Phase I Study of Panobinostat plus Everolimus in Patients with Relapsed or Refractory Lymphoma

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Abstract

Purpose: To evaluate the safety and efficacy of panobinostat plus everolimus in patients with relapsed Hodgkin and non-Hodgkin lymphoma. The concept was supported by the single-agent clinical activity of histone deacetylase inhibitors and mTOR inhibitors, and on the in vitro mechanism-based synergistic antiproliferative activity.

Experimental Design: This was a phase I study in patients with relapsed or refractory Hodgkin and non-Hodgkin lymphoma using panobinostat orally on Monday/Wednesday/Friday and everolimus orally daily. Toxicity and responses were assessed in dose-escalation cohort followed by expansion cohort at maximum-tolerated dose. Exploratory analysis of serum cytokine levels was performed.

Results: Thirty patients were enrolled onto four dose levels. The dose-limiting toxicity was thrombocytopenia. The maximal tolerated dose was panobinostat 20 mg and everolimus 10 mg. Grade 3/4 toxicity included thrombocytopenia (64%), neutropenia (47%), anemia (20%), infection (10%), fatigue (7%), and dyspnea (7%). A total of 10 patients (33%; indolent lymphoma, T-cell lymphoma, mantle cell lymphoma, and Hodgkin lymphoma) achieved objective responses. In patients with Hodgkin lymphoma (n = 14), the overall response rate was 43% with complete response rate of 15%. In patients with Hodgkin lymphoma, multiple serum cytokine levels decreased significantly after treatment with this combination therapy. Of note, clinical responses were associated with a decrease in serum interleukin-5 levels (day 8, P = 0.013, and day 15, P = 0.021).

Conclusions: Our data suggest that the combination therapy is active but with significant thrombocytopenia. Future studies should explore alternate scheduling and different compounds that target the same pathways to improve the tolerability of this novel combination.

Introduction

Patients with recurrent lymphoma after autologous stem-cell transplant, or those who are not candidate for stem-cell transplant, generally have a poor prognosis. Novel treatment strategies are needed in such patients with refractory or recurrent lymphoma. There are multiple new antitumor agents that are currently being evaluated for the treatment of patients with lymphoma (1, 2). However, when these compounds are tested in unselected patients with relapsed lymphoma, they typically produce low response rates with short response duration. We and others have shown that histone deacetylase (HDAC) inhibitors can produce clinical remissions in patients with relapsed Hodgkin lymphoma and non-Hodgkin lymphoma. In a recent phase II study, panobinostat produced a response rate of 27% and the median progression-free survival of 6.1 months in patients with relapsed or refractory Hodgkin lymphoma (3). Similar outcome was also observed using the isotype selective HDAC inhibitor, mocetinostat (4). Responses were also observed in non-Hodgkin lymphoma but activities are generally modest at best (5–7).

The phosphoinositide-3-kinase (PI3K)/AKT/mTOR pathway is one of the most frequently activated oncogenic signaling pathway in cancer (8). Both everolimus and temsirolimus have demonstrated clinical activity in patients with relapsed Hodgkin lymphoma and non-Hodgkin lymphoma, but the activity again is modest, with reported response rate of 35% or less and the response is generally short-lived (9–12). Future strategies should focus on selecting patients based on predictive biomarkers, and on mechanism-based rationally designed combination strategies (2).

Mechanistically, HDAC inhibitors can regulate multiple growth and survival pathways (13–18). For example,
panobinostat activated the caspase pathway, inhibited STAT5 and STAT6 phosphorylation, and downregulated hypoxia-inducible factor-1α (HIF-1α) and its downstream targets, glucose transporter 1 (GLUT1) and VEGF (14, 15). At the same time, however, panobinostat inhibited LKB1 and AMP-activated protein kinase (AMPK), leading to activation of mTOR that promotes survival (15). On the other hand, mTOR inhibitors can induce cell-cycle arrest and autophagy, but their antitumor activity can be attenuated by a negative feedback loop involving AKT activation (14).

The combination of panobinostat and everolimus showed synergistic antiproliferative activity by reciprocal inhibition of negative feedback loops induced by mTOR inhibitor and panobinostat therapy (14, 15). Similar synergy was observed using different compounds that target the same pathways in lymphoma and other cancer models (19, 20).

On the basis of the single-agent activity of mTOR and HDAC inhibitors as well as on synergistic effect of combination treatment observed in vitro (15, 19, 20), we conducted a phase I study of panobinostat in combination with everolimus in patients with relapsed Hodgkin lymphoma and non-Hodgkin lymphoma.

Materials and Methods

This was an open-label, non-randomized phase I study of panobinostat in combination with everolimus in patients with lymphoma. This study was approved by the institutional review board, and was registered at clinicaltrials.gov (identifier NCT00967044). All participants gave written informed consent. The primary objective of the study was to determine MTD and dose-limiting toxicity (DLT) of the combination of panobinostat and everolimus. We initially intended to proceed to phase II part of the study at MTD.

However, we noticed that treatment interruptions were frequently required in patients treated at MTD because of grade 3/4 thrombocytopenia. Thus, we amended the protocol to obtain the more detailed safety data at MTD and also to allow dose reduction in patients’ experienced toxicity in an expanded phase I study.

Eligibility

Eligible patients were required to have lymphoma of any histology excluding Burkitt lymphoma or lymphoblastic lymphoma who have relapsed or have been refractory to standard treatment; have no curative option available; be 18 years and older; have measurable disease ≥1.5 cm; have an Eastern Cooperative Oncology Group Performance Status 0 to 2; have absolute neutrophil count (ANC) ≥1,000/mm³ and platelet count ≥75 × 10³/mm³; have serum creatinine ≤1.5 × upper limit of normal (ULN), total bilirubin ≤1.5 × ULN, and transaminase levels ≤2.5 × ULN (≤5.0 × ULN if lymphomatous involvement in the liver); have plasma-free T4 level within normal limits with or without thyroid hormone replacement; fasting serum cholesterol ≤300 mg/dL or ≤7.75 mmol/L, and fasting triglycerides ≤2.5 × ULN. Patients were ineligible if they were pregnant, had chemotherapy or radiotherapy within 4 weeks; have HIV infection, have active viral hepatitis; have impaired cardiac function [QT interval corrected by the Fridericia formula (QTc) >450 ms, congenital long QT syndrome, heart rate less than 50 beats per minute, congestive heart failure of New York Heart Association (NYHA) class III or IV, bifascicular block defined as right bundle branch block with left anterior hemiblock, or uncontrolled hypertension]; have a history of serious cardiac events (sustained ventricular tachycardia, ventricular fibrillation, or Torsades de pointes); impaired gastrointestinal function that may significantly alter the absorption of oral drugs; or had other uncontrolled illnesses.

Treatment

Treatment cycle was every 28 days. Panobinostat was self-administered orally three times a week. This is based on the previous clinical experience with panobinostat in phase I studies, in which the starting dose was 20 mg orally three times a week (21), and the phase II dose for Hodgkin lymphoma was 40 mg orally three times a week (3). The starting dose in this study was 10 mg orally three times a week. Each dose of panobinostat was taken with at least 240 mL of water. Everolimus was self-administered orally once daily. A phase I study of everolimus in hematologic malignancies tested 5-mg daily dose and 10-mg daily dose (12) and a recommended phase II dose was 10 mg daily (9). The starting dose of everolimus in this study was 5 mg orally. Everolimus was taken in a fasting state or with no more than a light fat-free meal around the same time each day. Patients were required to avoid grapefruit or grapefruit juice and seville oranges during the study. The doses of panobinostat and everolimus were 10 mg and 5 mg in cohort 1, 20 mg and 5 mg in cohort 2, 20 mg and 10 mg in cohort 3, and 30 mg and 10 mg in cohort 4, respectively. Of note, previous early
acetylation increases in hematopoietic cells after oral clinical trial with correlative study showed that histone acetylation increases in hematopoietic cells after oral panobinostat at doses 20 mg and above (21).

Initially, 3 patients were treated at each dose level and were monitored for DLTs for 28 days. If no DLTs were observed in those 3 patients at the end of their first treatment cycle, escalation to the next dose level could commence. If a DLT is observed in 1 of the first 3 patients, the cohort was expanded to a maximum of 6 patients. If 2 or more DLTs are observed, no further escalation took place. If the MTD has been exceeded, the preceding dose level was recommended for expanded cohort.

**Toxicity**

Toxicity was graded on the basis of Common Terminology Criteria for Adverse Events Version 3. DLT was determined during the first cycle. For nonhematologic toxicity, DLT was defined as any grade 3 or greater toxicity except for grade-3 fatigue; grade-3 or -4 nausea and vomiting lasting less than 24 hours; grade-3 nonhematologic laboratory abnormalities that resolve to at least grade 2 or baseline within 14 days. For hematologic toxicity, DLT was defined as grade-4 neutropenia lasting more than 7 days, grade-3 febrile neutropenia requiring antibiotics, grade-4 febrile neutropenia, or grade-4 thrombocytopenia lasting more than 7 days.

The MTD was defined as the highest dose at which no more than 1 in 6 of the patients in the cohort experienced one or more DLT in the first treatment cycle. The MTD was established without the use of colony-stimulating factor in cycle 1. Any patient experiencing DLT lasting more than 7 days was discontinued from study. No dose reduction was allowed in the dose-finding cohort. A scheduled dose of panobinostat and everolimus was allowed to be held up to 14 days in patients who experienced non-DLT toxicity that had not returned to at least grade 2 or baseline at the time of the next scheduled dose.

Throughout the study, serum biochemistry values including serum potassium, calcium, phosphorous, and magnesium were monitored closely. On any day and time in which serum potassium, calcium, phosphorous, and magnesium were assessed, if the value is grade 2 or worse and clinically significant, then the patient’s potassium, calcium, phosphorous or magnesium needed to be supplemented at treating physician’s discretion. Patients then underwent a repeat biochemistry test to demonstrate values of grade 1 or better.

In the expanded cohort, dose interruptions longer than 2 weeks were allowed for the conditions as followings: nonhematologic toxicity of grade 3; intolerable nonhematologic toxicity of grade 2; grade-3 neutropenia; grade-4 neutropenia which improves within 7 days with growth factor support or 14 days after growth factor support; grade-3 febrile neutropenia; grade-4 thrombocytopenia. If grade-4 nonhematologic toxicity was observed, the treatment was discontinued. Dose reduction to the same level for cohort 2 was allowed if the dose interruption was due to grade-3 thrombocytopenia.

**Response**

Response assessment was performed every 2 cycles of therapy using Cheson criteria (22), and the response was coded as complete response (CR), partial response (PR), stable disease, or progressive disease. In patients who had bone-marrow involvement, bone-marrow evaluation was repeated when radiographically in CR. After discontinuation of therapy, patients were followed every 3 months for the first 2 years, then every 6 months thereafter, or until progression.

**Exploratory analysis of serum biomarkers**

We collected serum samples from consenting patients with Hodgkin lymphoma ($n = 14$) on day 1 before treatment, day 8 and day 15 after treatment for correlative biomarker study. We analyzed 52 cytokine levels (6CKine, BCA1, CTACK, EGF, ENA-78, Eotaxin, Eotaxin-2, Eotaxin-3, G-CSF, GM-CSF, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-10, IFN-α, IFN-β, IFN-γ, IL-1α, IL-1β, IL-1RA, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-10, IL-12p40, IL-12p70, IL-13, IL-15, IL-16, IL-17, IL-20, IL-21, IL-23, IL-28A, IL-33, IP-10, LIF, MCP-1, MCP-2, MCP-3, MCP-4, stem cell factor (SCF), SDF-1α, TARC, TNF-α, TNF-β, TPO, TRAIL, TSLP, and VEGF) in the serum using the Human Cytokine/Chemokine Magnetic Beads Panel kits (Millipore: HCYTMAG-60K-PX29 and MPXCHCYF2PK23) on Luminex-100 ELISA System (Luminex Corporation) and results were generated using Star Station Version 1.8 software (SAI software, free ware). Values were reported by the log2 ratios to the median value collected from normal individuals, and changes after treatment were recorded by the relative change from pretreatment value. The baseline values as well as changes in the values were assessed for their possible association with clinical response.

**Statistical analysis**

The initial phase I part of the study was based on 3+3 design. Once the MTD has been determined, we expanded the cohort at MTD to enroll 20 additional patients to obtain detailed toxicity profile. Response rate was not used to determine the number of patients to be enrolled. Progression-free survival (PFS) was calculated as the time-interval between the date on which a patient first received regimen and the documented date of disease progression or death whichever occurred first. Patients without an event were censored at the date they were last known to be in remission and alive for PFS. PFS function was estimated by the Kaplan–Meier method. The correlative analysis was reported descriptively. The cytokine levels after treatment were compared with the baseline levels using two-sample t test.

**Results**

**Patient characteristics**

Between December 2009 and August 2011, 31 patients were enrolled. All patients provided written informed consent. Fifteen had relapsed Hodgkin lymphoma and 16 had non-Hodgkin lymphoma. One patient with Hodgkin...
lymphoma withdrew consent before receiving treatment. Thus, a total of 30 patients were treated in the study. Table 1 lists the baseline characteristics of these patients. The median number of prior treatments was 3 (range, 1–7) and 12 had undergone autologous stem-cell transplant.

### Dose determination

The number of patients in each dosing cohort is detailed in Table 1. During the dose escalation, DLTs were not observed at dose-level 1 to 3 during the first cycle. At dose-level 4, 2 patients were treated and both experienced grade-4 thrombocytopenia requiring transfusion after the first cycle. Thus dose-level 3 was considered MTD. We expanded the dose-level 3 and enrolled 20 additional patients. However, one did not receive a study drug and thus, 19 are evaluable for toxicity in this expanded cohort.

### Safety and drug exposure

All 30 patients who received at least a dose of treatment were assessed for toxicity. All hematologic toxicity, all grade-3/4 nonhematologic toxicity, and grade-1/2 toxicity that was observed in 10% or more of patients are listed in Table 2. Thrombocytopenia was a common toxicity observed in this study. It was observed in a dose-dependent manner; grade-4 thrombocytopenia was observed in 33%, 33%, 59%, and 67% of patients in cohort 1, 2, 3, and 4, respectively.

A total of 13 patients discontinued the study drug because of toxicity, grade-2 fatigue (7 patients chose to discontinue from this toxicity), infectious pneumonia (n = 2), interstitial pneumonitis with dyspnea (n = 2), dyspnea without radiographic evidence of interstitial pneumonitis (n = 2), and prolonged thrombocytopenia (n = 1). Fourteen patients discontinued the treatment because of progression or lack of response. Other patients discontinued treatment because of treatment completion resulting in CR (n = 1), transplant pursued (n = 1), and poor compliance (n = 1).

Overall, 24 of 30 patients required dose interruption because of toxicity, including thrombocytopenia (n = 15), dyspnea (n = 8), mucositis (n = 5), neutropenia (n = 3), diarrhea (n = 3), infection (n = 1), hypertriglyceridemia (n = 1), elevated creatinine (n = 1), or poor compliance (n = 3). Among them, 13 patients needed to have dose interruption longer than 7 days because of one or more of toxicities, dyspnea (n = 6), hypertriglyceridemia (n = 1), infection (n = 1), thrombocytopenia (n = 4), neutropenia (n = 4), and mucositis (n = 2). In cohort 3, in which dose reduction was allowed, 1, 2, and 2 patients had dose reduction from the second, third, and fourth cycle of treatment because of neutropenia grade 4 (n = 2), thrombocytopenia grade 4 (n = 1), dyspnea and fatigue grade 2 (n = 1), and renal insufficiency grade 2 (n = 1).

### Efficacy

One patient who did receive treatment for 1 week but required radiotherapy for clinically progressive disease was included in the denominator of response evaluation, although she did not have radiographic response evaluation. A total of 30 patients were evaluated in an intention-to-treat–based response analysis. The best reduction in size in patients who had at least one radiographic response evaluation is shown in the Figure 1 as a waterfall chart (n = 29,

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**Table 1. Patient characteristics and cohort (n = 30)**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>N</th>
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<tbody>
<tr>
<td>Age</td>
<td></td>
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<tr>
<td>Median (range)</td>
<td>52 (20–74)</td>
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<tr>
<td>Histology</td>
<td></td>
</tr>
<tr>
<td>Classic Hodgkin lymphoma</td>
<td>14</td>
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<tr>
<td>Diffuse large B-cell lymphoma</td>
<td>7</td>
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<tr>
<td>Angioimmunoblastic</td>
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<tr>
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</tr>
<tr>
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<tr>
<td>Small lymphocytic lymphoma</td>
<td>1</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Male/female</td>
<td>22/8</td>
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<tr>
<td>Median number of prior regimens (range)</td>
<td>3 (1–7)</td>
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<tr>
<td>Prior autologous stem-cell transplant</td>
<td>12 (40%)</td>
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<tr>
<td>Less than partial response to the last treatment</td>
<td>20 (66%)</td>
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<table>
<thead>
<tr>
<th>Cohort</th>
<th>Panobinostat (three times weekly)</th>
<th>Everolimus (daily)</th>
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<tbody>
<tr>
<td>1</td>
<td>10 mg</td>
<td>5 mg</td>
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<td>2</td>
<td>20 mg</td>
<td>5 mg</td>
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<tr>
<td>3</td>
<td>20 mg</td>
<td>10 mg</td>
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<tr>
<td>4</td>
<td>30 mg</td>
<td>10 mg</td>
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excluding 1 who did not have official measurement post treatment). A total of 10 of 30 patients (33%) achieved a clinical response, including 7 PR (23%) and 3 CR (10%). Positron emission tomography (PET) scan became negative in 3 patients, including 1 who had less than 50% size-reduction of the nodes (coded as CR, as this was a patient with Hodgkin lymphoma), as indicated in Figure 1. The change in the PET scan before and after the treatment in a representative patient who achieved CR is shown in Figure 2. Response was observed in 6 of 14 patients (43%) with Hodgkin lymphoma and 4 of 16 patients (25%) with non-Hodgkin lymphoma. CR rate was 15% (2 in 14) in patients with Hodgkin lymphoma. Among patients with non-Hodgkin lymphoma, 3 patients with mantle cell lymphoma all achieved PR (100%), and 2 of 3 patients with indolent lymphoma achieved PR (67%).

### Table 2. Toxicity

<table>
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<tr>
<th>Toxicity</th>
<th>Grade</th>
<th>All cohort (n = 30)</th>
<th>Cohort 3 only (n = 22)</th>
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<td>1 (37%)</td>
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<td>6 (20%)</td>
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<td>7 (32%)</td>
<td>2 (9%)</td>
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<td>5 (17%)</td>
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<td>5 (17%)</td>
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<td>1 (3%)</td>
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<td>1 (5%)</td>
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<td>1 (5%)</td>
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<td>4 (13%)</td>
<td>1 (3%)</td>
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<td>7 (23%)</td>
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<td>3 (10%)</td>
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<td>2 (7%)</td>
<td>2 (9%)</td>
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<td>7 (23%)</td>
<td>17 (57%)</td>
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<td>2 (7%)</td>
<td>2 (9%)</td>
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<td></td>
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<td>13 (59%)</td>
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Abbreviations: ENT, ear, nose, and throat; ALKP, serum alkaline phosphatase; AST, serum aspartate aminotransferase.
7 patients with diffuse large B-cell lymphoma achieved response in this study.

The responses were observed across the different dosing cohorts. In cohort 1, we observed 1 PR in 3 patients. In cohort 2, we observed 1 PR in 3 patients. In cohort 3, we observed 5 PR and 1 CR in 22 patients. Among responders, 2 had one dose-level reduction due to toxicity after first and second cycle, respectively. In cohort 4, in which no dose reduction was allowed, we observed 1 PR and 1 CR in 2 patients.

PFS of patients treated in this study is shown in Figure 3. The median PFS duration was 4 [95% confidence interval, (CI) 3–6] months. In responders, the median PFS duration was 8.5 months (95% CI, 4–not determined). The impressive durable response was observed in 1 patient with mantle cell lymphoma. This patient was 72 years old and had shown excellent radiographic improvement after 4 cycles of treatment. His gastrointestinal involvement, however, persisted, which was confirmed by biopsy. We determined that he achieved PR, but because of dyspnea that was considered to be related to everolimus, he was taken off study. He has not had treatment since and has shown no sign of progression to date (PFS duration 20+ months).

**Serum biomarkers**

Exploratory analysis of 52 cytokine levels revealed decrease in the levels of 11 cytokines and increase in the level of one cytokine ($P < 0.1$ from linear regression) after treatment in Figure 4A. These changes however were not significantly associated with actual clinical response (data not shown). Interestingly, TRAIL levels tended to increase after treatment ($P = 0.087$). We also considered serum biomarkers as potential predictor for clinical response. When the baseline cytokine levels were analyzed for their correlation with the clinical response (CR+PR vs. others), none of them was associated with response. When the changes in the cytokine levels were analyzed for their association with the clinical response, relative decrease in IL-5 levels were significantly correlated with response (on average, 37% decrease among responders vs. 39% increase among nonresponders on day 8, 60% decrease among responders vs. 33% increase among nonresponders on day 15; $P = 0.013$ and 0.021 based on two-sample t test on day 8 and day 15, respectively). In contrast, decrease in SCF levels
(day 8, $P = 0.04$ and day 15, $P = 0.46$), cutaneous T-cell–attracting chemokine (CTACK) levels (day 8, $P = 0.16$ and day 15, $P = 0.084$), and granulocyte colony–stimulating factor (G-CSF; day 8, $P = 0.064$ and day 15, $P = 0.073$) tended to be inversely correlated with clinical response (Fig. 4B). These results, however, are based on limited number of patients and need validation in the future studies. Other cytokines, either baseline levels or changes of levels, were not significantly associated with clinical response in our study. It should be noted that several other studies have shown a correlation between baseline or changes in thymus and activation-regulated chemokine (TARC) levels and clinical response in patients with Hodgkin lymphoma. We however did not observe such correlation also potentially due to the limited number of patients analyzed in our study.

Discussion

We showed the result of clinical trial of the combination therapy using panobinostat and everolimus for patients who have refractory or recurrent lymphoma. Over the last decade, multiple targeted agents have been investigated in refractory Hodgkin lymphoma. With the exception of brentuximab vedotin, however, most agents showed only mild antilymphoma activity as a single agent. In a large-scale phase II study of single-agent panobinostat in patients with relapsed or refractory Hodgkin lymphoma ($n = 129$), the overall response rate was 27%, including CR rate of 4% (3). In a study of single-agent everolimus in similar patient population (38 evaluable patients in 55 enrolled), the overall response rate was 37%, including CR rate of 1% (9). Neither one of them was shown to be effective enough for approval as a drug as a single-agent treatment of refractory Hodgkin lymphoma. The current combination therapy is supported by in vitro studies suggesting the synergistic antilymphoma activity of deacetylase inhibitor and mTOR inhibitor (15, 19, 20). The clinical efficacy of the combination therapy in patients with Hodgkin lymphoma is promising given the overall response rate of 43% with CR rate of 15%, which seems favorable compared with single-agent studies; a single-agent panobinostat study (3) showed an overall response rate of 27%, with CR rate of
23%, and a single-agent everolimus study showed an overall response rate of 37%, including CR rate of 1%

Our study showed that the combination therapy is frequently associated with thrombocytopenia, which is the DLT of single-agent panobinostat (3), and also a relatively common toxicity of everolimus (9–12). In this study, 13 patients (59%) in cohort 3 required dose interruption because of thrombocytopenia. The toxicity was observed in a dose-dependent manner, whereas the response was observed across a different treatment cohort that we used in this study. Added toxicity can become a concern when two drugs are combined. The rate of grade-3/4 thrombocytopenia in this study was 68%, as compared with 79% and 18% in studies of single-agent panobinostat and everolimus, respectively. It should be noted that thrombocytopenia generally subsided as the treatment was postponed, and thus is considered reversible. The rate of grade-3/4 neutropenia, on the other hand, was as high as 50% in our combination study, as opposed to 21% in single-agent panobinostat study (3) and 5% in single-agent everolimus study (9). Therefore, caution for infectious event is warranted when these two drugs are combined.

Another clinically significant toxicity was pneumonitis. Single-agent everolimus is reported to be associated with grade-3/4 pneumonitis in up to 18% of patients depending on dose and frequency and this was most studied in patients with renal cell carcinoma (23, 24). Interestingly, preliminary data in renal cell carcinoma suggested that pneumonitis may be associated with disease stabilization (25). This toxicity can be clinically significant leading to discontinuation of treatment, but was generally well managed with short course of systemic steroid. The incidence and the severity of pneumonitis observed in our study were similar to the previous studies of single-agent everolimus, and seem not exacerbated by combining with panobinostat.

Our exploratory correlative study in patients with Hodgkin lymphoma showed that levels of many of serum cytokines decrease after treatment with panobinostat and everolimus in combination. Serum cytokines are of great interest of research as they can potentially be the surrogates of responses. However, in our small dataset, there was no obvious association between cytokine level profile and clinical response, except possible value in serum IL-5, CTACK, SCF, and GCSF levels. It should be noted that only a limited number of patients were analyzed in the current study and further analysis is needed in a larger patient population to better describe the role of biomarkers in the treatment of patients with Hodgkin lymphoma in both front-line setting as well as salvage settings.

In conclusion, as a class, HDAC inhibitor and PI3K/AKT/mTOR pathway inhibitors have synergy in preclinical studies. In fact, the combination therapy of everolimus and panobinostat showed promising clinical activity. However, this combination therapy was associated with significant toxicity of thrombocytopenia requiring dose interruptions. Future studies should investigate different combination regimens of PI3K/AKT/mTOR inhibitors with HDAC inhibitor, incorporating correlative analysis of serum cytokine levels to investigate the clinical relevance.

Disclosure of Potential Conflicts of Interest

Y. Oki received commercial research grant from Novartis. A. Younes received other commercial research support from Novartis, Johnson & Johnson, Seattle Genetics, Merck, Genentech, Infinity, and Gilead, and has honoraria from speakers bureau of Novartis, Seattle Genetics, Millennium, Celgene, Curis, Sanofi, Pharmacyclics, and Incyte. No potential conflicts of interest were disclosed by the other authors.

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