Lack of Therapeutic Effect of the Histone Deacetylase Inhibitor Vorinostat in Patients with Metastatic Radioiodine-Refractory Thyroid Carcinoma

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Context: Aberrant histone deacetylase activity is seen in a variety of malignancies, and histone deacetylase inhibitors such as vorinostat have been shown to induce cell death and sensitize cells to cytotoxic chemotherapy in thyroid cancer cell lines. This phase II study was undertaken to assess objective response to vorinostat in patients with advanced thyroid cancer.

Experimental Design: A total of 19 patients with differentiated thyroid cancer (n = 16) and medullary thyroid cancer (n = 3) were enrolled in the study. Patients received oral vorinostat at a starting dose of 200 mg twice daily, with dose adjustments allowed as necessary for toxicity. Patients were treated for 2 wk, followed by 1 wk off therapy (3-wk cycle) until disease progression or study withdrawal. Responses were measured by Response Evaluation Criteria in Solid Tumors criteria and correlated with tumor markers.

Results: No patient achieved a partial or complete response. Median duration of therapy in patients with differentiated thyroid cancer was 17 wk, whereas in medullary thyroid cancer patients it was 25 wk. Reasons for termination included progression of disease by RECIST criteria (n = 7), clinical progression (n = 3), and adverse events (AEs) (n = 9). AEs were primarily grade 1–3; no clinical grade 4 or grade 5 events were observed. Clinical grade 3 AEs consisted of fatigue, dehydration, ataxia, pneumonia, bruises, and deep vein thrombosis. Severe thrombocytopenia was seen in seven patients (grade 3, n = 5; grade 4, n = 2) and was associated with minor bleeding or bruises.

Conclusions: Vorinostat at this dose and schedule is not an effective treatment for advanced thyroid cancer. (***J Clin Endocrinol Metab*** **94: 164–170, 2009)**

Thyroid carcinoma is the most common malignancy of the endocrine system, and the vast majority of these carcinomas are of the papillary or follicular subgroups. The majority of these well-differentiated thyroid carcinomas (DTCs) are highly treatable by surgery followed, in most patients, by I^{131} and TSH-suppressive doses of levothyroxine (1). Indeed, the overall 10-yr survival rate is 93% for patients with papillary thyroid carcinoma (PTC) and 85% for patients with follicular thyroid carcinoma (FTC). However, about 2% of patients with PTC and 6% of those with FTC or Hurthle cell carcinoma have distant metastasis at the time of diagnosis (2), and an additional group of patients develop identifiable distant metastases during long-term follow-up (3, 4). The long-term disease-specific survival of patients with either DTC or medullary thyroid cancer (MTC) with distant metastases is less than 50% at 5 yr (2, 4, 5). Furthermore, a subgroup of these patients with distant metastases, including those with metastases that concentrate ^{131}I poorly, have brain, bone, or large lung metastases or bulky

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Abbreviations: AE, Adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CBC, complete blood count; CEA, carcinoma embryonic antigen; CR, complete response; DTC, differentiated thyroid carcinoma; FTC, follicular thyroid carcinoma; GI, gastrointestinal; HDAC, histone deacetylase; INR, international normalized ratio; MTC, medullary thyroid cancer; NIS, sodium-iodide symporter; PR, partial response; PT, prothrombin time; PTC, papillary thyroid carcinoma; RAI, radioactive iodide; RECIST, Response Evaluation Criteria in Solid Tumors; Tg, thyroglobulin.

fluorodeoxyglucose-avid metastases (6–8) that typically do not respond to ^{131}I therapy. Alternative systemic treatments for widely metastatic DTC using cytotoxic chemotherapy have been of limited utility.

Vorinostat [suberoylanilide hydroxamic acid (SAHA); NSC 701852] is a small molecule inhibitor of histone deacetylase (HDAC) that binds directly to the enzyme's active site in the presence of a zinc ion (9). DNA that is wrapped around condensed, nonacetylated histones is transcriptionally inactive, whereas acetylation of N-terminal histone lysine residues exposes DNA to important transcription factors that promote transcriptional activity (10, 11). The dynamic equilibrium between histone acetylation and deacetylation is regulated by histone acetyltransferases and HDACs, of which there are three classes found in mammals. The action of HDACs on nucleosomal histones leads to tight coiling of chromatin and silencing of expression of various genes, including those implicated in the regulation of cell survival, proliferation, differentiation, and apoptosis (12). HDACs also act as members of a protein complex to recruit transcription factors to the promoter region of genes, including those of tumor suppressors, and to affect the acetylation status of specific cell cycle regulatory proteins (11).

Because aberrant HDAC activity has been implicated in a variety of cancers, HDAC inhibitors have been developed as potential anticancer therapies. Although epigenetic modification by HDACs and histone acetyltransferases has been shown to be important in normal cells in addition to tumor cells, it has not yet been shown that inhibition of HDAC compromises normal cellular processes (13). Several HDAC inhibitors have been developed and are currently in clinical trials. Trichostatin A and butyric acid were among the first HDAC inhibitors to be administered to patients, but these were found to be clinically unsuitable due to potency and formulation issues (14, 15). Depsipeptide, an agent originally selected for clinical study based on its antiproliferative effects, was subsequently found to antagonize HDACs and was the first HDAC inhibitor to demonstrate clinical efficacy (16). Of the three classes of HDACs found in mammals, vorinostat targets class 1 and class 2 enzymes, whereas the third class of HDACs, which requires nicotinamide adenine dinucleotide for activity, is not inhibited by vorinostat. Among those currently in clinical trials, vorinostat is the most potent class 1 and 2 HDAC inhibitor that can be administered orally with excellent bioavailability. Although different HDAC inhibitors vary in their selectivity for different HDAC classes, there is no evidence as of yet that specific HDAC classes have a defined role in specific diseases (13).

In preclinical studies using thyroid cancer cell lines, vorinostat was found to induce growth arrest through p21-mediated inhibition of Rb phosphorylation (17). In these studies, vorinostat was also found to sensitize thyroid cancer cells to caspase-mediated death-receptor-mediated cell death as well as to augment antitumor activity of doxorubicin chemotherapy. In a phase I trial of vorinostat in advanced cancers that included six patients with DTC, one patient with PTC exhibited a partial response (PR) (18). Based on this clinical result as well as the preclinical data, this phase II study of vorinostat in advanced thyroid carcinoma was undertaken to determine whether vorinostat was active in patients with metastatic thyroid cancer who had not responded to standard therapy. The dosing schedule in our study is based on a phase I study that showed biological activity of histone deacetylation inhibition, linear pharmacokinetics, good bioavailability, and safety at doses of 400 mg daily, 200 mg twice daily, and 300 mg twice daily (18). Histone acetylation as evaluated by Western blot or ELISA on histones isolated from peripheral blood mononuclear cells in this study showed an accumulation of acetylated histone H3 at 2 h after administration of vorinostat and that duration of accumulation of acetylated histone H3 increased from 4 to 10 h as the dose of vorinostat increased from 200 to 600 mg.

Patients and Methods

Patient selection

Eligibility criteria included histologically confirmed differentiated (papillary, follicular, Hurthle cell) thyroid carcinoma or MTC at diagnosis. Eligible patients had locally advanced or metastatic measurable disease. The patients could not be candidates for radioactive I^{131} (RAI^{131}) and must have received no more than two prior chemotherapy regimens. No systemic chemotherapy, external beam radiation, or investigational tumor-specific therapy within 4 wk or RAI^{131} therapy within 24 wk of trial initiation was allowed. Patients were required to be more than 18 yr of age, have a life expectancy of more than 6 months, an Eastern Cooperative Oncology Group (ECOG) performance status of 0–1, and adequate organ and marrow function [leukocytes $\geq$3000/μl, absolute neutrophil count $\geq$1500/μl, platelets $\geq$100,000/μl, total bilirubin $\leq$1.5 mg/dl, aspartate aminotransferase (AST)/alanine aminotransferase (ALT) $\leq$ 2.5 $\times$ upper limit of normal, and serum creatinine $\leq$1.5 mg/dl]. Exclusion criteria included patients taking valproic acid or another HDAC inhibitor, concurrent second active malignancy, allergies to similar compounds, uncontrolled illness, HIV on combination antiretroviral therapy, and pregnancy.

Study design

Vorinostat was administered on an outpatient basis at a dose of 200 mg orally twice a day for 2 wk, followed by 1 wk off therapy (3-wk cycle). If tolerated, the dose could be increased in the second cycle to 300 mg twice each day for 2 wk, followed by 1 wk off therapy. Patients documented the time that their pills were taken in a patient diary that was monitored each cycle. In the event of grade 3 or grade 4 drug-related toxicity, therapy was held until toxicity resolved; then it was reinstituted at a reduced dose up to 200 mg orally twice per day. Treatment could be reduced to 300 mg daily if necessary (200 mg morning/100 mg evening). Treatment was continued until the patient had one of the following: progressive disease, off the study drug for more than 3 wk, limiting intercurrent illness, unacceptable adverse events (AEs), or withdrawal from the study by the patient or physician.

History, physical examination, and laboratory studies including complete blood count (CBC), chemistry profile, calcium, phosphorus, total protein, albumin, total bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, lactate dehydrogenase, uric acid, prothrombin time (PT), partial thromboplastin time, and international normalized ratio (INR) were obtained at baseline and on d 1 of each 3-wk treatment cycle. Patients on warfarin therapy had PT/INR performed weekly. A CBC was performed weekly on each patient due to risk of thrombocytopenia. Patients were evaluated once within 4 wk after the last dose of therapy. Patients removed from the study for unacceptable AEs were followed until resolution or stabilization of the AE.

Objective response and AE assessment

Patients were monitored for objective response every 12 wk by computed tomography or magnetic resonance imaging scans. Objective response was assessed using Response Evaluation Criteria in Solid Tumors (RECIST) criteria (19). Serum thyroglobulin (Tg) for patients with DTC and calcitonin and carcinoma embryonic antigen (CEA) for patients with MTC were obtained before the study and every 12 wk on the study to monitor for tumor marker response. AEs were assessed every 3 wk by telephone interview and/or during physician visit and were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 (http://ctep.cancer.gov/reporting/ctc.html).

Statistical considerations

The primary endpoint of this phase II study was to assess objective response [partial response (PR) + complete response (CR)] to vorinostat in patients with metastatic DTC, and the secondary endpoint was to assess AEs of vorinostat in these patients. For this phase II study, the minimax two-stage design of Simon was used, resulting in a study with two stages and decisions to continue after 16 and 25 patients with DTC are accrued (20). Given the relative rarity of metastatic MTC, these patients were enrolled for exploratory purposes only and were not included in the statistical analysis. Vorinostat was to be considered ineffective or uninteresting if the true response probability was less than 10%. The compound would be considered worthy of further study if the response rate was 30% or greater. These figures result in a two-stage design of 16 and 25 patients, with an α of 0.10 and β of 0.10. If one or no response was seen in the first 16 patients, the study would be terminated, and the regimen would be deemed ineffective. If two or more patients responded in the first 16, an additional nine patients would be treated for a total of 25 patients. If five or more of the 25 responded, we would recommend further study using this regimen.

TABLE 1. Patient characteristics

Characteristics	DTC	MTC
No. of patients	16	3
Age (yr)		
Median	62	65
Range	40–77	54–67
Sex		
Female	11 (69)	1 (33)
Male	5 (31)	2 (67)
ECOG performance status		
0	6 (38)	2 (67)
1	10 (62)	1 (33)
Site of metastasis		
Lungs	16 (100)	0
Lymph nodes	8 (50)	1 (33)
Bones	4 (25)	2 (67)
Brain	4 (25)	0
1–2 sites	13 (81)	1 (33)
More than 2 sites	3 (19)	2 (67)
Previous therapies		
Surgery	15 (94)	3 (100)
I^{131}	16 (100)	0
External beam radiation	6 (38)	2 (67)
Cytotoxic chemotherapy	6 (38)	2 (67)
Pathology of thyroid carcinoma		
Classic PTC	12 (75)	0
Follicular variant of PTC	2 (13)	0
FTC	1 (6)	0
Hurthle cell	1 (6)	0
MTC	0	3 (100)

Data represent number (percent).

Results

Patients

After obtaining informed consent from each patient, 16 patients with metastatic DTC and three patients with metastatic MTC were enrolled in this Institutional Review Board-approved phase II study between December 2005 and July 2006 at The Ohio State University Comprehensive Cancer Center. Baseline patient characteristics are outlined in Table 1.

Treatment administered

Median duration of therapy in 16 patients with DTC was 17 wk (range, 5–62 wk), whereas in the three MTC patients it was 25 wk (range, 22–29 wk). Dose escalation up to 300 mg twice daily occurred in 10 patients (53%) (nine patients with DTC and one patient with MTC). Once escalated, dose reduction back to 200 mg twice daily (n = 4) or 300 mg daily (n = 11) was necessary at some point. Reasons for dose reduction included thrombocytopenia (n = 8), hyperglycemia (n = 2), diarrhea (n = 1), hypocalcemia (n = 1), weakness (n = 1), nausea (n = 1), and increased INR (n = 1).

Reasons for termination included progression of disease by RECIST criteria (n = 6 in DTC, n = 1 in MTC); clinical progression (n = 1 in DTC, n = 2 in MTC); grade 3–4 AEs, all in DTC patients, such as hyperglycemia and hypertension (n = 1) and aortic thrombus (n = 1); recurrent or persistent grade 1–2 AEs, including fatigue, dyspnea, dizziness, anorexia, or diarrhea (n = 6); and withdrawal due to concerns over risk/benefit ratio (n = 1).

Objective response

Among 19 patients evaluable for response, no patients achieved a PR or CR. Stable disease was noted in nine patients (56%) with DTC (median duration, 24 wk). Progression by RECIST criteria was noted in patients at less than 12 wk (n = 3), 12 wk (n = 1), 24 wk (n = 1), and 36 wk (n = 1); and clinical progression was noted at wk 16 (n = 1) in patients with DTC. In the patients with MTC, progression by RECIST criteria was noted in one patient at 24 wk, whereas clinical progression was noted in two patients with MTC at wk 21 and 29.

Tumor marker response

Serum tumor marker (Tg for DTC patients; calcitonin and CEA for MTC patients) results are outlined in Table 2. Of the 16 patients with metastatic DTC, 12 had an elevated Tg level without detectable antibodies at baseline, two had Tg antibodies, and two had undetectable Tg levels. Serial Tg levels were obtained on 10 of these assessable patients because two patients went off study before their first planned response assessment. Changes in serum Tg, calcitonin, or CEA levels did not correlate with objective response to therapy.

AEs

Most reported AEs were mild (grade 1–2) and not therapy-limiting. All AEs with possible, probable, and definite attribution

TABLE 2. Tumor marker response

	Baseline	Wk 12	Wk 24	Objective response at 12 wk/24 wk	Reason off study
Assessable patients with DTC (n = 10)[a]					
	242	239 (−1%)	215 (−11%)	PD/(n/a)	Progression wk 10
	109	76 (−30%)	81 (−26%)	SD/PD	Progression wk 25
	221	140 (−37%)	127 (−43%)	SD/(n/a)	Withdrew
	4,245	4,791 (+13%)	5,702 (+34%)	SD/SD	Withdrew
	10	6 (−35%)	N/A	SD/(n/a)	Withdrew
	23	29 (+24%)	17 (−26%)	SD/SD	Withdrew
	20,223	19,610 (−3%)	16,678 (−18%)	SD/SD	Withdrew
	426	400 (−6%)	457 (+7%)	SD/SD	Withdrew
	1050	1,183 (+12%)	1,465 (+39%)	SD/SD	Progression wk 35
	71	100 (+41%)	N/A	SD/(n/a)	Withdrew
Patients with MTC (n = 3)[b]					
	2,361/(n/a)	4,321/(n/a) (+83%/n/a)	N/A	SD/PD	Progression wk 21
	6,800/439	7,480/864 (+10%/+97%)	9,504/761 (+40%/+73%)	SD/SD	Progression wk 29
	4,272/349	8,718/334 (+100%/−4%)	10,638/389 (+150%/+11%)	SD/PD	Progression wk 25

SD, Stable disease; PD, progressive disease; n/a, not applicable.

[a] Tg (ng/ml).

[b] Calcitonin/CEA (ng/ml).

to the study drug are outlined in Tables 3 and 4. The most common side effect was fatigue, with grade 1–3 fatigue occurring in 89% of patients. Of the grade 1–2 AEs, the most common were hematological, gastrointestinal (GI), and constitutional. Grade 1–2 anemia (79%), leukopenia (63%), and thrombocytopenia (47%) were common but were not associated with any infection or bleeding. The most common GI and constitutional AEs included grade 1–2 nausea/vomiting and diarrhea (69%), anorexia (85%), and weight loss (69%) that were reversible upon discontinuation of the study drug.

No grade 5 and no clinical grade 4 AEs were noted on the study. Two patients experienced grade 4 hyperglycemia that led to withdrawal from the study. Grade 3 clinical AEs were infrequent and consisted of fatigue, dehydration, ataxia, pneumonia, bruises, and deep vein thrombosis. Severe thrombocytopenia was seen in seven patients (grade 3, n = 5; grade 4, n = 2) and was associated with minor bleeding or bruises. Of patients with grade 2 or higher thrombocytopenia, the nadir could be seen in any of the first three cycles, with a median of day 16 (range, d 13–18) of the cycle. Recovery was reliably seen with a median of 6 d (range, 4–9 d) from the nadir. Platelet transfusions were required in four patients, and dose reduction was required in two. Of the three patients who were taking warfarin during the study, INR values were higher during the 2-wk period of each cycle while the patients were taking vorinostat, and dose adjustments in warfarin were necessary for two of the three patients.

Discussion

Because of the correlation between cancer development and aberrant HDAC activity, preclinical data suggesting utility of HDAC inhibitors in thyroid cancer, and a phase I trial suggesting a benefit of vorinostat in a patient with advanced thyroid cancer, we chose to study the efficacy of vorinostat in patients with metastatic thyroid carcinoma. Despite the promising characteristics of this agent, no objective RECIST-defined response was seen at the specific dose and schedule of vorinostat used in patients with DTC. In the patients who experienced a significant duration of stable disease, there could be some antitumor effect; however, the slow-growing nature of thyroid carcinoma makes this difficult to evaluate because progressive disease was not an entry criterion for this study. This dosing schedule in our study was based on a phase I study that determined this dosing schedule to be safe (18). Although patients achieved stable disease for all doses in this phase I study, PRs or CRs were noted at doses of 300 mg twice daily, 400 mg twice daily, or 600 mg daily (18). The patients in our study, however, generally did not tolerate dose escalation to these levels. Of note, six patients with metastatic thyroid cancer (four poorly differentiated PTC, one Hurthle cell, and one MTC) on this study maintained on oral vorinostat for a median of 27 months (range, 12 to 37 months). One of three PTC patients who had posttherapy RAI scans performed showed an improvement in the RAI scan after therapy. Regarding use in cutaneous T-cell lymphoma, two studies showed responses at vorinostat dosing of 400 mg orally once daily (21, 22). Of note, the 300 mg twice daily regimen had higher toxicity with no additional clinical benefit over the 400 mg once daily regimen in patients with cutaneous T-cell lymphoma (21).

All of the patients who had stable disease during this trial eventually withdrew from the study, either due to serious AEs or quality of life concerns with mild AEs. If future studies using this drug for thyroid cancer patients were to investigate progression-free survival in patients with progressive disease, the therapy may be more tolerable at lower doses or with less frequent dosing. AEs were similar to those reported in the Food and Drug Administration package insert, with a fairly similar rate of thrombocytopenia, fatigue, and GI effects. Among other phase II trials using

TABLE 3. Clinical AEs (n = 19) (possible, probable, or definite attribution to the drug)

AEs	Grade 1	Grade 2	Grade 3
Systemic			
Fatigue	3 (16)	9 (47)	5 (26)
Anorexia	14 (74)	2 (11)	
Weight loss	10 (53)	3 (16)	
Chills/sweating	2 (11)		
General weakness	6 (32)	1 (5)	
Gastroinstestinal			
Nausea/vomiting	10 (53)	3 (16)	
Diarrhea	7 (37)	6 (32)	
Heartburn	3 (16)		
Abdominal cramping	2 (11)	1 (5)	
Flatulence/bloating	6 (32)		
Dry mouth	4 (21)	1 (5)	
Mouth sores	4 (21)		
Taste changes	9 (47)		
Dehydration			2 (11)
Neurological			
Headache	2 (11)		
Dizziness	2 (11)		
Blurry vision	2 (11)		
Paresthesias	1 (5)		
Tremor	2 (11)		
Memory loss	3 (16)		
Anxiety	1 (5)		
Confusion		1 (5)	
Ataxia		2 (11)	1 (5)
Musculoskeletal/skin			
Muscle cramps	5 (26)		
Chest pain (muscle)	3 (16)		
General pain		1 (5)	
Rash	2 (11)		
Alopecia	8 (42)		
Flushing	2 (11)		
Nail changes	3 (16)		
Respiratory/infectious			
Dyspnea	2 (11)	1 (5)	
Cough	3 (16)		
Bronchitis/pneumonia		1 (5)	2 (11)
Herpes zoster		2 (11)	
Vascular			
Hypertension		1 (5)	
Bruising/hematoma	2 (11)		1 (5)
Minor bleeding	5 (26)		
Deep vein thrombosis			1 (5)
Arterial thrombus			1 (5)

Data are expressed as number (percent). Worst grade experienced by patient on study is counted in the above table. See text for grade 4–5 AEs.

TABLE 4. Laboratory AEs (n = 19) (possible, probable, or definite attribution to the drug)

AEs	Grade 1	Grade 2	Grade 3
Hematological			
Anemia	14 (74)	1 (5)	
Leucopenia	11 (58)	1 (5)	
Neutropenia	2 (11)	4 (21)	1 (5)
Lymphopenia	1 (5)		1 (5)
Thrombocytopenia	8 (42)	1 (5)	5 (26)
High PTT	1 (5)	1 (5)	
High PT/INR	1 (5)	1 (5)	2 (11)
Chemistry			
Hyperglycemia	3 (16)	6 (32)	1 (5)
Elevated LDH	6 (32)		
Elevated bilirubin	3 (16)		
Elevated AST	1 (5)		
Low calcium	1 (5)	3 (16)	2 (11)
Elevated creatinine	4 (21)	4 (21)	
Low sodium	2 (11)		
Low albumin	2 (11)		
Low potassium	3 (16)		
Low phosphorus	1 (5)		

Data are expressed as number (percent). Worst grade experienced by patient on study is counted in the above table. See text for grade 4–5 AEs. PTT, Partial thromboplastin time; LDH, lactate dehydrogenase.

vorinostat as a solitary agent, AEs were similar, although different doses were used. Serious AEs of thromboembolism, infection, and thrombocytopenia have been reported at similar rates (21–23). In this study, as in previous studies, warfarin interactions were unpredictable (21, 22). Of the three patients on warfarin during the study, dose adjustments in warfarin were required, suggesting possible drug interactions with vorinostat. Because of the risk of severe thrombocytopenia due to vorinostat and unpredictable increase in INR in patients taking concomitant warfarin, twice a week testing of PT/INR as well as CBC should be considered in patients taking vorinostat and warfarin. The AE of arterial thrombus observed in this study has not been previously described.

Although this study suggests that vorinostat alone is not effective in metastatic thyroid carcinoma, there remains the question of whether combination therapy including vorinostat may be effective. *In vitro* studies of vorinostat have combined this agent with various antitumor agents including DNA hypomethylating agents (5-azacytidine or decitabine) (24), antimetabolites (5-fluorouricil) (25), and proteasome inhibitors (bortezomib) (26). Although these agents have not been shown as yet to be beneficial in metastatic thyroid carcinoma as solitary agents, it is possible that the combination with vorinostat may show additive or synergistic actions and that these *in vitro* effects might show promise *in vivo*. In fact, preclinical studies have shown that vorinostat has a synergistic effect with paraplatin, doxorubicin, and paclitaxel in the killing of anaplastic thyroid cancer cells (27), which may translate into clinical utility.

Other HDAC inhibitors have demonstrated utility in combination therapy as well. Valproic acid, a low-potency HDAC inhibitor, has been shown to enhance paclitaxel-induced apoptosis in anaplastic thyroid cancer cell lines, likely through the inhibition of tubular deacetylation (28). Similarly, valproic acid has been shown in anaplastic thyroid cancer cell lines to enhance the apoptotic effect of doxorubicin at least 2-fold (29). These combinations had the added benefit of reducing the dose of the chemotherapeutic agent required for effect, which could be a promising strategy for patients in whom the toxicity of these drugs precludes use at target doses. HDAC inhibitors have also been associated *in vitro* with increasing tumor uptake of RAI. Advanced thyroid cancer is often resistant to RAI^{131}, likely mediated by decreased iodide uptake by the sodium-iodide symporter (NIS) (30). Trichostatin A, an early HDAC inhibitor not in clin-

ical use, was found to induce increased levels of NIS (31). Depsipeptide, another HDAC inhibitor, was also shown to increase NIS expression and uptake of I^{125} (32, 33). These findings have not been replicated using vorinostat and were not addressed in this trial, but they represent an area where vorinostat may prove clinically useful in thyroid cancer.

This study also suggested that Tg levels in patients taking vorinostat are not reliably associated with clinical change. It has been shown previously that HDAC inhibitors increase thyroid-specific mRNA and related proteins, including Tg (33). This suggests that in patients being treated with HDAC inhibitors, Tg, and potentially calcitonin as well, may not be reliable indicators of clinical response, and should not be used as such.

Conclusions

No patient with metastatic DTC or MTC who was treated with vorinostat achieved a PR or CR. No patient with MTC demonstrated stable disease. These findings suggest that vorinostat monotherapy at the dose and treatment schedule used in the study is insufficient to induce PR or CR for these patient populations. Consideration of studies using alternative vorinostat dosing or treatment schedules designed to detect progression-free survival or studies in which vorinostat is used in combination with other therapies may be reasonable.

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