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ORIGINAL ARTICLE

Pharmacokinetic and pharmacodynamic properties of an oral formulation of the histone deacetylase inhibitor Belinostat (PXD101)

N. L. Steele · J. A. Plumb · L. Vidal · J. Tjørnelund · P. Knoblauch · P. Buhl-Jensen · R. Molife · R. Brown · J. S. de Bono · T. R. J. Evans

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Abstract
Purpose The primary objective of this sub-study, undertaken as an extension to the previously reported phase-I study, was to explore the feasibility, tolerability and pharmacokinetics (PK) of belinostat when administered by the oral route. Preliminary pharmacodynamic (PD) studies were also performed to enable comparison of the biological effects of the oral and intravenous formulations.
Patients and methods Oral belinostat was administered in a range of doses and schedules (once, twice or thrice daily), on either day 1 or days 1–5, of the second or a subsequent treatment cycle in 15 patients who were included in the phase-I trial of intravenous belinostat. Serial blood samples were collected for PK and PD (histone acetylation) analyses, and the results compared with corresponding analyses following intravenous administration.
Results A total mean daily AUC of 2,767 ± 1,453 ng h/ml (8.7 ± 4.6 μM h) resulted from a dose of 1,000 mg/m^2 once daily (qd). There was no clear evidence of drug accumulation on twice daily dosing (bid); however, a trend towards accumulation was apparent when belinostat was given three times daily (tid). Mean half-life (*T½*) of a single dose of 1,000 mg/m^2 was 1.5 h (±0.3 h) and peak levels were reached in an average of 1.9 h (±0.3 h). The half-life was found to be independent of dose, but a trend towards increasing half-life following multiple dosing was observed. Histone H4 hyperacetylation in PBMCs estimated after oral dosing was comparable to that achieved after intravenous administration.
Conclusions High doses of oral belinostat, up to 1,000 mg/m^2 bid for 5 consecutive days, have been tolerated in this small study. An oral formulation could lead to enhanced drug exposure and, more importantly, prolonged effects on the intended drug target. Future trials are required to establish the optimal dose and schedule of oral administration of belinostat.

Keywords Histone deacetylase · Phase-1 trial · Pharmacokinetics · Pharmacodynamics · Bioavailability

N. L. Steele and J. A. Plumb contributed equally to this work.

N. L. Steele (✉) · T. R. J. Evans
Beatson West of Scotland Cancer Centre,
1053 Great Western Road, Glasgow G12 0YN,
United Kingdom
e-mail: nicola.steele@ggc.scot.nhs.uk

N. L. Steele · J. A. Plumb · R. Brown · T. R. J. Evans
Centre for Oncology and Applied Pharmacology,
University of Glasgow, Garscube Estate,
Switchback Road, Glasgow G61 1BD, United Kingdom

L. Vidal · R. Molife · J. S. de Bono
Royal Marsden Hospital, Downs Road,
Sutton, Surrey SM2 5PT, United Kingdom

J. Tjørnelund · P. Knoblauch · P. Buhl-Jensen
Topotarget, Symbion Science Park,
Fruebjergvej 3, 2100 Copenhagen, Denmark

Introduction

Deregulation of the balance between histone acetylation and deacetylation plays a role in the generation and suppression of neoplasia. The histone deacetylase (HDAC) enzymes catalyse the removal of an acetyl group from the terminal lysine residues of histone proteins, leading to more compact chromatin and repression of associated genes. Inhibitors of HDAC enzymes alter patterns of gene expression, induce cellular differentiation and promote cell cycle

arrest and apoptosis [1]. Pharmacologic inhibition of histone deacetylation may therefore regulate gene expression patterns and, subsequently, cellular characteristics, making them attractive anti-cancer therapies. Histone deacetylase inhibitors (HDACi) are relatively selective for cancer cells, possibly due to their effects being limited to only a small number of genes [2]. In addition, acetylation of non-histone proteins e.g. p53 [3] and Rb [4] may play a role in the anti-tumour activity of these compounds.

Belinostat (PXD101) is a novel hydroxamic acid HDAC inhibitor with potent anti-proliferative and HDAC inhibitory activity both in vitro and in vivo [5]. Inhibition of tumour growth by belinostat is associated with a marked increase in the level of acetylation of histone proteins [5]. We have previously reported the results of a phase-I trial of belinostat administered as a 30-min intravenous infusion on days 1–5 of a 21-day cycle [6]. In this trial, belinostat was well tolerated, exhibited dose-dependent pharmacodynamic (PD) effects, and had promising anti-tumour activity. The maximum tolerated dose of belinostat administered intravenously in this dose and schedule was 1,000 mg/m^2/day [6].

However, pharmacodynamic effects of belinostat on histone acetylation were most marked in the first few hours following intravenous drug administration. Consequently, a protracted or continuous daily oral dosing schedule could be advantageous, allowing continual target inhibition. In addition, patient convenience and health economic benefits also favour an oral route of administration. Furthermore, the availability of both intravenous and oral routes of administration would allow greater flexibility to design combination regimens with other anti-cancer agents in subsequent clinical studies.

The primary objective of this sub-study, undertaken as an extension to the previously reported phase-I study, was to explore the feasibility, tolerability and pharmacokinetics (PK) of belinostat when administered by the oral route. Preliminary PD studies were also performed to enable comparison of the biological effects of the oral and intravenous formulations.

Patients and methods

Patient eligibility

This study was conducted as an extension to the phase-1 trial of intravenous belinostat which has previously been reported [6]. Eligible patients were those with histological or cytological confirmed advanced malignancy, refractory to standard therapy, or for whom no standard therapy existed. Other inclusion criteria included age $\geq$ 18 years, ECOG performance status (PS) $\leq$2 and estimated life expectancy of $\geq$ 3 months. Adequate bone marrow, hepatic and renal function for trial entry was defined as: Hb $\geq$ 9.0 g/dl, absolute neutrophil count $\geq 1.5 \times 10^9$/l, platelets $\geq 100 \times 10^9$/l, total bilirubin $\leq$ 1.5 $\times$ upper limit of normal (ULN), AST and ALT $\leq$ 2.5 $\times$ ULN (or $\leq$ 5 $\times$ ULN if liver metastases were present), serum creatinine $\leq$ 1.5 $\times$ ULN. Female patients of reproductive potential were required to have a negative pregnancy test.

Patients were excluded from the trial if they had received any anti-cancer therapy within the preceding 4 weeks. Continuation of bisphosphonates, LHRH agonists or corticosteroids was permitted provided dosing was stable before and during the trial. Other exclusions were co-existing illness likely to interfere with trial procedures, uncontrolled brain metastases, persistent neuropathy $\geq$ NCI-CTCAE grade 2 of any cause, pregnant or lactating women, and known HIV infection.

Amendments to the original trial protocol of intravenous belinostat, to allow oral administration using a variety of schedules, were approved by the Research Ethics Committees at both participating institutions. Specific written informed consent for the oral sub-study was obtained from each patient in addition to the consent previously obtained for the main trial of intravenous belinostat.

Study design

All patients received belinostat as a 30-min intravenous infusion daily on days 1–5 of a 21-day cycle. The starting dose was 150 mg/m^2. Sequential cohorts of 3–6 patients were entered into one of the escalating dose levels. Dose escalation was in 100% increments until grade 2 toxicity was observed, at which point dose escalation was in 50% increments until grade 3 toxicity was seen, following which further dose increments would be of 33%.

Following the initiation of the phase-I trial of intravenous belinostat, a limited preliminary study of oral drug administration was planned in patients already enrolled to the main trial. On the basis that pre-clinical data from dogs had demonstrated an oral bioavailability for belinostat of 30–35% (Topotarget, personal communication), eligible patients with stable disease after two cycles of intravenous belinostat were given a single oral dose of belinostat on day 1 of cycle 3. The dose administered was equal to the dose that had been tolerated when administered intravenously to the same patient. Following the single oral dose, all subsequent doses for this, and subsequent, cycles were administered intravenously. Following further amendments to the trial protocol belinostat was subsequently administered orally, at the same dose as administered intravenously, twice or three times daily to eligible patients on day 1 only of their second, or subsequent, cycle and then administered, again at the same dose as

administered intravenously, in a further cohort of patients once daily on days 1–5 of the second or third cycle. All other doses in all subsequent cycles were administered intravenously.

Toxicities were assessed weekly and graded and reported according to NCI-CTCAE v3.0. Patient assessments for toxicity and anti-tumour activity were not influenced by participation in this sub-study of oral administration of belinostat. Dose limiting toxicity (DLT) was based on the toxicities observed in the first 21 day cycle of intravenous belinostat. However, patients participating in the oral dosing sub-study were observed for any toxicity in addition to those seen with intravenous treatment.

Drug preparation and administration

Belinostat was supplied by Topotarget, Copenhagen, Denmark. Belinostat powder was formulated in standard gelatine capsules containing 250 mg for oral administration. Patients were not required to fast prior to drug administration.

Pharmacokinetic studies

PK samples were taken from 14 of the 15 patients enrolled in the oral study. Samples of 5 ml of blood were collected at the following time points: once daily dosing schedule—time 0 (before oral administration of belinostat) then at 5, 15, 30, 60 and 90 min and 2, 4, 6, 8, 10 and 24 h after administration; twice daily dosing schedule—time 0, then at 15, 30, 60 and 90 min and 2, 4, 6, 8 and 12 h (immediately before the second oral dose) after administration, and at 2, 4, 6, 8 and 12 h (prior to the next intravenous dose) after administration of the second oral dose; thrice daily dosing schedule—time 0, then at 15, 30, 60 and 90 min and 2, 4, 6 and 8 h (immediately before the second dose) following the first dose, at 2, 4, 6 and 8 h (prior to the third dose) following the second dose, and then at 8 h (prior to the next intravenous dose) following the third dose.

Lithium heparinised blood samples were placed on ice then centrifuged at 4°C. Two millilitre aliquots of plasma were stored at −70°C until analysis. The concentration of belinostat in plasma was analysed by liquid chromatography with tandem mass spectrometry detection as previously described [6]. PK calculations were performed using a non-compartmental method (WinNonLin version 5.1.0, model 200). The area under the plasma concentration time curve (AUC) was calculated using the linear trapezoid method and uniform weighting, and the elimination half-life was calculated by the log-linear method.

Pharmacodynamic studies

Histone hyperacetylation in peripheral blood mononuclear cells

Histone acetylation was evaluated by Western blotting for histone H4 on histones isolated from peripheral blood mononuclear cells (PBMCs). Samples for histone acetylation were taken at various time points after intravenous administration of belinostat in cycle 1 and after oral administration in cycle 2. Blood samples (6 ml) were collected in lithium heparin vacutainer tubes, placed on ice and processed immediately using a modification of the method described by Yoshida et al. [7] and as previously described [6]. Densitometry was carried out on the resulting Western blots and the results were expressed relative to a control sample (histones extracted from A2780 ovarian cancer cell line treated for 1 h with belinostat 0.2 μM). The same cell line standard was used in all blots. AUC for histone acetylation was calculated by non-compartmental analysis using WinNonLin Version 4.0 software (Pharsight, Mountain View, USA).

Results

Patient characteristics

A total of 46 patients were recruited into the phase-1 trial of belinostat, by intravenous administration, between October 2003 and February 2006 as previously reported [6]. Fifteen of these patients were also enrolled into this sub-study of oral belinostat between August 2004 and January 2006. Details of the oral dosing schedule for each patient are summarised in Table 1. One patient received two schedules of oral belinostat in different treatment cycles. Baseline characteristics for these 15 patients are summarised in Table 2.

Toxicity assessments

There were no toxicities, in addition to those observed with the intravenous formulation, in any of the 15 patients who were treated in this sub-study with oral belinostat. The most frequent toxicities associated with the brief duration of the oral dosing schedules were nausea (two patients), vomiting (two patients), fatigue (two patients) and decreased lymphocyte counts (three patients). These were all mild and self-limiting. Nausea and vomiting tended to occur several hours after oral dosing compared with the intravenous administration treatment schedule in which nausea and vomiting tended to occur at the end of the 30-min intravenous infusion.

Table 1 Oral belinostat doses and schedules

Patient	Dose level (mg/m^2/day)	Actual dose (mg)	Oral dosing schedule
1	900	1,250	Day 1 q.d.
2	900	1,500	Day 1 q.d.
3a	1,000	1,750	Day 1–5 q.d.
3b	1,000	1,750	Day 1 t.i.d.
4	1,000	2,000	Day 1–5 q.d.
5	1,000	1,500	Day 1–5 q.d.
6	1,000	1,500	Day 1 b.i.d.
7	1,000	1,750	Day 1 b.i.d.
8	1,000	1,750	Day 1 b.i.d.
9	1,000	1,750	Day 1 b.i.d.
10	1,000	2,000	Day 1 b.i.d.
11	1,000	1,750	Day 1–5 b.i.d.
12	1,000	2,000	Day 1–5 b.i.d.
13	1,000	1,500	Day 1–5 b.i.d.
14	1,000	2,000	Day 1 t.i.d.
15	1,200	2,500	Day 1 q.d.

Table 2 Patient characteristics

Characteristic	No. of patients
Total	15
Age (years)	
Median	57
Range	25–70
Sex	
Male	8
Female	7
ECOG performance status	
0	6
1	9
Tumour type	
Colorectal	3
Melanoma	1
Renal	2
Oesophago-gastric	1
Sarcoma	3
Ovary	1
Thymoma	1
Breast	1
Prostate cancer	1
NSCLC	1

Pharmacokinetics

The pharmacokinetic profile of oral belinostat was evaluated in 14 patients using a variety of dosing schedules and compared with the pharmacokinetic profile of belinostat by intravenous administration in the same patients. These results are summarised in Table 3. The exposure following oral dosing of belinostat was variable but sufficient to achieve histone acetylation (Fig. 2) and in a potentially therapeutic range based on observations in pre-clinical models [8–10]. Total mean daily AUC of 2,767 ± 1,453 ng h/ml (8.7 ± 4.6 μM h) resulted from a dose of 1,000 mg/m^2 once daily (qd). There was no clear evidence of drug accumulation on twice daily dosing (bid) however a trend towards accumulation was apparent when belinostat was given three times daily (tid). Mean half-life ($T½$) of a single dose of 1,000 mg/m^2 was 1.5 h (±0.3 h) and peak levels were reached in an average of 1.9 h (±0.3 h). The half-life was found to be independent of dose, but a trend towards increasing half-life following multiple dosing was observed. Assessment of dose linearity was not performed due to the small number of patients in this sub-study combined with the large variation in clearance.

Pharmacodynamic studies

Histone H4 hyperacetylation in peripheral blood mononuclear cells

Histone H4 acetylation levels following intravenous and oral administration of belinostat are shown in Fig. 1. The pre-treatment level of histone acetylation was slightly higher in the group given oral belinostat. Histone acetylation increases rapidly after intravenous administration of belinostat (Tmax 77.1 ± 20.3). The rate of increase is slower following oral administration (Tmax 210.0 min ± 46.8) although increased levels are sustained for longer. For two patients, samples were collected at 12 h, immediately before a second oral dose was administered. At 12 h, the level of acetylation was above the baseline level and histone acetylation increased rapidly after the second oral dose. The AUC for histone acetylation measured over the first 6 h is 272.2 ± 14.9 for intravenous and 276.6 ± 16.0 for oral administration ($n = 7$).

Clinical outcomes

Objective response and survival for patients treated with intravenous belinostat have previously been reported [6]. It was not anticipated that these would have been influenced by oral dosing as each patient only had limited exposure to the oral formulation. Consequently, there is no efficacy data from this preliminary sub-study.

Discussion

The preliminary data reported in this study are limited by the small sample size and the heterogenous dosing cohorts,

Table 3 Summary of mean (±SD) PK parameters after oral administration of belinostat

Administration schedule (number of patients)	Dose (mg/m2)	Dose (mg)	Cmax (ng/ml)	Tmax (h)	*T½* (h)	Vz (l)	CL (l/h)	AUC_{0-t} (ng*h/ml)	$AUC_{0-\infty}$ (ng*h/ml)	AUC_{0-t} $AUC_{0-\infty}$
Single day, qd $n = 2$	900	1,375 (±177)	3,229 (±1376)	1.7 (±0.2)	0.9 (±0.2)	293 (±50)	219 (±1)	6,266 (±862)	6,292 (±862)	1.00
Five days, qd day 1 $n = 3$	1,000	1,750 (±250)	681 (±350)	1.9 (±0.3)	1.5 (±0.3)	1,511 (±592)	767 (±441)	2,695 (±1,461)	2,767 (±1,453)	0.97
Five days, qd day 5 $n = 3$	1,000	1,750 (±250)	1,317 (±736)	2.0 (±0.1)	1.7 (±1.1)	1,416 (±1213)	516 (±134)	3,016 (±573)	3,476 (±648)	0.87
Single day, qd $n = 1$	1,200	2,500	1,729	1.3	1.4	719	348	7,139	7,174	1.00
Single day, bid, am $n = 7$	1,000	1,750 (±189)	1,447 (±782)	2.1 (±1.3)	1.6 (±0.4)	1,104 (±691)	492 (±308)	4,187 (±1,552)	4,357 (±1,636)	0.96
Single day, bid, pm[a] $n = 6$	1,000	1,792 (±188)	817 (±299)	1.5 (±0.9)	2.6 (±1.6)	1,356 (±736)	374 (±65)	4,011 (±1,278)	4,706 (±711)	0.85
Five days, bid am[a] ($n = 3$)	1,000	1,917 (±144)	1,054 (±663)	1.2 (±0.6)	3.4 (0.4)	2,053 (±1180)	410 (±198)	3,990 (±2270)	5,116 (±2,732)	0.78
Single day, tid $n = 2$ 1st dose[a]	1,000	1,875 (±177)	1,227 (±780)	1.0 (±0.1)	2.0	1,077	369	3,688 (±1,082)	4,748	0.78
Single day, tid $n = 2$ 2nd dose	1,000	1,875 (±177)	1,103 (±74)	3.1 (±1.5)	2.6 (±0.8)	1,515 (±979)	378 (±138)	4,557 (±1,642)	5,219 (±1,432)	0.87
Single day, tid $n = 2$ 3rd dose	1,000	1,875 (±177)	974 (±485)	2.1 (± 0.0)	3.0 (±0.6)	1,640 (±782)	370 (±104)	4,327 (±1,876)	5,360 (±1,984)	0.81

[a] Data not sufficient for calculation of *T½*, AUC0-∞, Vz and Cl for one patient

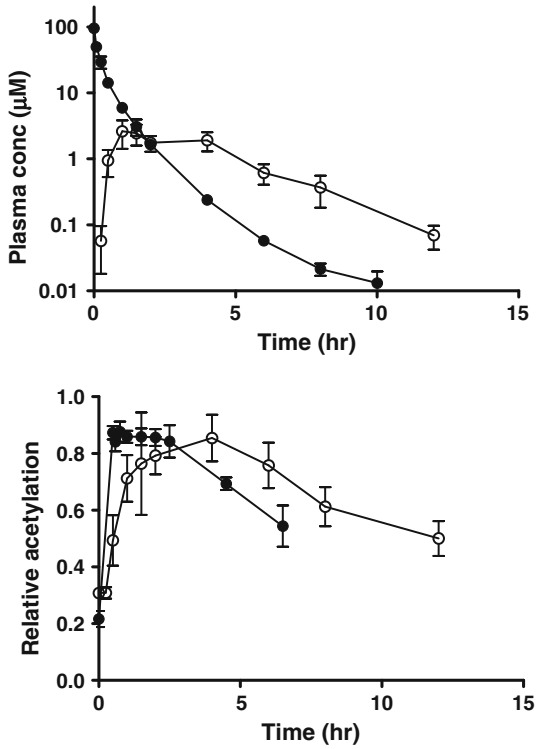

Fig. 1 *Upper figure*: plasma concentrations following intravenous administration of belinostat (*bullet symbols*, $n = 7$) and subsequent oral administration of belinostat to the same patients (*open symbols*); *Lower figure*: Histone H4 acetylation levels in PBMCs taken at various times following intravenous administration of belinostat (*bullet symbols*, $n = 7$) and subsequent oral administration of belinostat to the same patients (*open symbols*)

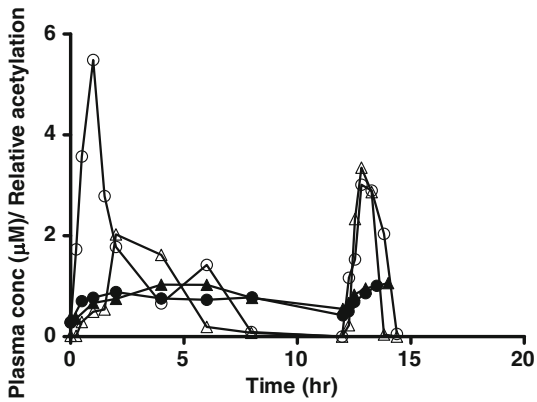

Fig. 2 Plasma concentrations (*open symbols*) and histone H4 acetylation levels (*closed symbols*) in two patients following oral administration of belinostat at $t = 0$ and again at $t = 720$ min

particularly with the thrice daily schedule which was only administered to two patients. Nevertheless, these preliminary data provide support for the continued development of an oral formulation of the HDAC inhibitor belinostat. Oral belinostat was well tolerated at high doses and provides higher exposure (AUC) in plasma than other orally

dosed HDAC inhibitors such as MS-275, vorinostat and MGCD0103 at their recommended doses or at their respective maximum tolerated doses [11–13]. A slight increase in the AUC of belinostat from day 1 to 5 was observed (qd = 26%; bid = 17%), although it is unclear if this observation is due to drug accumulation. No significant accumulation was found following intravenous infusion of belinostat for 5 consecutive days [6]. Intake of food or fluid with the oral formulation was not controlled in this small study, and no pre-clinical food effect studies have been performed. Consequently, an effect of food on drug pharmacokinetics may have contributed to the variable and, in some cases, increased exposure similar to that reported for vorinostat [14] and MGD0103 [11].

The variability in clearance with oral belinostat is rather large. The coefficient of variation (CV) for the clearance has been calculated for dose groups with more than two patients. CV is 62% ($n = 11$) for the 1,000 mg/m^2 dose level (qd and bid cohorts), whereas CVs are 39% ($n = 4$), 45% ($n = 5$), and 71% ($n = 3$) for the 1,500, 1,750 and 2,000 mg groups, respectively. This indicates that dosing by body surface area does not eliminate variance in clearance for belinostat, similar to reported findings for MS-275 [15]. The reason for the variation in clearance has not been identified in this small study, but correction for the patients' surface area may not be required for oral dosing of belinostat.

The mean apparent half-life ($t½$) of 1.9 h following oral administration of 1,000 mg/m^2 on day 1 and 1.7 h on day 5 was longer than the mean apparent $t½$ of 0.8 h following intravenous administration of the oral-equivalent dose of belinostat. This suggests an absorption-rate-limited drug disposition in the GI tract and possibly entero-hepatic recirculation. This observation is supported by pre-clinical studies with radiolabelled belinostat in the rat. In the intact rat, 45% of an oral dose is excreted via urine compared to 20% in bile duct—cannulated rats. Influence of feeding conditions on absorption has been reported for other hydroxamate HDAC inhibitors including vorinostat [13] and MS-275 [15].

The effects of belinostat on histone acetylation were comparable for the two routes of administration suggesting that oral dosing is an effective route of administration (Fig. 1). Levels of acetylation increase more rapidly after intravenous than after oral administration which is consistent with the drug pharmacokinetics where the Tmax is later following oral drug administration. The level of acetylation was very low in untreated patients but was higher in the pre-treatment sample taken from patients prior to oral dosing. This could be explained by the effects of previous cycles of treatment. For two patients, levels of histone H4 acetylation were measured following the second oral dose (Fig. 2). Acetylation levels increased rapidly as seen after the first dose indicating that twice daily dosing has a more prolonged effect on the drug target.

High doses of oral belinostat, up to 1,000 mg/m^2 bid for 5 consecutive days, have been tolerated in this small study. Preliminary indications of anti-tumour activity observed in the phase-1 trial of intravenous belinostat are encouraging and support further trials of this drug. An oral formulation could lead to enhanced drug exposure and, more importantly, prolonged effects on the intended drug target. A trial is ongoing to establish the optimal dose and schedule of oral administration of belinostat.

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