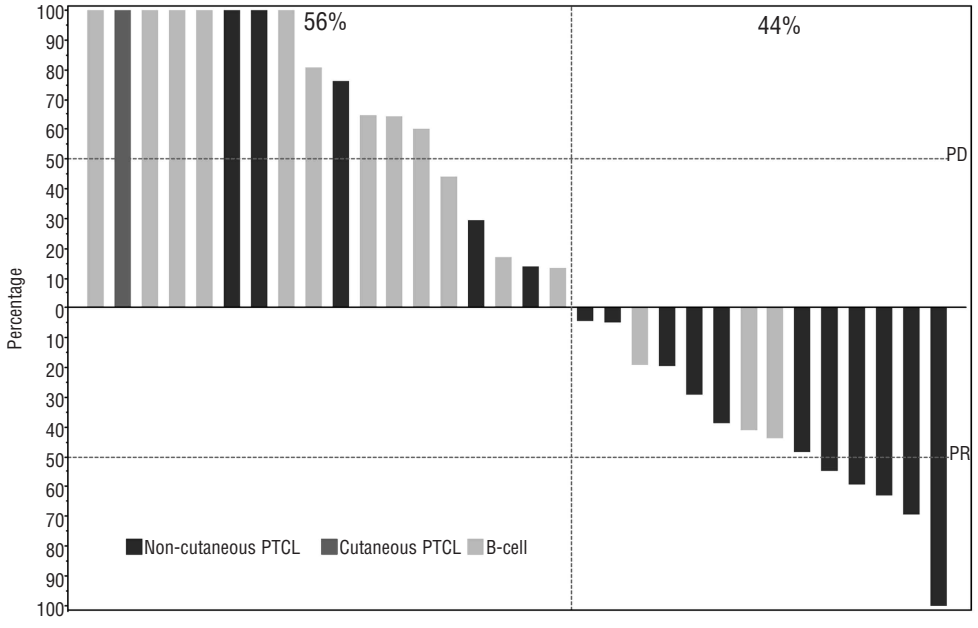


Figure 2. Waterfall chart of measurement changes in tumor size during treatment with plitidepsin in patients with measurable disease. In addition, one patient with bone marrow involvement at baseline showed a clear infiltrate on repeat bone marrow aspirates and biopsies, and was considered to have achieved a complete response.

of plitidepsin whole blood clearance with baseline hemoglobin, albumin, β_2-microglobulin, body surface area, body weight and serum creatinine; and of whole blood V_{ss} with baseline hemoglobin, serum albumin, body surface area, creatinine and body weight. In the multivariate analysis, hemoglobin was the only parameter to retain a statistically significant influence, although its significance disappeared when serum albumin was added to the model.

Discussion

This exploratory phase II clinical trial was designed to evaluate the efficacy, tolerability and PK of plitidepsin at a dose of 3.2 mg/m^2 as a 1-hour infusion given on days 1, 8 and 15 every 4 weeks to adult patients with histologically confirmed aggressive NHL that had relapsed after standard or high-dose chemotherapy, or that was refractory to its more recent chemotherapy. This schedule was evaluated in two cohorts: patients with non-cutaneous PTCL and patients with other lymphomas. PTCL is a heterogeneous form of NHL that is generally associated with a poor clinical outcome. Several drugs have been evaluated as single agents in phase II trials for PTCL (Table 4). Some (e.g., the anti-CD52 monoclonal antibody alemtuzumab or the purine nucleoside nelarabine) have shown antitumor activity for this indication but have been associated with significant and unacceptable toxicity and their development has, therefore, been discontinued.[16,17] In other cases (e.g., bortezomib, gemcitabine, lenalidomide, denileukin diftitox, romidepsin, and zanolimumab), overall response rates ranging between 24% and 55% and good safety profiles have been found, but the data currently available are still inconclusive and need to be confirmed in further clinical trials.[18-23] Finally, weekly administration of the antifolate pralatrexate for 6 weeks in 7-week cycles produced an overall response rate of 27% in adults with relapsed/refractory PTCL (with 12% of response lasting >14 weeks) while showing a toxicity profile similar to that

Table 2. Objective tumor response according to International Working Group criteria in patients with relapsed/refractory non-Hodgkin's lymphoma treated with plitidepsin.

Patient response	Non-cutaneous PTCL (n=34)		Other lymphomas (n=33)	
	N.	%	N.	%
Complete response	2	5.9	-	-
Partial response	4	11.8	-	-
Stable disease	6	17.6	6	18.2
Progressive disease	17	50.0	24	72.7
Not evaluable	5	14.7	3	9.1
ORR (95% CI)*	20.7% (8.0-39.7%)		.	

** Evaluable patients. PTCL: peripheral T-cell lymphoma; ORR: overall response rate; CI: confidence interval.*

of other antifolates. These results were considered as likely predictive of clinical benefit, and in 2009 pralatrexate was granted accelerated approval for the treatment of relapsed/refractory PTCL.[24] To date, no other drug has been approved for this indication.

In the cohort of patients with non-cutaneous PTCL, the overall response rate to plitidepsin of 20.7% in this phase II trial was lower than the 28.6% pre-established by the study protocol to consider this schedule worthy of further evaluation. However, the finding of two complete responses in patients who had been pretreated with stem cell transplantation, which in one case was long-lasting (more than 27 months) and in the other case included complete bone marrow remission for 2.8 months, suggests that plitidepsin may have a role in the management of non-cutaneous PTCL in combination with other chemotherapeutic drugs. The short median duration of response (2.2 months) achieved in this cohort is not surprising, given that the patients were heavily pretreated (median of 1.5 lines per patient). Of note, the dose of prophylactic dexamethasone given to these patients (8 mg weekly) was low and unlikely to explain this antitumor

activity. Plitidepsin induces apoptosis of tumor cells through the induction of early oxidative stress and activation of the JNK pathway. A preclinical study showed that plitidepsin combined with the cell cycle blocker gemcitabine was generally more effective than either drug alone.[25] A phase I clinical trial is currently evaluating this plitidepsin schedule combined with gemcitabine in mature non-cutaneous T-cell lymphomas.

No responses were found in the cohort with other lymphomas and, therefore, further evaluation of this plitidepsin schedule in patients with relapsed/refractory B-cell lymphomas or T-cell lymphomas other than non-cutaneous PTCL is not warranted.

Plitidepsin was generally well tolerated and showed manageable toxicity when given to patients with relapsed/refractory NHL. Most plitidepsin-related adverse events were mild or moderate. The most common were nausea, fatigue and myalgia. The most common severe hematologic abnormalities were grade 3 anemia and grade 3/4 lymphopenia, while the most common severe biochemical abnormalities were grade 3 ALT/AST and grade 3/4 CPK increases. These abnormalities were transient and were mostly managed by dosing delay, omission or reduction. The overall safety profile was in accordance with that reported in a previous phase I clinical trial with this single-agent schedule in patients with solid tumors.[12] Of note, many of the side effects commonly induced by cytotoxic agents, such as alopecia, mucositis/stomatitis or clinically relevant myelosuppression, were not characteristic of plitidepsin.

The PK profile of plitidepsin in NHL patients was similar to that found in patients treated with the same dose and schedule in a phase I study of patients with solid tumors.[12] The time course of plitidepsin whole blood concentrations in NHL patients was appropriately described by an open,

Table 3. Worst grade plitidepsin-related adverse events (at least 5% of patients).

Adverse event	All patients (n=64)*							
	Grade 1/2		Grade 3		Grade 4		Total	
	N.	%	N.	%	N.	%	N.	%
Plitidepsin-related adverse events								
Constipation	4	6	.	.	.	.	4	6
Diarrhea	5	8	.	.	.	.	5	8
Fatigue	15	23	.	.	1	2	16	25
Muscle cramps	4	6	.	.	.	.	4	6
Muscle weakness	4	6	1	2	1	2	6	9
Myalgia	13	20	1	2	.	.	14	22
Nausea	22	34	.	.	.	.	22	34
Pyrexia	5	8	.	.	.	.	5	8
Vomiting	9	14	.	.	.	.	9	14
Hematologic abnormalities								
Anemia	51	80	10	16	.	.	61	95
Leukopenia	17	27	2	3	2	3	21	33
Lymphopenia	24	38	17	27	4	6	45	71
Neutropenia	9	14	4	6	3	5	16	25
Thrombocytopenia	24	38	4	6	6	9	34	53
Biochemical abnormalities								
ALT increased	38	60	14	22	.	.	52	83
Amylase increased	3	6	1	2	.	.	4	8
AP increased	27	43	2	3	.	.	29	46
AST increased	42	67	7	11	.	.	49	78
CPK increased	9	15	1	2	4	7	14	23
Creatinine increased	18	28	1	2	.	.	19	30
Total bilirubin increased	19	31	1	2	.	.	20	33

** Patients evaluable for safety. Data shown are number and percentage of patients (based on patients with available data). Only laboratory abnormalities reaching grade 3 or 4 are shown. PTCL: peripheral Tcell lymphoma; ALT: alanine aminotransferase; AP: alkaline phosphatase; AST: aspartate aminotransferase; CPK: creatine phosphokinase.*

Table 4. Results of chemotherapeutic agents tested as single-agent therapies in phase II trials that included patients with relapsed/refractory peripheral T-cell lymphoma.[16-24]

Study	Drug/schedule and dose	N. of patients with PTCL	Responses in PTCL	ORR (%)	Types of response
Enblad *et al.* 2004	Alemtuzumab 30 mg i.v. qwk	14	5 / 14	36	3 CR + 2 PR
Czuczman *et al.* 2007	Nelarabine 1.5 g/m^2 i.v. on Days 1, 3 and 5 q3wk	8	1 / 8	25	1 PR
Dang *et al.* 2007	Denileukin diftitox 18 μg/kg/d x 5 d q3wk	27	13 / 27	48	6 CR + 7 PR
Zinzani *et al.* 2010	Gemcitabine 1200 mg/m^2 i.v. on Days 1, 8 and 15 q4wk	20	11 / 20	55	6 CR + 5 PR
Dueck *et al.* 2010	Lenalidomide 25 mg p.o. on Days 1-21 q4wk	23	7 / 23	30	7 PR
d'Amore *et al.* 2010	Zanolimumab 980 mg i.v. qwk	21	5 / 21	24	2 CRu + 3 PR
Coiffier *et al.* 2010	Romidepsin 14 mg/m^2 on Days 1, 8 and 15 q4wk	130	34 / 130	26	19 CR/CRu + 15 PR
Piekarz *et al.* 2011	Romidepsin 14 mg/m^2 on Days 1, 8 and 15 q4wk	31	17 / 31	55	7 CR + 10 PR
O'Connor *et al.* 2011	Pralatretaxe 30 mg/m^2 i.v. qwk for 6 weeks + 1-week rest	109	32 / 109	29	12 CR/CRu + 20 PR
Current trial	Plitidepsin 3.2 mg/m^2 i.v. on Days 1, 8, 15 q4wk	29	6 / 29	21	2 CR + 4 PR

** Only patients with cutaneous forms of the disease were included. PTCL: peripheral Tcell lymphoma; ORR: objective response rate; i.v.: intravenously; CR: complete response; PR: partial response; qwk: weekly; q3wk: every 3 weeks; q4wk: every 4 weeks; p.o.: orally; CRu: unconfirmed complete response.*

three-compartment population PK model with linear elimination and distribution from the central compartment, and a non-linear distribution to blood cells. This same model was defined for plitidepsin in a population PK meta-analysis of data from 283 patients with advanced solid tumors who received the drug as monotherapy at doses ranging from 0.13 to 8.0 mg/m^2 and at different schedules, one of which was the one evaluated in the present study.[26]

In conclusion, single-agent plitidepsin has shown antitumor activity and a tolerable safety profile in patients with relapsed/refractory non-cutaneous PTCL. These results therefore support the conduct of further clinical trials to evaluate plitidepsin-containing combined therapies in this disease setting.

Authorship and Disclosures

Information on authorship, contributions, and financial & other disclosures was provided by the authors and is available with the online version of this article at www.haematologica.org.

References

1. Jemal A, Siegel R, Xu J, Ward E. Cancer statistics, 2010. CA Cancer J Clin. 2010;60 (5):277-300.
2. Ferlay J, Parkin DM, Steliarova-Foucher E. Estimates of cancer incidence and mortality in Europe in 2008. Eur J Cancer. 2010;46 (4):765-81.
3. Feugier P, Van Hoof A, Sebban C, Solal-Celigny P, Bouabdallah R, Ferme C, et al. Long-term results of the R-CHOP study in the treatment of elderly patients with diffuse large B-cell lymphoma: a study by the Groupe d'Etude des Lymphomes de l'Adulte. J Clin Oncol. 2005;23(18):4117-26.
4. Rudiger T, Weisenburger DD, Anderson JR, Armitage JO, Diebold J, MacLennan KA, et al. Peripheral T-cell lymphoma (excluding anaplastic large-cell lymphoma): results from the Non-Hodgkin's Lymphoma Classification Project. Ann Oncol. 2002; 13(1):140-9.
5. Foss FM, Zinzani PL, Vose JM, Gascoyne RD, Rosen ST, Tobinai K. Peripheral T-cell lymphoma. Blood. 2011;117(25):6756-67.
6. Savage KJ, Chhanabhai M, Gascoyne RD, Connors JM. Characterization of peripheral T-cell lymphomas in a single North American institution by the WHO classification. Ann Oncol. 2004;15(10):1467-75.
7. Cheson BD. Novel therapies for peripheral T-cell non-Hodgkin's lymphomas. Curr Opin Hematol. 2009;16(4):299-305.
8. Howman RA, Prince HM. New drug therapies in peripheral T-cell lymphoma. Expert Rev Anticancer Ther. 2011;11(3):457-72.
9. Erba E, Serafini M, Gaipa G, Tognon G, Marchini S, Celli N, et al. Effect of Aplidin in acute lymphoblastic leukaemia cells. Br J Cancer. 2003;89(4):763-73.
10. Aplidin increases sensitivity to treatment in leukemia and lymphoma cells. Expert Rev Anticancer Ther. 2003;3(2):133-4.
11. Depenbrock H, Peter R, Faircloth GT, Manzanares I, Jimeno J, Hanauske AR. In vitro activity of aplidine, a new marine-derived anti-cancer compound, on freshly explanted clonogenic human tumour cells and haematopoietic precursor cells. Br J Cancer. 1998;78(6):739-44.
12. Izquierdo MA, Bowman A, Garcia M, Jodrell D, Martinez M, Pardo B, et al. Phase I clinical and pharmacokinetic study of plitidepsin as a 1-hour weekly intravenous infusion in patients with advanced solid tumors. Clin Cancer Res. 2008;14(10):3105-12.
13. Cheson BD, Horning SJ, Coiffier B, Shipp MA, Fisher RI, Connors JM, et al. Report of an international workshop to standardize response criteria for non-Hodgkin's lymphomas. J Clin Oncol. 1999;17(4):1244-53.
14. Simon R. Optimal two-stage designs for phase II clinical trials. Control Clin Trials. 1989;10(1):1-10.
15. Celli N, Mariani B, Di Carlo F, Zucchetti M, Lopez-Lazaro L, D'Incalci M, et al. Determination of aplidin (dehydrodidemnin B) in human plasma, whole blood and urine by liquid chromatography with electrospray ionisation tandem mass spectrometry detection. J Pharm Biomed Anal. 2004;34(3):619-30.
16. Enblad G, Hagberg H, Erlanson M, Lundin J, MacDonald AP, Repp R, et al. A pilot study of alemtuzumab (anti-CD52 monoclonal antibody) therapy for patients with relapsed or chemotherapy-refractory peripheral T-cell lymphomas. Blood. 2004;103(8):2920-4.
17. Czuczman MS, Porcu P, Johnson J, Niedzwiecki D, Kelly M, Hsi ED, et al. Results of a phase II study of 506U78 in cutaneous T-cell lymphoma and peripheral T-cell lymphoma: CALGB 59901. Leuk Lymphoma. 2007;48(1):97-103.
18. Dang NH, Pro B, Hagemeister FB, Samaniego F, Jones D, Samuels BI, et al. Phase II trial of denileukin diftitox for relapsed/refractory T-cell non-Hodgkin lymphoma. Br J Haematol. 2007;136 (3):439-47.
19. Zinzani PL, Venturini F, Stefoni V, Fina M, Pellegrini C, Derenzini E, et al. Gemcitabine as single agent in pretreated T-cell lymphoma patients: evaluation of the long-term outcome. Ann Oncol. 2010;21(4):860-3.
20. Dueck G, Chua N, Prasad A, Finch D, Stewart D, White D, et al. Interim report of a phase 2 clinical trial of lenalidomide for T-cell non-Hodgkin lymphoma. Cancer. 2010;116(19):4541-8.
21. d'Amore F, Radford J, Relander T, Jerkeman M, Tilly H, Osterborg A, et al. Phase II trial of zanolimumab (HuMax-CD4) in relapsed or refractory non-cutaneous peripheral T cell lymphoma. Br J Haematol. 2010;150 (5):565-73.
22. Coiffier B, Pro B, Prince HM, Foss FM, Sokol L, Greenwood M, et al. Final results from a pivotal, multicenter, international, open-label, phase 2 study of romidepsin In progressive or relapsed peripheral T-cell lymphoma (PTCL) following prior systemic therapy. 52nd Annual Meeting and Exposition of the American Society of Hematology (December 4-7); 2010; Orlando, FL, USA.
23. Piekarz RL, Frye R, Prince HM, Kirschbaum MH, Zain J, Allen SL, et al. Phase 2 trial of romidepsin in patients with peripheral T-cell lymphoma. Blood. 2011;117(22):5827-34.
24. O'Connor OA, Pro B, Pinter-Brown L, Bartlett N, Popplewell L, Coiffier B, et al. Pralatrexate in patients with relapsed or refractory peripheral T-cell lymphoma: results from the pivotal PROPEL study. J Clin Oncol. 2011;29(9):1182-9.
25. Mishra PJ, Longo GSA, Mishra PJ, Aracil M, Paz de Paz MF, Bertino JR, et al. Synergistic action of plitidepsin and gemcitabine against pancreatic cancer in vitro and in vivo. 100th American Association for Cancer Research Annual Meeting; 2009; Denver, CO, USA.
26. Nalda-Molina R, Valenzuela B, Ramon-Lopez A, Miguel-Lillo B, Soto-Matos A, Perez-Ruixo JJ. Population pharmacokinetics meta-analysis of plitidepsin (Aplidin) in cancer subjects. Cancer Chemother Pharmacol. 2009;64(1):97-108.