Phase II trial of oral vorinostat (suberoylanilide hydroxamic acid) in relapsed diffuse large-B-cell lymphoma


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Background: Vorinostat has demonstrated activity in refractory cutaneous T-cell lymphoma. In a phase I trial, an encouraging activity in diffuse large-B-cell lymphoma (DLBCL) was noted.

Patients and methods: We carried out a phase II trial (NCT00097929) of oral vorinostat 300 mg b.i.d. (14 days/3 weeks or 3 days/week) in patients with measurable, relapsed DLBCL who had received two or more systemic therapies. Response rate and duration (DOR), time to progression (TTP) and safety were assessed.

Results: Eighteen patients were enrolled (median age: 66 years; median prior therapies: 2). Seven received 300 mg b.i.d. 14 days/3 weeks, but four had grade 3 or 4 toxicity (dose-limiting toxicity, DLT). The schedule was amended to 300 mg b.i.d. 3 days/week, and none had DLT. One achieved a complete response (TTR = 85 days; DOR > 468 days) and one had stable disease (301 days). Sixteen discontinued for progressive disease; median TTP was 44 days. Median number of cycles was 2 (1 to > 19). Common drug-related adverse experiences (AEs; mostly grade 1/2) were diarrhea, fatigue, nausea, anemia and vomiting. Three patients had dose reduction; none discontinued for drug-related AEs. Drug-related AE grade 3 included thrombocytopenia (16.7%) and asthenia (11.1%).

Conclusion: Vorinostat was well tolerated at 300 mg b.i.d. 3 days/week or 200 mg b.i.d. 14 days/3 weeks but had limited activity against relapsed DLBCL.

Key words: diffuse large-B-cell lymphoma, DLBCL, HDAC, histone deacetylase inhibitor, SAHA, suberoylanilide hydroxamic acid, vorinostat

original article

introduction

Diffuse large-B-cell lymphoma (DLBCL) is the most common subtype of non-Hodgkin’s lymphoma and represents a heterogenous group of tumors [1]. Combination chemotherapy with cyclophosphamide, doxorubicin, vincristine, prednisone and rituximab (CHOP-R) is considered the standard treatment regimen for patients with DLBCL, but the 5-year progression-free survival (PFS) and overall survival among high-risk patients remain <50% [2, 3]. High-dose chemotherapy followed by autologous stem-cell transplantation (ASCT) is the standard approach for chemosensitive relapsed DLBCL patients [4, 5]. However, elderly patients may not be candidates for this treatment and relapse following transplant is common. Novel therapies that improve disease control and survival clearly are still needed for patients with DLBCL.

Vorinostat is a histone deacetylase (HDAC) inhibitor which has been shown to induce cell cycle arrest and apoptosis and prolong survival in preclinical models of B-cell lymphoma [6]. HDAC inhibitors appear to promote B-cell lymphoma cell death through downstream effects of acetylation and possibly through inactivation of BCL-6, a proto-oncogene implicated in the pathogenesis of DLBCL [7, 8]. Vorinostat was approved by the USA Food and Drug Administration in October, 2006, for the treatment of cutaneous T-cell lymphoma [9, 10].

In a phase I trial, antitumor activity was observed in DLBCL patients treated with oral vorinostat, as three of seven patients achieved a response [11, 12]. The current phase II trial was conducted to further evaluate the efficacy and safety of oral vorinostat in patients with relapsed DLBCL. The dose regimens studied (300 mg b.i.d. for 3 days followed by a 4-day rest and 300 mg b.i.d. for 14 days followed by a 7-day rest) were based on the findings of phase I oral vorinostat trials [11, 13].

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methods
This multicentre, open-label, single-arm, nonrandomized phase II trial (Protocol 013) was approved by the investigational review boards of the participating sites. Written informed consent was obtained from all patients before enrollment. The primary objective was to determine the overall objective response rate (ORR) as measured by computed tomography (CT) and 2-[fluorine-18]fluoro-2-deoxy-D-glucose–positron emission tomography (FDG–PET). Assessment of time to response (TtR), response duration (DOR), time to progression (TTP), PFS and safety in this patient population was the secondary objective.

patient eligibility
All patients must have had measurable, relapsed DLBCL following at least two systemic therapies. Patients who relapsed after or who were not candidates for systemic salvage therapy and stem-cell transplantation were also eligible. Patients must have discontinued prior therapy for at least 4 weeks, recovered from prior toxic effects and had at least 3 months of stable disease (SD) or response since the beginning of their last treatment. Patients had to be at least 18 years old with an Eastern Cooperative Oncology Group (ECOG) performance status of zero to two and have adequate coagulation, bone marrow and hepatic and renal functions. Male and nonsterilized, premenopausal female patients must have agreed to use adequate contraception or avoid pregnancy.

Patients with lymphoma that progressed following more than three prior therapies, had an allogeneic transplant or had prior treatment with an HDAC inhibitor were excluded. Other exclusion criteria included the following: acute infection within 2 weeks of starting therapy, uncontrolled intercurrent illness, active hepatitis B or C infection, known human immunodeficiency virus infection, central nervous system metastases or cancer other than DLBCL (except basal cell carcinoma, cervical carcinoma in situ or disease in remission for at least 5 years). Patients on systemic steroids of >10 mg/day of prednisone or equivalent during the 4 weeks before using the study drug; who had a gastrointestinal condition that may affect drug absorption; or who were pregnant, lactating or allergic to any component of the study drug were also excluded.

study design
Patients were treated on an outpatient basis and instructed to take oral vorinostat with food and maintain adequate fluid intake. The initial dose of vorinostat was 300 mg b.i.d. for 14 days followed by a 7-day rest. Due to toxicity (mainly thrombocytopenia, see results) the protocol was amended to a weekly schedule of 300 mg b.i.d. for 3 days followed by a 4-day rest. For patients on the 14-day schedule with drug-related grade 3 or greater adverse experiences (AEs), the dose could be reduced to 200 mg. For patients on the 3 days/week schedule who encountered drug-related grade 3 or greater adverse experiences (AEs), the dose could be reduced to 200 mg. For patients on the 14-day schedule with drug-related grade 3 or greater adverse experiences (AEs), the dose could be reduced to 200 mg.

Compliance with the study drug was assessed by capsule counts and adequate coagulation, bone marrow and hepatic and renal functions. Male and nonsterilized, premenopausal female patients must have agreed to use adequate contraception or avoid pregnancy.

Visits were conducted at baseline, weekly during the first cycle, during the first week of every subsequent cycle and within 4 weeks of study discontinuation. Baseline evaluation included a patient history and physical examination; ECOG performance status; complete blood count; comprehensive chemistry panel; fasting glucose; insulin, HbA1c, prothrombin time; internal normalization ratio; lactate dehydrogenase (LDH); urinalysis; β-hCG (in women of childbearing potential); electrocardiogram (ECG); bone marrow aspiration and biopsy; CT scans of neck, chest, abdomen, and pelvis; FDG–PET scan; and optional blood or tumor biopsy samples for correlative studies. ECGs were recorded within 2 h of dosing on week 3 (day 15) of cycle 1. Fasting glucose, insulin and HbA1c were repeated in patients with nonfasting glucose levels exceeding 140 mg/dl that represented at least one grade increase from baseline. CT and FDG–PET scans were carried out after two treatment cycles (six weeks of treatment on the 3 days/week schedule) and repeated after four treatment cycles and subsequently in patients who showed no signs of progressive disease (PD) to document response. Bone marrow aspiration and biopsy were performed to document a complete response (CR) or PD at the end of treatment if PD–PET or CT scan findings were unavailable.

safety and efficacy measurements
The severity of AEs was graded according to the National Cancer Institute Common Terminology for Adverse Events, v3.0. The relationship of each AE to vorinostat was determined by the investigators. The primary efficacy measurement was the objective tumor response based on integrated FDG–PET and CT scan findings [14, 15].

The response criteria were similar to those recently proposed [16]. CR was defined as complete disappearance of all detectable radiographic evidence of disease with negative FDG–PET scans, regression of all lymph nodes and nodal masses to normal size (≤1.5 cm in maximum diameter), resolution of all target focal splenic or extranodal lesions to undetectable, regression of enlarged spleen or liver by at least 25%, normalization of LDH and negative bone marrow biopsy by histology. Complete response unconfirmed required all CR criteria, but with an indeterminate bone marrow biopsy. Partial response (PR) required at least a 50% reduction in the sum of the products of the greatest dimensions (SPD) of the target lesions. Nontarget lesions must have been at least stable, with no increase in the size of liver or spleen and no new sites of disease by FDG–PET. FDG–PET may have been positive in one or more previously identified nodes or masses in previously unidentified areas without corresponding CT scan findings. SD was defined as being less than a radiographic PR, but not PD and as having a positive FDG–PET scan in any previously identified node or mass that did not regress to <1.5 cm (if previously ≥1.5 cm). PD required >50% increase in the SPD from blood cell count nadir of index lesions or >50% increase in the greatest diameter of any nonindex abnormal nodes (≥2 cm), appearance of new lesions (≥2 cm) and/or new lesions by FDG–PET scan. A biopsy to confirm the presence of tumor in the latter case, however, was not required. TIR was the time from start of therapy until first response. DOR was the time from first response until PD. TTP was the time from start of therapy until PD. PFS was measured from start of therapy until PD or death.

statistical analysis
All data from 13 May 2005 to 29 March 2007, were analyzed. All patients who received one or more doses of oral vorinostat were assessable for efficacy and safety. A two-stage design was utilized with a planned interim analysis after the first 25 patients completed four treatment cycles. The study could be stopped due to a low response rate (<10%) or poor quality response rates (11%–29%) with short DOR. The total planned enrollment was 50 patients. Vorinostat would be considered active for the treatment of advanced, relapsed DLBCL if the ORR was at least 20%
with the lower bound of the corresponding 95% exact confidence interval excluding 5%. With 50 patients, this study would have 90% power to observe ≥10 responses (20% response rate) if the true response rate is 27% and would have 84% power if the true response rate is 25%.

Due to lack of activity and slow accrual, the study was terminated after enrollment of 18 patients by the decision of the sponsor. The interim analysis was not carried out because <25 patients were enrolled.

results

patient population

A total of 25 patients were screened, and 18 were enrolled in the trial. The baseline patient and disease characteristics are shown in Table 1. Their median age was 66 years (range: 59–86 years). Most patients had stage III or IV disease and had received two or three prior therapies. In all, 6 of 18 had prior ASCT and 10 had high- or high-intermediate risk baseline International Prognostic Index scores.

Table 1. Baseline patient characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All patients (n = 18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>66.5</td>
</tr>
<tr>
<td>Range</td>
<td>59–86</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>9 (50)</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>15 (83.3)</td>
</tr>
<tr>
<td>Asian</td>
<td>1 (5.6)</td>
</tr>
<tr>
<td>Black</td>
<td>1 (5.6)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>1 (5.6)</td>
</tr>
<tr>
<td>ECOG performance status, n (%)</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>8 (44.4)</td>
</tr>
<tr>
<td>1</td>
<td>6 (33.3)</td>
</tr>
<tr>
<td>2</td>
<td>4 (22.2)</td>
</tr>
<tr>
<td>Time from initial diagnosis to study entry, years</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>2.9</td>
</tr>
<tr>
<td>Range</td>
<td>1.1–14.3</td>
</tr>
<tr>
<td>Prior systemic anticancer therapies, n (%)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1 (5.6)</td>
</tr>
<tr>
<td>2</td>
<td>10 (55.6)</td>
</tr>
<tr>
<td>3</td>
<td>6 (33.3)</td>
</tr>
<tr>
<td>&gt;4</td>
<td>1 (5.6)</td>
</tr>
<tr>
<td>Prior autologous stem cell transplantation, n (%)</td>
<td></td>
</tr>
<tr>
<td>#</td>
<td>6 (33.3)</td>
</tr>
<tr>
<td>Most recent disease stage, n (%)</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>2 (11.1)</td>
</tr>
<tr>
<td>III</td>
<td>10 (55.6)</td>
</tr>
<tr>
<td>IV</td>
<td>6 (33.3)</td>
</tr>
<tr>
<td>Baseline IPI score, n (%)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1 (5.6)</td>
</tr>
<tr>
<td>2</td>
<td>7 (38.9)</td>
</tr>
<tr>
<td>3</td>
<td>7 (38.9)</td>
</tr>
<tr>
<td>4</td>
<td>3 (16.7)</td>
</tr>
<tr>
<td>Time since stop of last therapy, months</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>6.2</td>
</tr>
<tr>
<td>Range</td>
<td>2.3–19.2</td>
</tr>
</tbody>
</table>

ECOG, Eastern Cooperative Oncology Group; IPI, International Prognostic Index.

efficacy

Of the 18 patients assessable for response, 1 had a CR, 1 had prolonged SD (301 days) and the other 16 had PD (ORR 5.6%). The responding patient received vorinostat 300 mg b.i.d. for 3 days followed by a 4-day rest. This 59-year-old female had stage IVA disease and had received prior CHOP-R; rituximab, ifosfamide, carboplatin, etoposide plus methotrexate, and ASCT. At baseline, disease was detected in the right lung and the paratracheal, subcarinal and hilar lymph nodes. The patient met CR criteria on day 85 (TtR = 85 days, Figure 1) and remains in CR as of 13 August 2007 (DOR = >468 days).

The patient with prolonged SD was on vorinostat 300 mg b.i.d. for 14 days followed by a 7-day rest. The median TtP for the study cohort was 44 days; PFS rates at 3 and 6 months were 16.7% and 11.1%, respectively.

compliance with vorinostat

The median number of cycles received was 2 (range: 1 to >19). Compliance with study drug was excellent: the median percentage of doses taken based on capsule counts was 97.4 (range: 64.9–100.0). Seventeen patients discontinued treatment: 16 due to PD and 1 due to a clinical AE unrelated to vorinostat (intestinal obstruction on day 7, cycle 1, in a patient taking 300 mg b.i.d. for 14 days). One patient remains on vorinostat treatment (>581 days).

safety and toxicity

The initial seven patients were treated with oral vorinostat 300 mg b.i.d. for 14 days followed by a 7-day rest, but four had dose-limiting toxic effects (DLTs; grade 3 muscle spasms in cycle 1, day 15; grade 4 thrombocytopenia in cycle 1, day 15; grade 3 thrombocytopenia in cycle 3, day 14 and grade 4 thrombocytopenia and anemia in cycle 1, day 8). Three of these patients had dose modification according to study protocol (to 200 mg b.i.d.) and did not have subsequent DLTs or require further dose reduction. The other patient discontinued treatment because of disease progression-related AEs before scheduled dose reduction. Due to the toxicity (mainly thrombocytopenia) encountered with the 300 mg b.i.d. for 14 days every 3 weeks schedule in this and another clinical trial [9], the protocol schedule was amended to 300 mg b.i.d. for 3 days with a 4-day rest each week [11]. No patient treated on the amended dose schedule had DLTs or required dose modification.

Seven patients had a total of 15 serious AEs. Five of these events were related to vorinostat (300 mg b.i.d. 3 days/week: general physical health deterioration, hyponatremia; 300 mg b.i.d. 14 days/3 weeks: anemia, thrombocytopenia, n = 2). Two patients died on study of causes unrelated to vorinostat. One patient died due to acute myocardial infarction 13 days after drug discontinuation (day 95) and another died due to gastrointestinal hemorrhage and hemorrhagic shock secondary to PD 10 days after drug discontinuation (day 40).

The most common drug-related AEs are shown in Table 2. These events were mostly grade 2 or less and included diarrhea (61%), fatigue (50%), nausea (39%), anemia (33%) and vomiting (33%). The most common drug-related grade 3/4 AEs included thrombocytopenia (n = 3; 300 mg b.i.d. 14 days...
every 3 weeks) and asthenia (n = 2; 300 mg b.i.d. 3 days/week).
Of the 18 patients enrolled, 15 had at least one postbaseline
ECG. The maximum QTc change from baseline was ≤30 ms
in 14 patients and >30 to ≤60 ms in one patient. This patient
was treated with vorinostat 300 mg b.i.d. for 14 days every
3 weeks and was asymptomatic.

discussion
This multicentre, open-label, nonrandomized single-arm
phase II study was conducted because of the activity seen in
phase I trials of vorinostat in patients with relapsed DLBCL,
and in T-cell lymphoma [11, 12]. Despite promising early
results, in this study only one of 18 patients responded, and
it was elected to close the trial earlier than planned due to
lack of activity and slow accrual. The number of patients
evaluated has 90% power to detect a response rate of at least
20%, so it is unlikely that a larger trial would have provided
a different result in this patient population. It is possible that
the trial may have been stopped prematurely, and additional
data on the amended schedule (300 mg b.i.d. for 3 days
followed by a 4-day rest) or an alternative schedule may yield
different results. Activity in relapsed or refractory DLBCL or
other types of lymphoma has been observed with vorinostat
in previous trials [9–12, 17] as well as with other HDAC
inhibitors [18–22]. Correlative studies evaluating levels of
histone acetylation, or that of other target proteins, in tumor
biopsies would be helpful in identification of patients with
DLBCL who may respond to HDAC inhibitor therapy.
An additional objective was to assess the safety and
tolerability of vorinostat in this patient population. When
this study was initiated, the maximum tolerated dose (MTD)
of oral vorinostat for 14 days every 3 weeks was 250 mg
three times daily (total daily dose of 750 mg) in patients with
leukemia and myelodysplasia [13]. The major DLTs were
fatigue, nausea, vomiting and diarrhea. The first seven
patients treated in this study received oral vorinostat 300 mg
b.i.d. for 14 days every 3 weeks (total daily dose of 600 mg)

![Figure 1. 2-[Fluorine-18]fluoro-2-deoxy-D-glucose–positron emission tomography (FDG–PET) and computed tomography (CT) scans of a 59-year-old patient with relapsed, stage IVA disease who achieved a complete response on vorinostat. (A) FDG–PET scans at baseline (2 February 2006) and on day 29 (7 March 2006) are shown. Corresponding CT scans are shown in (B) and (C). The patient achieved a complete response on day 85 (2 May 2006), has maintained this response as of day >553 (13 August 2007) and remained on therapy as of day >581 (14 September 2007).](image-url)
but experienced significant thrombocytopenia, which had not
been observed as a DLT in the phase I trial in patients with
advanced leukemia and myelodysplastic syndromes [13].
Thrombocytopenia was later observed in a phase II trial in
patients with cutaneous T-cell lymphoma (CTCL) using
a similar dose and schedule (42% grade 3/4) [9]. The schedule
was therefore amended to 300 mg b.i.d. for 3 days followed
by a 4-day rest each week, the MTD determined in another
This regimen was well tolerated as there were no additional
DLTs. These results indicate that frequent drug holidays (4 out
of every 7 days in this trial) may be necessary for optimal
drug exposure and response remains to be determined.

In summary, although the number of patients evaluated on
each of the two schedules used in this study was small,
vorinostat showed limited activity in patients with relapsed
DLBCL. Oral vorinostat 300 mg b.i.d. for 14 days every 3 weeks
was not tolerable in these heavily pretreated patients. The
optimal dose and schedule in patients with B-cell lymphoma as
well as predictive response biomarkers require further
investigation.

acknowledgements

This study was presented at the 14th European Cancer
Conference in Barcelona, Spain, on 26 September 2007.

Table 2. Most common drug-related clinical adverse experiences
(N = 18)

<table>
<thead>
<tr>
<th>Experience</th>
<th>Grade 1–4, n (%)</th>
<th>Grade 3–4, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>11 (61)</td>
<td>0</td>
</tr>
<tr>
<td>Fatigue</td>
<td>9 (50)</td>
<td>1 (6)</td>
</tr>
<tr>
<td>Nausea</td>
<td>7 (39)</td>
<td>0</td>
</tr>
<tr>
<td>Anemia</td>
<td>6 (33)</td>
<td>1 (6)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>6 (33)</td>
<td>0</td>
</tr>
<tr>
<td>Anorexia</td>
<td>5 (28)</td>
<td>0</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>5 (28)</td>
<td>3 (17)</td>
</tr>
<tr>
<td>Anemia</td>
<td>4 (22)</td>
<td>2 (11)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>2 (11)</td>
<td>0</td>
</tr>
<tr>
<td>Alopecia</td>
<td>2 (11)</td>
<td>0</td>
</tr>
<tr>
<td>Constipation</td>
<td>2 (11)</td>
<td>0</td>
</tr>
<tr>
<td>Contusion</td>
<td>2 (11)</td>
<td>0</td>
</tr>
<tr>
<td>Dizziness</td>
<td>2 (11)</td>
<td>0</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>2 (11)</td>
<td>0</td>
</tr>
<tr>
<td>Fever</td>
<td>2 (11)</td>
<td>0</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>2 (11)</td>
<td>1 (6)</td>
</tr>
<tr>
<td>Hyponatremia</td>
<td>2 (11)</td>
<td>2 (11)</td>
</tr>
<tr>
<td>Muscle spasms</td>
<td>2 (11)</td>
<td>1 (6)</td>
</tr>
<tr>
<td>Weight loss</td>
<td>2 (11)</td>
<td>0</td>
</tr>
</tbody>
</table>

A patient was counted only once per specific adverse experience and only
the highest grade of a given adverse experience was counted per patient.

references

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