Review

DOI: 10.5582/irdr.2016.01024

Development of chidamide for peripheral T-cell lymphoma, the first orphan drug approved in China

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Summary **Peripheral T-cell lymphoma (PTCL) is a set of rare and highly heterogeneous group of mature T- and NK-cell neoplasms associated with poor outcomes and lack of standard and effective therapies. The total number of newly diagnosed cases of PTCL yearly in China is estimated about 50,000. Chidamide (CS055) is a novel and orally active benzamide class of histone deacetylase (HDAC) inhibitor that selectively inhibits activity of HDAC1, 2, 3 and 10, the enzymes that are involved and play an important role in tumor initiation and development in both tumor cells and their surrounding micro-environment. Functioning as a genuine epigenetic modulator, chidamide induces growth arrest and apoptosis in tumor cells and enhances cellular antitumor immunity. Based on the overall results from preclinical and phase I clinical studies, exploratory and pivotal phase II trials of chidamide for relapsed or refractory PTCL were conducted from March 2009 to May 2012, and the results led to CFDA approval of chidamide for the indication in December 2014, being the first approved orphan drug according to the research & development approach of orphan drugs in China, as well as the first orally active drug for PTCL in China and worldwide.**

Keywords: Chidamide, HDAC inhibitor, epigenetic, T-cell lymphoma, orphan drug

1. Introduction

Peripheral T-cell lymphoma (PTCL) is a set of rare and heterogeneous groups of mature T- and natural killer (NK)-cell neoplasms associated with poor outcomes. The median overall survival (OS) is about 1 to 3 years for various types of PTCL (*1-3*). PTCL makes up 25-30% of all NHL cases in China, with an estimated 50,000 new patients diagnosed annually. Subtype distribution of PTCL is significantly different between China and North American or European countries (*4*). According to the WHO classification, the most common subtype of PTCL in China is extranodal NK/T-cell lymphoma, nasal type (ENKL), followed by PTCL not otherwise specified (PTCL NOS), anaplastic large-cell lymphoma (ALCL), and angioimmunoblastic T-cell lymphoma (AITL) (*4,5*).

Worldwide, there is still no consensus on first-line therapy for patients with PTCL due to the rarity of the disease and the lack of randomized clinical trials. For relapsed or refractory chemotherapy sensitive patients, autologous or allogeneic stem cell transplant (SCT) following high-dose therapies is the treatment goal. To obtain this goal, clinical trials or second-line chemotherapies are suggested. The treatment options for patients who are in two or more relapses are clinical trials, best supportive care, alternative chemotherapy and palliative radiotherapy (*6*).

In Western countries, the development of new agents for the treatment of chemorefractory PTCL as second-line therapy has made great progress in recent years. Pralatrexate (an antifolate agent), romidepsin (a cyclic peptide HDAC inhibitor), and belinostat (a hydroxamate pan HDAC inhibitor), were approved by the US Food and Drug Administration (FDA) for patients with relapsed or refractory PTCL in September 2009, June 2011, and July 2014, respectively. The overall response rates (ORR) by independent central review for those three approved drugs were 29%, 25% and 26% for pralatrexate, romidepsin and belinostat, respectively (*7-9*).

Released online in J-STAGE as advance publication August 17, 2016.

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Epigenetic modifications, including DNA methylation, histone modification and nucleosome remodeling, function cooperatively to determine chromatin configuration and unique transcriptional profiles in cells. Disruption of epigenetic processes may cause altered gene function and play an essential role in malignant cellular transformation and progression (*10*). These findings have provided the rationale for epigenetic agents targeting DNA methyltransferases (DNMT) and histone deacetylases (HDAC) for cancer treatment (*11*).

Chidamide (CS055), discovered and developed by Chipscreen Biosciences, is a novel orally active HDAC inhibitor with subtype selective activity against HDAC1, 2, 3 and 10. Functioning as a genuine epigenetic modulator, chidamide induces growth arrest and apoptosis in tumor cells and enhances cellular antitumor immunity. In the current article, we present the main results from preclinical and clinical studies, with emphasis on the single agent chidamide for PTCL and its development and regulatory path as the first approved orphan drug according to the research & development approach of orphan drugs in China, as well as the first orally active drug for PTCL in China and worldwide.

2. Discovery and preclinical development

2.1. *Discovery and mechanisms of action*

HDACs are involved in the remodeling of chromatin and play a key role in the epigenetic regulation of gene expression. At least 18 human HDACs have been identified and are grouped into four classes, including class I (HDAC1, 2, 3, and 8), class II (HDAC4, 5, 7, and 9 as IIa, and HDAC6 and 10 as IIb), and class IV (HDAC11) (*12*). Elevated expression or activity of HDACs is implicated in the development and progression of cancer (*13*). Inhibition of HDAC enzymes results in increased histone acetylation, thereby inducing an open chromatin conformation and transcription of previously dormant genes. Although the precise biological functions of individual HDACs are still largely unknown, the importance of HDAC enzymes in the malignant phenotype has been most closely associated with Class I HDACs 1-3 (*12-14*).

Back in 2001, when Chipscreen was set up, we initiated an exploratory program in discovery of novel HDAC inhibitors with high subtype selectivity and oral bioavailability. Based on the large members of HDAC enzyme families and variety of enzyme structures of individual subtypes, we hypothesized that the existing HDAC inhibitors at the time with different chemical structures should have had different selectivity in HDAC subtypes, and thus elicit different biological responses. We carried out chemical genomic analysis to differentiate whether these chemically divergent inhibitors were biologically different. As a result, we found that among the HDAC inhibitors evaluated, only the benzamide class compounds, but not hydroxamic acid-based ones, exhibited induction of expression of epithelial differentiation related genes (*e.g.*, EMP1, EPLIN), T-cell receptor (TCR) and MHC I cluster genes, and death receptor 6 (DR6)-related apoptosis genes. Preferential repression of genes related to drug resistant and protein modification/degradation pathways was also observed in benzamide class compounds (*15*). These findings led us to focus on the chemical scaffold of benzamide class of HDAC inhibitors, and CS055 (later named chidamide) was discovered from a variety of benzamide-prototype compounds based on computational and medicinal chemistry, and further evaluated by chemical genomic-based analysis and other molecular biological means both *in vitro* and *in vivo*. In summary, chidamide has demonstrated to selectively inhibit activity of HDAC1, 2, 3 and 10, and to perform its anti-cancer functions as a genuine epigenetic modulator by the following mechanisms: induction of growth arrest and apoptosis in blood and lymphoid-derived tumor cells, reversal of epithelial–mesenchymal transitions and drug resistance of tumor cells, and importantly, enhancement of NK-cell and antigen-specific CD8+ cytotoxic T-lymphocyte-mediated cellular antitumor immunity (*15-19*).

2.2. *Preclinical studies*

Chidamide was initially assessed in preclinical animal studies that employed a daily dose regimen. Chidamide exhibits a broad-spectrum of anti-tumor activity *in vivo*, including activities against lung, colon, breast and liver carcinoma, evaluated by using athymic nude mice subcutaneously inoculated with different human tumor cell lines (*16*). Using a daily dose regimen, the ED_{50} in average for those animal models was 11.5 mg/kg.

Nonclinical pharmacokinetic studies were conducted in rodent and non-rodent animals after single and multiple oral dosing with a daily dose regimen. Plasma concentrations in animals were observed to be slightly less than dose-proportional across the species. Oral dosing was characterized by variable plasma elimination half-lives in different animal species, ranging from 21 to 38 hours, that was apparently independent of dose levels/exposure. In rat studies, chidamide was shown to mainly distribute to the gastrointestinal tract, pancreas, lungs and immune organs.

IND-enabling safety studies of chidamide were conducted in rats and dogs with repeat dosing for 28 days with a daily dose regimen. In rats, an every-three-day dosing regimen was also employed. All the studies incorporated toxicokinetic analyses. Overall target organ toxicities were similar in rats and dogs, regardless of dosing regimens employed. Typical findings included dose-dependent reductions in body weight and food consumption, hematologic

abnormalities, and changes in clinical chemistry parameters. In repeat toxicity studies, rats tolerated 10 times more dose exposure in animals with an every-three-day dosing regimen compared with those under a daily dose regimen, although significant accumulation of plasma drug substance was seen for both regimens from single-dose to the last dose administration in 28 days. Interestingly to note, there was no significant loss of efficacy in mice when chidamide was administered with regimens of either every-other-day or every-three-day dosing compared with a daily dose regimen when the total dose-exposure was similar with different dosing regimens in a total 28-day period of evaluations. Taken together, the efficacy and tolerance window was dramatically increased by interval dosing regimens, which formed a good foundation rationale for a phase I trial in humans.

3. Phase I study

A phase I clinical study was conducted in patients with advanced solid tumors or lymphomas (*20*). A total of 31 patients were enrolled who received oral doses of 5, 10, 17.5, 25, 32.5, or 50 mg chidamide twice weekly (BIW), or 32.5 or 50 mg chidamide three-times weekly (TIW) for four consecutive weeks, followed by a two-week drug-free holiday. A complete treatment cycle was 6 weeks. Treatment-related adverse events (AE) were mostly grade 1 (72%), with 17% grade 2 and 11% grade 3. The most common AEs were fatigue (35%, limited to grade 1), thrombocytopenia (26%), anorexia (26%), leucopenia or neutropenia (23%), reduced hemoglobin (19%), nausea (16%), and diarrhea (16%). In general, the number and severity of AEs increased with drug exposure, particularly with respect to myelosuppression and GI events. No dose-limiting toxicities (DLT) were identified in the BIW cohorts up to 50 mg. DLTs were grade 3 diarrhea and vomiting in two patients in the TIW cohort at 50 mg, respectively.

Out of the 25 patients who had measurable lesions for efficacy evaluation, there were 5 patients with partial response (PR). Four of the 5 patients (80%) with PRs were T-cell non-Hodgkin's lymphoma (T-NHL) patients assigned to the 5, 32.5, and 50 mg BIW cohorts and the 32.5 TIW cohort. The other PR patient was enrolled with adenoid cystic carcinoma of the submandibular gland and was treated in the 32.5 mg BIW cohort.

Single-dose PK studies were performed in patients who received 25, 32.5, and 50 mg chidamide, regardless of dosing schedules. Peak plasma concentrations for the majority of patients were observed within 0.5-2 h of drug administration and returned to close to baseline level within 48 h, but remained quantifiable at 72 h after a single dose. Systemic exposures (Cmax and AUC) were generally dose dependent across the 25-50 mg dose range. The elimination half-life ($t_{½}$) was similar among the different dose groups, with mean values ranging from 16.8 to 18.3 h. Preliminary multi-dose PK analysis suggested an increased systemic exposure on the TIW dosing schedule.

Inhibition of HDAC enzymes results in increased histone acetylation, which is usually considered as an important parameter for a pharmacodynamics (PD) study on HDAC inhibitors (*21*). PD analysis was carried out by examining histone H3 acetylation in peripheral white blood cells (WBCs) from 19 patients. In general, peak induction of H3 acetylation in WBCs was observed between 24 and 48 h after treatment, with increased acetylation persisting for up to > 72 h after a single dose of chidamide at 25, 32.5, and 50 mg.

Microarray gene expression studies were performed on peripheral WBCs from patients with T-cell lymphoma before and after administration of the first dose of chidamide. The expression of genes involved in immune cell-mediated antitumor functions was significantly up-regulated by chidamide dosing. Further laboratory studies have demonstrated that *ex vivo* treatment with nanomolar concentrations of chidamide enhances immune cell-mediated cytotoxicity by human peripheral mononuclear cells, accompanied by increased expression of proteins involved in NK-cell activities (*16*).

In conclusion, the phase I study showed that chidamide was generally well tolerated in patients with advanced solid tumors or lymphomas in tested regimens. Favorable PK and PD profiles were also demonstrated. Encouraging preliminary anti-tumor activity was observed, particularly from patients with T-cell lymphomas.

4. Clinical development for PTCL as an orphan drug

4.1. *Exploratory phase II trial*

The exploratory phase II trial was a multi-centered, open label, non-randomized study. Eligible patients with PTCL NOS subtype were assigned randomly to receive either 30 mg or 50 mg twice per week for 2 consecutive weeks in a 3-week-cycle. The total drug exposure for the two dosing cohorts in a 3-week period was 120 and 200 mg, respectively. Response assessment was performed once every 6 weeks, using the International Workshop to Standardize Response Criteria for Non-Hodgkin's Lymphoma (IWC). The primary endpoint was ORR, and secondary endpoints included duration of response (DOR) and progression free survival (PFS). Safety was evaluated once every 3 weeks, and AEs were graded by the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events v3.0 (CTCAE).

A total of 19 patients were enrolled in the exploratory phase II trial, including 9 patients in the 30 mg cohort and 10 patients in the 50 mg cohort. Baseline

Table 1. Baseline characteristics of the exploratory phase II trial

Characteristics	30 mg cohort (*n* = 9)	50 mg cohort (*n* = 10)	All (*n* = 19)
Gender			
Male	6 (66.7%)	8 (80.0%)	14 (73.7%)
Female	3 (33.3%)	2 (20.0%)	5 (26.3%)
Age (years)			
Median	51.0	52.0	51.0
Mean	53.2	51.9	52.5
Disease stage			
II	2 (22.2%)	1 (10.0%)	3 (15.8%)
III	3 (33.3%)	2 (20.0%)	5 (26.3%)
IV	4 (44.4%)	7 (70.0%)	11 (57.9%)
Years since first diagnosis			
Median	1.5	1.1	1.4
Range	0.2-8.1	0.2-2.5	0.2-8.1

Table 2. Adverse events in ≥ 2 patients in the exploratory phase II trial

Event	30 mg cohort (*n* = 9)		50 mg cohort (*n* = 10)		All (*n* = 19)	
	Total (%)	≥ Grade 3 (%)	Total (%)	≥ Grade 3 (%)	Total (%)	≥ Grade 3 (%)
Thrombocytopenia	3 (33.3)	2 (22.2)	6 (60.0)	4 (40.0)	9 (47.4)	6 (31.6)
Leucopenia	1 (11.1)	1 (11.1)	4 (40.0)	1 (10.0)	5 (26.3)	2 (10.5)
Fever	1 (11.1)	0	3 (30.0)	0	4 (21.1)	0
Fatigue	0	0	3 (30.0)	0	3 (15.8)	0
Anemia	1 (11.1)	1 (11.1)	1 (10.0)	0	2 (10.5)	1 (5.3)
Nausea	0	0	2 (20.0)	0	2 (10.5)	0

characteristics of patients are presented in Table 1, which did not show a significantly different distribution in these two cohorts.

One patient obtained complete response (CR) in the 30 mg cohort. Four patients responded to the treatment in the 50 mg cohort, including 1 patient with CR, 1 patient with complete response unconfirmed (CRu) and 2 patients with PR. The ORR was 11.1% (95% CI: 0.3%-48.2%) and 40.0% (95% CI: 12.2%-73.8%) for the 30 mg and 50 mg cohort, respectively. The DOR for the patient with CR in the 30 mg cohort was 1,091 days at the data cutoff date, and continued with the treatment after that. The median PFS for the 30 mg cohort was 84 days. As for the 50 mg cohort, the DORs for the 4 responding patients were 59, 259, 440 and 1,010 days. The patient with the longest DOR (1,010 days) continued the treatment after the data cutoff date. The median PFS for the cohort was 44 days.

Fourteen patients (73.7%) out of the 19 patients had at least one AE. The most common AEs (≥ 2 patients in the two cohorts in total), as listed in Table 2, were thrombocytopenia (9, 47.4%), leucopenia (5, 26.3%), fever (4, 21.1%), fatigue (3, 15.8%), anemia (2, 10.5%) and nausea (2, 10.5%). Most AEs were grade 1-2. Grade 3 AEs included thrombocytopenia (2 patients in each cohort), leucopenia (1 patient in each cohort), anemia (1 patient in the 30 mg cohort), and edema (1 patient in the 30 mg cohort). The only two Grade 4 AEs of thrombocytopenia were reported from the 50 mg cohort.

4.2. *Pivotal phase II trial*

Based on the overall results from the phase I study on patients with solid tumors/lymphomas and exploratory phase II trial in patients with PTCL NOS, together with the progress that pralatrexate was approved by FDA for relapsed or refractory PTCL under the orphan drug designation in December 2010, we initiated the process to communicate with and had positive feedback from the Center for Drug Evaluation (CDE) of the China Food and Drug Administration (CFDA) to explore the possibility to design and conduct a pivotal phase II trial for chidamide in relapsed or refractory PTCL.

The pivotal phase II trial was an open-label, single-arm, multicenter study of chidamide monotherapy. Patients with relapsed or refractory PTCL of any subtype that investigators considered as suitable were eligible for this study, but underwent a central pathology review to evaluate final eligibility. By overall evaluation of efficacy and safety profiles from the two dosing cohorts in the exploratory phase II trial, patients in the pivotal trial were administered 30 mg chidamide twice weekly without 1-week-drug-free breaks, which accounted for a total dosage of 180 mg in a 3-week period. Patients continued to receive chidamide treatment until progression of the disease, unacceptable toxicity, or patient/investigator discretion. The primary endpoint was ORR as assessed by an independent review committee. Of the 83 patients enrolled, 79 with eligible PTCL histology were for efficacy assessments.

Table 3. Baseline characteristics of the pivotal trials from the four approved drugs

Characteristics	Pralatrexate (*n* = 111)	Romidepsin (*n* = 130)	Belinostat (*n* = 120)	Chidamide (*n* = 79)
Age (years)				
Median	58.0	61	64.0	53.0
Mean	57.7	/	/	49.6
Gender				
Male	76 (68%)	88 (38%)	62 (52%)	53 (67%)
Female	35 (32%)	42 (32%)	58 (48%)	26 (33%)
Years since first diagnosis	1.3	1.3	1.0	1.1
Prior systemic therapy				
Median	3	2	2	3
Range	1~ 13	1 ~ 8	1 ~ 8	1 ~ 9
Subtype n (%)				
PTCL NOS	59 (54)	69 (53)	77 (64)	27 (34)
ALCL	17 (15)	22 (17)	15 (13)	17 (22)
ALK negative	11 (10)	21 (16)	13 (11)	11 (14)
ALK positive/unknown	6 (5)	1 (1%)	2 (2)	6 (8)
AITL	13 (12)	27 (21)	22 (18)	10 (13)
ENKL	2 (2)	1 (1)	2 (2)	16 (20)
Others	18 (17)	11 (8)	4 (3)	9 (11)

PTCL NOS, PTCL not otherwisespecified; ALCL, anaplastic large cell lymphoma; AITL, angioimmuoblastic T-cell lymphoma; ENKL, extranodal NK/T-cell lymphoma, nasal type.

Table 4. Efficacy parameters of the pivotal trials from the four approved drugs

Parameter	Pralatrexate (*n* = 109)	Romidepsin (*n* = 130)	Belinostat (*n* = 120)	Chidamide (*n* = 79)
PR, *n* (%)	20 (18)	14 (11)	18 (15)	11 (14)
CR + CRu, *n* (%)	12 (11)	19 (15)	13 (11)	11 (14)
ORR, *n* (%)	32 (29)	33 (25)	31 (26)	22 (28)
DOR > 3m, *n* (%)	13 (12)	/	/	19 (24)
PFS (month)				
Median	3.5	4.0	1.6	2.1
Range	1 day-23.9	/	/	1 day-44.9
OS (month)				
Median	14.5	11.3	7.9	21.4
Range	1-24.1	/	/	0.3-50.1
Response rates for individual subtypes, %				
PTCL NOS	32 (19/59)	29 (20/69)	23 (18/77)	22 (6/27)
ALCL	35 (6/17)	23 (5/22)	13 (2/15)	41 (7/17)
ALK negative	NA	24 (5/21)	15 (2/13)	45 (5/11)
ALK positive/unknown	NA	0 (0/1)	0 (0/2)	33 (2/6)
AITL	8 (1/13)	30 (8/27)	45 (10/22)	50 (5/10)
ENKL	0 (0/2)	0 (0/1)	50 (1/2)	19 (3/16)
Others	33 (6/18)	0 (0/11)	0 (0/4)	11 (1/9)

PR, partial response; CR, complete response; CRu, complete response unconfirmed; DOR, duration of response; PFS, progression free survival; OS, overall survival; PTCL NOS, PTCL not otherwisespecified; ALCL, anaplastic large cell lymphoma; AITL, angioimmuoblastic T-cell lymphoma; ENKL, extranodal NK/T-cell lymphoma, nasal type.

The ORR was 28% (22 of 79) including 14% (11 of 79) with CR/CRu. Median PFS and OS were 2.1 and 21.4 months, respectively. Patients with AITL tended to have a higher response rate and more durable responses to chidamide treatment. The most common AEs ≥ grade 3 were thrombocytopenia (22%), leucopenia (13%), and neutropenia (11%), respectively. Results led to CFDA approval of chidamide in relapsed or refractory PTCL in December 2014.The full report of the pivotal phase II study can be found in a recent publication (*22*).

It would be interesting to compare the results of chidamide with the other three FDA approved PTCL drugs, all derived from their pivotal phase II trials (*7-9,22*). While there were similar patient baseline characteristics from these trials in terms of age, gender, years since first diagnosis and prior systemic therapy numbers, a significant difference presented in the pathological subtypes of patients enrolled between the chidamide trial and the others (Table 3). Four major subtypes of PTCL (PTCL NOS, ALCL, AITL and ENKL) accounted for 83-97% of patients for all four trials. However, the chidamide trial enrolled a lower percentage of PTCL NOS patients, but significantly higher numbers of NKTL patients. Patients enrolled with ENKL in this study were 20% in total, whereas only1-2% of patients with this subtype were included

in other trials, reflecting a significant difference in geographic or racial population of this PTCL subtype in China compared with the studies carried out in Western countries for romidepsin, pralatrexate or belinostat.

Although the ORRs were very similar in general among these drugs at a range of 25-29%, there were remarkable differences in response rates in some individual PTCL subtypes (Table 4). For instance, patients with chemorefractory AITL tended to have higher response rates in response to treatment with chidamide, as well as romidepsin and belinostat, the three HDAC inhibitors. In contrast, only 8% of patients (1 of 13 patients) responded to the pralatrexate treatment. Chidamide showed an apparently longer OS in relapsed or refractory PTCL including 20% of patients with ENKL known usually to have very poor prognosis. However, we should be cautious to look at this potential benefit for chidamide and make a direct comparison with other drugs, because of limited patient numbers, different geographic or racial populations, as well as different subtype distributions, all account for the efficacy profiles in these different trials.

We believe that the successful development of chidamide in PTCL in China, may have significance in the field: first, chidamide is the first HDAC inhibitor with subtype-selectivity and oral availability approved for PTCL worldwide. The results summarized in the current article not only form the foundation for providing a much needed treatment option for PTCL patients in China, but also have made a significant scientific contribution to the field. Second, subtype distribution of PTCL patients enrolled in our pivotal phase II trial, which was the largest clinical trial in a Chinese PTCL population to date, was significantly different compared with studies in Western countries, particularly in the ENKL subtype. The subtype distribution profiles in different trials not only reflect the significant differences in geographic or racial population, but also may have impacts on interpretation of overall results of efficacy from different trials for the indication. Our study on chidamide would be very important for and an essential addition to new drug clinical trials for PTCL patients worldwide. And third, PTCL patients treated with chidamide showed a potential long-term survival benefit even compared with recently approved drugs, particularly to patients of certain subtypes, such as AITL, which may be associated with unique epigenetic modulating mechanisms of chidamide (*23,24*).

Acknowledgements

The authors thank the patients involved in the clinical trials. We thank medical staff and physicians, led by Prof. Shi YK from Cancer Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, who participated in the chidamide clinical studies. Clinical trials stated in this review were coordinated by Tigermed Consulting. The authors acknowledge Pan DS, Shan S, GuoX, Zhang JW, Zhou Y and many other colleagues from Chipscreen who played a great part in chidamide discovery and development.

Chidamide clinical development was partly supported by grants from the Chinese National '863' Project (2006AA020603, 2008AA02Z303), National 'New Drug Innovation' (2009ZX09401-003, 2008ZX09312, 2012ZX09303012) and Significant Project in Biotech Field from Guangdong Province (2011A080501009, 2003A10903) and Shenzhen Municipal Government (2010-1600).

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(Received April 15, 2016; Revised July 19, 2016; Accepted August 1, 2016)