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ORIGINAL ARTICLE

A phase II multiple dose clinical trial of histone deacetylase inhibitor ITF2357 in patients with relapsed or progressive multiple myeloma

Monica Galli · Silvia Salmoiraghi · Joseé Golay · Antonella Gozzini · Claudia Crippa · Norbert Pescosta · Alessandro Rambaldi

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Abstract ITF2357, an orally effective member of the family of histone deacetylase inhibitors, is a potent inducer of apoptosis and death of multiple myeloma (MM) cells. We performed a phase-II, multiple-dose clinical trial in 19 patients with relapsed or progressive MM to determine the maximum tolerated dose (MTD) of ITF2357 administered twice daily for four consecutive days every week for 4 weeks (i.e., first cycle). The first six patients received 150 mg ITF2357 twice daily. Since two of them experienced a dose-limiting toxicity (DLT) during the first cycle, the subsequent patients received 100 mg ITF2357 twice daily. This was the MTD, as only one DLT occurred. Up to 12 weeks (i.e., three cycles) of treatment were scheduled. Oral dexamethasone was allowed to a maximum weekly amount of 20 mg. Median duration of treatment was 6 weeks, ranging from two (two patients) to 12 weeks (five patients). Four patients suffered from serious adverse events. Three patients experienced grade 3–4 gastro-intestinal toxicity and three had transient electro-cardiographic abnormalities. Thrombocytopenia occurred in all but one patient (grade 3–4 in ten patients). At last follow-up, five patients were in stable disease, five had disease progression, and nine had died all of progressive MM. In conclusion, when given at a dose of 100 mg twice daily alone or combined with dexamethasone, ITF2357 proved tolerable but showed a modest clinical benefit in advanced MM.

Keywords Histone deacetylase inhibitor · ITF2357 · Multiple myeloma · Clinical trial

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Introduction

Multiple myeloma (MM) is a B-cell neoplasm that manifests as one or more lytic bone lesions, monoclonal protein in the blood or urine, and disease in the bone marrow (BM) [1]. The malignant plasma cells accumulate in the BM, and MM cells engage in intricate interactions with the BM microenvironment, frequently causing bone destruction, which, in turn, stimulates tumor growth [2]. The tumor itself, its products, and the host response to it result in the multitude of symptoms and organ dysfunction characteristic of MM, including bone pain, renal failure, susceptibility to infections, anemia, and hypercalcemia. Despite many treatment efforts, MM remains incurable.

Histone deacetylase inhibitors (HDACIs) are a novel class of agents that can induce tumor cell growth arrest, differentiation, and/or apoptosis in vitro and inhibit tumor growth in animals [3, 4]. One class of HDACIs is the hydroxamate derivatives family of compounds whose prototype is suberoyl anilide hydroxamic acid (SAHA) [5], which is being tested clinically in several hematological malignancies and has obtained FDA approval for the treatment of cutaneous T-cell lymphoma [6–15]. Our group

has recently reported that ITF2357, an orally effective member of the family of hydroxamate-derived HDACIs, is a potent inducer of apoptosis and death of MM cells in vitro [16]. In fact, eight of nine MM cell lines and freshly isolated BM samples from four MM patients underwent significant apoptosis when exposed to ITF2357 with a mean IC50 of about 0.17 μM. ITF2357 targeted clonogenic MM cells, as it totally abolished colony growth of the RPMI8226 MM cell line with a similar IC50. As a comparison, SAHA was also cytotoxic, although at concentrations three to four times higher. ITF2357 was strongly cytotoxic for MM cell lines cultured on mesenchymal stromal cells (MSC), but not for the MSCs themselves. Finally, ITF2357 inhibited by 85–90% the production of IL-6, VGEF, and IFN-γ by MSCs. Based on these observations, we performed a phase-II, multiple-dose clinical trial to determine the maximum tolerated dose (MTD) and to evaluate the anti-tumor activity of ITF2357 in patients with relapsed or progressive MM.

Patients and methods

Patients

Between June 2005 and April 2007, 19 patients with relapsed or progressive MM after at least two previous lines of therapy were enrolled in five Italian hematological centers. Table 1 reports their main clinical and laboratory details. Minimum age for enrolment was 18 years, with no upper age limit. Further eligibility criteria included Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2, quantifiable monoclonal component in serum or urine, adequate BM reserve (defined as absolute neutrophil count of at least 1,000/mmc, platelet count of at least 75,000/mmc), adequate liver function (defined as total bilirubin within the normal institutional upper limit and transaminase levels within 2.5 times the upper institutional limit), normal renal function (defined as serum creatinine level equal or below 2 mg/dl or creatinine clearance equal or above 60 ml/min), ability to swallow capsules, life expectancy of at least 3 months, and no prior chemotherapy or other investigational drugs within the last 3 weeks. All patients gave their written informed consent. The study was approved by each local institution's Ethical Committee

Study design

The study was a multicenter, open-label, phase-II, non-randomized, uncontrolled study, whose primary endpoints were (1) to determine the MTD of oral ITF2357 on a twice daily dosing schedule of four consecutive days followed by a 3-day rest every week in a 4-week cycle and (2) to evaluate the anti-tumor activity of ITF2357 in patients with relapsed or progressive MM.

Table 1 Main characteristics of the 19 patients at diagnosis of MM

Gender	
Male/female	11/8
Age, years	
Range (median)	45–75 (61)
Main associated diseases[a]	
Cardiac	4
Blood hypertension	4
Endocrine	3
Previous solid cancer	1
HBs antigen positivity	1
Characteristics of MM	
Isotype	
A	4
G	10
Light chain	3
Plasmacytoma	2
Clinical stage of MM[b]	
II	7
III	10
A	12
B	5

[a] The same patient may have suffered from more than one co-morbidity

[b] The two patients with plasmacytoma were excluded

A conventional "3+3" enrolment scheme was utilized, and treatment with oral ITF2357 was started at a dose of 150 mg twice daily. This dose level has been selected based on pharmacokinetic data obtained in previous studies with ITF 2357, both in healthy volunteers and in patients, and on efficacy data from "in vitro" tests. Down escalation was permitted by 50-mg/dose decrements in case of dose-limiting toxicity (DLT) during the first cycle. Patients continued on treatment until disease progression, intolerable toxicity, withdrawal of consent, or at the investigator's discretion. In any event, the overall treatment duration did not exceed 12 weeks (i.e., three cycles). Dosing of ITF2357 was held at the occurrence of any of the following events: grade 4 thrombocytopenia, grade 4 neutropenia lasting longer than 5 days despite colony-stimulating factor therapy, neutropenic fever, or grade 3 or 4 non-hematological toxicity. On resolution of the above toxicity signs to grade 1 or baseline, drug administration was restarted, reducing the number of consecutive treatment days from four to three every week, without affecting the total daily dose. If DLT recurred, a second dose modification could be applied, reducing the number of treatment days from three to two every week. Once a patient was dose-reduced, the reduced dose was maintained for the remaining part of the study

treatment. A patient who required more than two dose modifications had to be withdrawn from the study unless the patient derived remarkable clinical benefit from the treatment. Treatment could be delayed up to 2 weeks to allow recovery from drug-induced toxicity. If recovery criteria were not met after 2 weeks delay, the patient was considered to have experienced DLT and was removed from the study unless, in the opinion of the principal investigator, the patient was experiencing a clinical benefit, in which case decisions regarding continuation of treatment were made on an individual basis. Patients with stable or progressive disease after the first cycle of therapy could receive up to 20 mg oral dexamethasone every week of treatment. Bisphosphonate administration was allowed.

Evaluation of patients

The pretreatment evaluation included medical history, physical examination including vital signs, height, weight, and ECOG performance status, ECG, baseline evaluation of symptoms and medications, complete blood counts, tests for renal and liver function, serum and urine protein electrophoresis, quantitative immunoglobulin, quantification of monoclonal component, beta2-microglobulin, and C-reactive protein. A skeletal X-ray survey, chest X-ray, and BM aspirate or biopsy were optional procedures performed at the investigator's discretion. Patients were followed-up on an out-patient basis every week during the first cycle and every 2 weeks during the second and third cycles (unless otherwise required). At each planned visit, a complete blood count was obtained. At the beginning of the second and third cycles and 1 month after the end of treatment, physical examination with vital signs, tests for renal and liver function, serum and urine protein electrophoresis, quantitative immunoglobulin, quantification of monoclonal component, beta2-microglobulin, and C-reactive protein were performed.

Assessment of adverse events

All patients, irrespective of the duration of treatment, were included in the evaluation of adverse events. Adverse events were categorized according to their relationship to the study drug (not, possibly, probably, or definitely related) and were graded according to the National Cancer Institute Common Toxicity Criteria v3.0.

Assessment of response

Only patients who completed at least one treatment cycle were assessed for response. Response was evaluated after each cycle and 1 month after the end of treatment. Response criteria were defined essentially according to Bladé et al. [17].

Results

Clinical characteristics of patients at diagnosis of MM

The main demographic and clinical characteristics of the 19 patients at diagnosis of MM are reported in Table 1. Their first-line therapy consisted of: local radiotherapy in the two cases of plasmacytoma; autotransplant-based regimens in the setting of the “total therapy I” [18] or the “total therapy II” [19]; conventional chemotherapy, such as standard oral MP (melphalan and prednisone) for 7 days every 4 to 6 weeks; vincristine, adriamycin, and dexamethasone (VAD); vincristine, cyclophosphamide, melphalan, and prednisone (VMCP); and idarubicin and dexamethasone every 28 days (Table 2). All patients had relapsed or progressed and received at least another line of therapy (up to eight further lines, median three) before enrolment in the study (Table 2).

Treatment with ITF2357: safety and toxicity

Patients entered the study 2 to 12 years after the initial diagnosis of MM. All of them were in relapse/progression of MM at the time of enrolment. The first 3+3 patients started ITF2357 treatment at a dose of 150 mg twice daily given orally for four consecutive days every week. Since two of them experienced grade 3 gastro-intestinal toxicity (diarrhea) during the first cycle (i.e., a DLT), the subsequent patients received 100 mg twice daily in the same weekly schedule. Only one other DLT (sudden death) occurred during week 2 of treatment (as autopsy was not performed, the cause of death was not ascertained). Thus, 100 mg every 12 h for four consecutive days every week was the MTD. Oral dexamethasone was given up to 20 mg every week to 13 patients. Median duration of treatment was 7 weeks, ranging from two (two patients) to 12 weeks (five patients).

Table 3 shows the main ITF2357-related adverse events. The most common was thrombocytopenia, which occurred in all but one patient. Neutropenia occurred in nine patients: none of them required granulocyte colony-stimulating factor. Gastro-intestinal toxicity (diarrhea) occurred in four cases. It was accompanied by nausea and vomiting in one patient and anorexia in another one. Five patients developed mild blood hypertension, which did not require specific treatment. Two months after the end of treatment, one patient developed atrial fibrillation, which required therapy. Three other patients had transient electrocardiographic abnormalities (i.e., grades 1–2 heart-rate corrected QT interval prolongation), which did not require any treatment. We did not record neurological toxicity, apart from mild tremors of upper extremities in one patient. Four patients were hospitalized for serious adverse events:

Table 2 Treatment of the 19 MM patients before enrolment in the study

	Number of patients
First-line treatment	
Autotransplant-based	
TTI[a]	6
TTII[b]	3
Conventional melphalan/prednisone	4
Local radiotherapy	2
Idarubicin/dexamethasone	2
Vincristine/melphalan/cyclophosphamide/prednisone (VMCP)	1
Vincristine/adriamycin/dexamethasone (VAD)	1
Second-line treatment	
Thalidomide/dexamethasone	8
Thalidomide alone	4
Vincristin/epirubicin/dexamethasone	2
Conventional melphalan/prednisone	1
Melphalan/prednisone/thalidomide	1
Vincristine/adriamycin/dexamethasone (VAD)	1
Cyclophosphamide	1
Vincristine/idarubicin/etoposide	1
≥ Third-line treatment[c]	
Bortezomib/dexamethasone	8
Thalidomide alone	6
Conventional melphalan/prednisone	3
Cyclophosphamide	3
Autotransplant-based	1
Bortezomib/dexamethasone/allotransplant	1
Melphalan/prednisone/thalidomide	1
Interferon alone	1
Dexamethasone/cyclophosphamide/etoposide/ Cis-platinum (DCEP)	1
Melphalan alone	1
Dexamethasone alone	1

TTI total therapy I, *TTII* total therapy II

[a] Total therapy I according to Barlogie et al. [18], i.e., three VAD cycles, high-dose cyclophosphamide, and subsequent stem cell collection and double autotransplant conditioned with high-dose melphalan

[b] Total therapy II according to Shaughnessy et al. [19], i.e., one VAD cycle, one DCEP cycle, one CAD cycle, and subsequent stem cell collection, another DCEP cycle and double autotransplant conditioned with high-dose melphalan

[c] The same patient may have received more lines of treatment

pneumonia (neutrophil count at the time of event: 860/mmc), severe deterioration of general conditions, cerebral ischemia with leg deep vein thrombosis (platelet count at the time of events: 64,000/mmc), pneumonia, and severe deterioration of general conditions (neutrophil count at the time of event: 930/mmc). This last patient finally succumbed to progressive MM during week 7 of treatment. Two more patients died from progression of MM at weeks 5 and 10 of treatment, respectively.

Table 3 ITF2357-related adverse events* of 19 MM patients

Adverse event	All grades, number of patients	Grade 3–4, number of patients
Thrombocytopenia	18	10
Neutropenia	9	4
Gastrointestinal	4	2
Diarrhea	4	2
Nausea	1	0
Vomiting	1	0
Anorexia	1	0
Cardiovascular	5	0
Atrial fibrillation	1	
ECG abnormalities	3	
Hypertension	5	
Neurological	1	0
Tremor	1	

[a] The same patient may have experienced more than one adverse event

Clinical outcome

Of the15 patients who completed at least one treatment cycle, six had stable disease (SD) as best response, because their MM did not further progress after 12 weeks (three patients) and 5 weeks (three patients) of treatment. All but one of them were also receiving dexamethasone. Of the latter three patients, two withdrew the consent to continue the study, and the other one was hospitalized for thrombo-embolic complications. MM progressed in spite of ITF2357 treatment in eight patients. Three of them were also taking dexamethasone. One patient died at week 7 of ITF2357 and dexamethasone treatment.

At last follow-up, of the 19 patients enrolled in the study, five remained in SD, another five were alive with progressive MM under other forms of treatment, and the remaining nine patients had died.

Discussion

The evidence that HDACIs may be useful in the treatment of MM has increased over the last decade. Phase I–II clinical trials are underway or have been recently performed with SAHA in patients with advanced hematological malignancies, including MM [6–13]. Overall, these studies showed that SAHA was tolerable, although its toxicity profile was not negligible. Fatigue, dispepsia, diarrhea,

dehydration, and thrombocytopenia were the most common adverse events. These effects, particularly those affecting the gastro-intestinal system, were more common when SAHA was given orally than intravenously. Grade 3–4 gastrointestinal toxicity was also more common in patients with hematological malignancies than in those with solid tumors. Not unexpectedly, patients treated with SAHA for hematological malignancies experienced more grade 3–4 hematological toxicity than patients with solid tumors [6, 14]. Thrombocytopenia occurring with SAHA was associated with the presence of hypolobular megakaryocytes, and not with an absolute reduction in the number of megakaryocytes [7]. This may raise the possibility that SAHA impairs megakaryocyte differentiation. In most cases, thrombocytopenia recovered within 3 to 7 days after drug discontinuation.

Our study in a group of heavily pretreated MM patients showed that the toxicity profile of ITF2357 was remarkably similar to that of SAHA. Thrombocytopenia was the most common hematological toxicity, which was surely attributable to the study drug because platelet count usually recovered after discontinuing ITF2357. Grade 3 neutropenia occurred in four patients: two of them developed pneumonia, which recovered without need of granulocyte-colony stimulating factor administration. The major non-hematological toxicity affected the gastro-intestinal system. Grade 3–4 diarrhea required the down-scaling of the daily dose of ITF2357 from 150 to 100 mg twice daily. Following this dose reduction, the patients experienced occasional and much milder gastro-intestinal symptoms. ITF2357 administration was also associated with some cardiovascular toxicity. This was mainly represented by mild blood hypertension (grades 1–2) and ECG abnormalities, which did not require specific treatment. Quite likely, they were related to ITF2357 because they developed after a few weeks of treatment and resolved after drug discontinuation. Similar cardiac abnormalities have also been reported for other HADACIs [20, 21]. Only one patient needed anti-arrhythmic therapy for atrial fibrillation, which developed 2 months after the end of ITF2357 treatment. It is, therefore, doubtful that such an event was related to the study drug.

With respect to clinical outcome, ITF2357 and SAHA showed, again, similar efficacy profiles in patients with advanced MM. In a phase-I trial with single-agent SAHA, one out of 13 patients showed a minimal response and nine had SD [11]. ITF2357 stabilized MM in six patients, with a durable effect in three of them. However, most patients progressed in spite of ITF2357 and required further treatments. The addition of dexamethasone did not improve its efficacy.

In conclusion, ITF2357 had an acceptable safety profile and was, in general, well tolerated. At the MTD of 100 mg twice daily for four consecutive days every week, ITF2357, alone or in combination with dexamethasone, is unlikely to play a significant therapeutic activity in advanced MM. Thus, similar to what is already ongoing for other HDACIs [12], further clinical investigation of ITF2357 in combination with other drugs commonly used in the treatment of advanced MM, such as thalidomide, bortezomib, lenalidomide, or melphalan is warranted.

References

1. Alastair Smith FW (2006) Diana Samson, Guidelines on the diagnosis and management of multiple myeloma 2005. Br J Haematol 132:410–451. doi:10.1111/j.1365-2141.2005.05867.x
2. Mitsiades CS, Mitsiades N, Munshi NC, Anderson KC (2004) Focus on multiple myeloma. Cancer Cell 6:439–444. doi:10.1016/j.ccr.2004.10.020
3. Richon VM, Webb Y, Merger R et al (1996) Second generation hybrid polar compounds are potent inducers of transformed cell differentiation. Proc Natl Acad Sci USA 93:5705–5708. doi:10.1073/pnas.93.12.5705
4. Cohen LA, Amin S, Marks PA, Rifkind RA, Desai D, Richon VM (1999) Chemoprevention of carcinogen-induced mammary tumorigenesis by the hybrid polar cytodifferentiation agent, suberanilohydroxamic acid (SAHA). Anticancer Res 19:4999–5005
5. Butler LM, Agus DB, Scher HI et al (2000) Suberoylanilide hydroxamic acid, an inhibitor of histone deacetylase, suppresses the growth of prostate cancer cells in vitro and in vivo. Cancer Res 60:5165–5170
6. Kelly WK, O'Connor OA, Krug LM et al (2005) Phase I study of an oral histone deacetylase inhibitor, suberoylanilide hydroxamic acid, in patients with advanced cancer. J Clin Oncol 23:3923–3931. doi:10.1200/JCO.2005.14.167
7. O'Connor OA, Heaney ML, Schwartz L et al (2006) Clinical experience with intravenous and oral formulations of the novel histone deacetylase inhibitor suberoylanilide hydroxamic acid in patients with advanced hematologic malignancies. J Clin Oncol 24:166–173. doi:10.1200/JCO.2005.01.9679
8. Garcia-Manero G, Yang H, Bueso-Ramos C et al (2008) Phase 1 study of the histone deacetylase inhibitor vorinostat (suberoylanilide hydroxamic acid [SAHA]) in patients with advanced leukemias and myelodysplastic syndromes. Blood 111:1060–1066. doi:10.1182/blood-2007-06-098061
9. Duvic M, Talpur R, Ni X et al (2007) Phase 2 trial of oral vorinostat (suberoylanilide hydroxamic acid, SAHA) for refractory cutaneous T-cell lymphoma (CTCL). Blood 109:31–39. doi:10.1182/blood-2006-06-025999
10. Olsen EA, Kim YH, Kuzel TM et al (2007) Phase IIB multicenter trial of vorinostat in patients with persistent, progressive, or treatment refractory cutaneous T-cell lymphoma. J Clin Oncol 25:3109–3115. doi:10.1200/JCO.2006.10.2434
11. Richardson P, Mitsiades C, Colson K et al (2008) Phase I trial of oral vorinostat (suberoylanilide hydroxamic acid, SAHA) in patients with advanced multiple myeloma. Leuk Lymphoma 49:502–507
12. Badros A, Philip S, Niesvizky R et al (2007) Phase I trial of suberoylanilide hydroxamic acid (SAHA) + bortezomib (Bort) in relapsed multiple myeloma (MM) patients (pts). ASH Annual Meeting Abstracts 110:1168
13. Weber DM, Jagannath S, Mazumder A et al (2007) Phase I trial of oral vorinostat (Suberoylanilide Hydroxamic Acid, SAHA) in combination with bortezomib in patients with advanced multiple myeloma. ASH Annual Meeting Abstracts 110:1172

14. Kelly WK, Richon VM, O'Connor O et al (2003) Phase I clinical trial of histone deacetylase inhibitor: suberoylanilide hydroxamic acid administered intravenously. Clin Cancer Res 9:3578–3588
15. Mann BS, Johnson JR, Cohen MH, Justice R, Pazdur R (2007) FDA approval summary: vorinostat for treatment of advanced primary cutaneous T-cell lymphoma. Oncologist 12:1247–1252
16. Golay J, Cuppini L, Leoni F et al (2007) The histone deacetylase inhibitor ITF2357 has anti-leukemic activity in vitro and in vivo and inhibits IL-6 and VEGF production by stromal cells. Leukemia 21:1892–1900
17. Blade J, Samson D, Reece D et al (1998) Criteria for evaluating disease response and progression in patients with multiple myeloma treated by high-dose therapy and haemopoietic stem cell transplantation. Myeloma subcommittee of the EBMT. European group for blood and marrow transplant. Br J Haematol 102:1115–1123
18. Barlogie B, Jagannath S, Desikan KR et al (1999) Total therapy with tandem transplants for newly diagnosed multiple myeloma. Blood 93:55–65
19. Shaughnessy J Jr, Tian E, Sawyer J et al (2003) Prognostic impact of cytogenetic and interphase fluorescence in situ hybridization-defined chromosome 13 deletion in multiple myeloma: early results of total therapy II. Br J Haematol 120:44–52
20. Piekarz RL, Frye AR, Wright JJ et al (2006) Cardiac studies in patients treated with depsipeptide, FK228, in a phase II trial for T-cell lymphoma. Clin Cancer Res 12:3762–3773
21. Strevel EL, Ing DJ, Siu LL (2007) Molecularly targeted oncology therapeutics and prolongation of the QT interval. J Clin Oncol 25:3362–3371