Vorinostat approved in Japan for treatment of cutaneous T-cell lymphomas: status and prospects

Abstract: Histone acetylation and deacetylation play important roles in the regulation of gene transcription and in the modulation of chromatin structure. The levels of histone acetylation are determined by the activities of histone acetyltransferases and histone deacetylases (HDACs). HDACs are associated with a number of oncogenes and tumor suppressor genes and can be aberrantly expressed and/or inappropriately activated in cancer cells. HDAC inhibitors have therefore recently emerged as a novel treatment modality against malignancies. They regulate gene expression by enhancing the acetylation of not only histones but also nonhistone proteins, including transcription factors, transcription regulators, signal transduction mediators, and DNA repair enzymes, and they inhibit cancer growth. Vorinostat (suberoylanilide hydroxamic acid) is one of the most potent HDAC inhibitors, and was approved in Japan in 2011 for the treatment of cutaneous T-cell lymphoma. Numerous clinical trials have shown it to be effective against cutaneous T-cell lymphoma but less so against other types of cancer. Because vorinostat can overcome resistance to or enhance the efficacy of other anticancer agents, such as 5-fluorouracil, carboplatin, paclitaxel, bortezomib, and tamoxifen, combination therapies using vorinostat and these agents have been investigated. This review introduces the background and mechanism of action of vorinostat and describes the results of clinical trials using vorinostat, both as a single agent and in combination with other anticancer agents, against cutaneous T-cell lymphoma and other malignancies.

Keywords: vorinostat, T-cell lymphoma, cancer, novel treatment

Introduction

Treatment modalities for advanced malignancies are limited, and new approaches are urgently needed. The acetylation and deacetylation of histones play important roles in the regulation of gene transcription and in the modulation of chromatin structure. In general, increased histone acetylation is associated with increased transcriptional activity, whereas decreased acetylation is associated with repression of gene expression. The levels of histone acetylation reflect the balance between the activities of histone acetyltransferases and histone deacetylases (HDACs), and 18 HDAC enzymes have been identified in humans. HDACs 1, 2, 3, and 8 are class I HDACs, and HDACs 4, 5, 6, 7, 9, and 10 are class II HDACs. Unlike the class I and class II HDACs, class III HDACs (sirtuins) are nicotinamide adenine dinucleotide-dependent protein deacetylases. Class IV consists of HDAC 11, which has residues in the catalytic core region that are also found in class I and II HDACs. Deacetylation of histones tightens their interaction with DNA, resulting in a closed chromatin structure and inhibiting gene transcription. Furthermore, HDACs also deacetylate many other proteins, including transcription factors, signal transduction mediators, and DNA repair enzymes.

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Introduction

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proteins other than histones, thereby increasing or decreasing the function or stability of those proteins. Among the non-histone proteins targeted by HDACs are transcription factors, transcription regulators, signal transduction mediators, DNA repair enzymes, nuclear import regulators, chaperone proteins, structural proteins, inflammation mediators, and viral proteins. HDACs are thus associated with a number of cellular oncogenes and tumor suppressor genes, leading to aberrant recruitment of HDAC activity, which results in changes in gene expression. HDACs can be aberrantly expressed and/or inappropriately activated in cancer: HDAC1 is overexpressed in prostate, gastric, colon, and breast cancers, and HDAC2 is overexpressed in colorectal, cervical, and gastric cancers. Compounds targeting HDACs have therefore generated a great deal of interest as anticancer drugs. Vorinostat (suberoylanilide hydroxamic acid), first reported by Richon et al, is one of the most potent HDAC inhibitors and is the first approved by the US Food and Drug Administration.

This review introduces the background and mechanism of action of vorinostat and describes the results of clinical trials using vorinostat, both as a single agent and in combination with other anticancer agents, against cutaneous T-cell lymphoma (CTCL) and other malignancies.

Development of vorinostat

The development of vorinostat started with the discovery of hexamethylene bisacetamide (HMBA), a hybrid polar compound that induces terminal differentiation of transformed cells. It was thought to modulate the membrane surface potential of transformed cells and thereby perhaps activate a signaling pathway, but its molecular target was not identified. HMBA was not well tolerated by patients because the high optimal concentration (millimolar level) was associated with toxic side effects, such as thrombocytopenia. Vorinostat is one of the second-generation hybrid polar compounds with about 2000-fold greater potency that were developed in efforts to overcome these problems. Unlike HMBA but like trichostatin A, these novel compounds can inhibit HDACs.

HDAC inhibitors

Numerous HDAC inhibitors have been developed and many of them have been tested in preclinical and early clinical studies. HDAC inhibitors can be classified as hydroxamic acids, aliphatic acids, cyclic peptides, or benzamides. Vorinostat is a hydroxamic acid and has structure similar to that of trichostatin A, the first natural hydroxamate found to inhibit HDACs. Panobinostat is also an analog of hydroxamic acids and has been investigated in patients with refractory hematologic malignancies, CTCL, Hodgkin lymphoma, renal cell cancer, and castration-resistant prostate cancer. Belinostat is another hydroxamic acid-derived type of HDAC inhibitor, and its efficacy has been examined in clinical trials in patients with advanced hematological neoplasia, advanced solid tumors, recurrent or refractory advanced thymic epithelial tumors, platinum-resistant epithelial ovarian cancer and micropapillary ovarian tumors, and advanced malignant pleural mesothelioma.

Phenylbutyrate and valproic acid are aliphatic acid HDAC inhibitors, but their optimal concentrations are at millimolar levels and their inhibitory effects are weak. Depsipeptide (romidepsin, FK228) is one of the cyclic peptides that the Food and Drug Administration approved (in November 2009) for the treatment of CTCL. It has also been clinically investigated in patients with other malignancies, such as chronic lymphocytic and acute myeloid leukemias, refractory metastatic renal cell cancer, lung cancer, myelodysplastic syndromes, previously treated advanced colorectal cancer, metastatic castration-resistant prostate cancer, refractory multiple myeloma, and recurrent malignant glioma. Entinostat (SNDX-275, MS-275) is a synthetic benzamide derivative and has been investigated in clinical trials in patients with refractory solid tumors and lymphoma, refractory and relapsed acute leukemias, and pretreated metastatic melanoma. The effectiveness of entinostat is also being investigated in a Phase II trial in patients with relapsed or refractory Hodgkin lymphoma. Vorinostat is one of the most potent HDAC inhibitors and in October 2006 became the first one approved by the Food and Drug Administration for the treatment of advanced primary CTCL.

Molecular effect of vorinostat

Vorinostat inhibits HDACs and induces the accumulation of acetylated histones and acetylated nonhistone proteins, which alter gene expression as mentioned earlier. It thus has a broad spectrum of epigenetic activities and, consequently, diverse effects on cancer cells. Vorinostat induces apoptosis by upregulating proapoptotic proteins and downregulating the expression of antiapoptotic molecules, including the intracellular inhibitors of apoptosis FLIP and survivin. It decreases the expression of cyclin D1 by inhibiting its translation through affecting activity of PI3K and its downstream proteins. It has also been shown to decrease the expression of CDK4 along with that of cyclin D1.
Furthermore, vorinostat induces expression of p21 through histone acetylation, inhibiting the function of the cyclin D/CDK4 complex. Thus vorinostat affects the cell-cycle by suppressing the expression and function of cell-cycle-associated proteins. Inhibition of angiogenesis is another aspect of its action. Vorinostat reportedly inhibits angiogenesis by decreasing the expression of the vascular endothelial growth factor (VEGF) receptor and inhibits VEGF-induced angiogenesis. Vorinostat inhibits HDAC6 and this may be another important mechanism of action. Ablation of HDAC6 has been shown to induce hyperacetylation of heat shock protein 90, thereby abrogating its ATP binding activity and disrupting its chaperone function and resulting in polyubiquitination. This mechanism theoretically supports the use of vorinostat in combination with proteasome inhibitors, which is discussed later in this review.

Efficacy of vorinostat as a single agent

The results of clinical trials investigating the efficacy of vorinostat as a single agent are summarized in Table 1. The following sections review the results of selected clinical trials in patients with CTCL, other hematological malignancies, or solid tumors.

Primary CTCL

CTCL comprises a heterogeneous group of lymphoproliferative disorders characterized by skin lesions composed of malignant clonal T lymphocytes. Mycosis fungoides, Sézary syndrome, and other cutaneous T-cell lymphomas arising in the skin are parts of a broader spectrum of CTCL. Numerous therapeutic options are available, both local (corticosteroids, nitrogen mustard, Carmustine, topical retinoids, ruxinoid, ultraviolet light therapy, and irradiation) and systemic (bexarotene and denileukin diftitox), but none has been shown to be curative. Vorinostat was approved by the Food and Drug Administration in October 2006 for the treatment of advanced primary CTCL. According to a Phase I clinical trial recruiting 73 patients, for continuous daily dosing the maximum tolerated dose was 400 mg once daily or 200 mg twice daily, and for three consecutive days per week dosing it was 300 mg twice daily; the major dose-limiting toxicities were anorexia, dehydration, diarrhea, and fatigue. According to a Phase I study in Japanese patients with solid tumors, doses of 200 mg twice daily or 500 mg once daily for 14 days followed by a 7-day rest were well tolerated. In a Phase II trial enrolling 33 patients with refractory CTCL, patients were given either 400 mg daily, 300 mg twice daily for 3 days with 4 days of rest, or 300 mg twice daily for 14 days with 7 days of rest followed by 200 mg twice daily. Eight patients achieved a partial response, seven with advanced disease and four with Sézary syndrome. The median time to response, duration of response, and time to progression were, respectively, 11.9, 15.1, and 12.1 weeks. Fourteen of the 31 evaluable patients had relief of pruritus. In another Phase II study enrolling 74 patients with stage IB-IVA mycosis fungoides/Sézary syndrome and treating them with 400 mg of oral vorinostat daily until disease progression or intolerable toxicity, the overall objective response rate was 29.7%, the median overall duration of response was more than 185 days, the median time to progression was 4.9 months overall and more than 9.8 months for stage IIIB or higher responders, and 32% of the patients had relief of pruritus. The most common adverse events were mild (below grade 2), ie, diarrhea (49%), fatigue (46%), nausea (43%), and anorexia (26%). Grade 3 or higher events were fatigue (5%), pulmonary embolism (5%), thrombocytopenia (5%), and nausea (4%). Vorinostat has thus been shown to be a safe, effective, and tolerable agent in the treatment of CTCL.

In July 2011 the Japanese Ministry of Health, Labour, and Welfare approved vorinostat for the treatment of CTCL.

Other hematological malignances

In a Phase II trial, 37 patients with relapsed or untreated acute myeloid leukemia were treated with vorinostat at doses of either 400 mg daily or 200 mg three times daily for 14 days followed by one week of rest. One complete response was observed, with a duration of response of more than 398 days. The median time to progression was 42 days for the patients given 400 mg daily and 46 days for the patients given 200 mg three times daily. In another Phase II study, 18 patients with relapsed diffuse large B cell lymphoma were recruited and given oral vorinostat 300 mg twice a day. Median time to progression was 44 days. One patient had a complete response with duration of response ≥468 days and one had stable disease (301 days). Grade 1 and 2 toxicities were diarrhea, fatigue, nausea, anemia, and vomiting. Toxicities of grade 3 or higher were thrombocytopenia (16.7%) and asthenia (11.1%). A Phase I trial was conducted using oral vorinostat to treat patients with relapsed or refractory multiple myeloma. Ten patients given 200, 250, or 300 mg twice daily 5 days a week for 4 weeks or 200, 300, or 400 mg twice daily for 14 days of a 21-day cycle were evaluable. There was one patient with a minimal response and nine with stable disease. Toxicities were mostly below grade 2 and included fatigue, anorexia, dehydration, diarrhea,
### Table 1 Results of clinical trials investigating the efficacy of vorinostat as a single agent in various types of cancer

<table>
<thead>
<tr>
<th>Trial</th>
<th>Disease</th>
<th>No of evaluable patients</th>
<th>Regimen</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase II (Duvic M, et al)</td>
<td>Refractory CTCL</td>
<td>33</td>
<td>400 mg daily, 300 mg twice daily for 3 days with 4 days rest or 300 mg twice daily for 14 days with 7 days rest followed by 200 mg twice daily</td>
<td>PR = 24.2%; TTP = 12.1 wks</td>
</tr>
<tr>
<td>Phase Iib (Olsen EA, et al)</td>
<td>Persistent, progressive, or refractory CTCL</td>
<td>74</td>
<td>400 mg daily</td>
<td>ORR = 29.7%; TTP = 4.9 mos</td>
</tr>
<tr>
<td>Phase II (Schaefar EW, et al)</td>
<td>Relapsed or untreated acute myeloid leukemia</td>
<td>37</td>
<td>400 mg daily (arm A) or 200 mg three times daily (arm B) for 14 days followed by 1-week rest (arm A), 46 days (arms B)</td>
<td>CR = 4.5% (arm B); TTP = 42 days (arm A)</td>
</tr>
<tr>
<td>Phase II (Crump M, et al)</td>
<td>Relapsed diffuse large B-cell lymphoma</td>
<td>18</td>
<td>300 mg twice daily for 14 days/3 weeks or 3 days/week</td>
<td>PR = 24%; TTP = 3.6 wks</td>
</tr>
<tr>
<td>Phase I (Richardson P, et al)</td>
<td>Relapsed or refractory multiple myeloma</td>
<td>10</td>
<td>200, 250 or 300 mg twice daily for 5 days/week or 200, 300, or 400 mg twice daily for 14 days/3-week cycle</td>
<td>Minimal response = 10%; SD = 90%</td>
</tr>
<tr>
<td>Phase I (Watanabe T, et al)</td>
<td>Malignant lymphoma follicular lymphoma, mantle cell lymphoma, diffuse large B-cell lymphoma, and CTCL</td>
<td>10</td>
<td>100 or 200 mg twice daily for 14 days followed by 1-week rest</td>
<td>ORR = 40% (CRu = 30%; PR = 10%)</td>
</tr>
<tr>
<td>Phase I (Krischbaum M, et al)</td>
<td>Relapsed or refractory indolent non-Hodgkin's lymphoma and mantle cell lymphoma</td>
<td>35</td>
<td>200 mg twice daily for 14 days followed by 1-week rest</td>
<td>ORR = 29% (CR = 14%; PR = 14%); 2-year PFSR = 37%; 2-year OSR = 77%</td>
</tr>
<tr>
<td>Phase II (Blumenschein GR Jr, et al)</td>
<td>Recurrent and/or metastatic head and neck cancer</td>
<td>12</td>
<td>400 mg daily</td>
<td>PRu = 8.3%; SD = 25%</td>
</tr>
<tr>
<td>Phase II (Modesitt SC, et al)</td>
<td>Recurrent or persistent epithelial ovarian or primary peritoneal carcinoma</td>
<td>27</td>
<td>400 mg daily</td>
<td>PR = 3.7%; PFSR over 6 mos = 7.4%</td>
</tr>
<tr>
<td>Phase II (Vansteenkiste J, et al)</td>
<td>Relapsed or refractory breast cancer, NSCLC, colorectal cancer</td>
<td>16</td>
<td>200, 300 or 400 mg twice daily for 14 days followed by 1-week rest</td>
<td>SD = 50%; TTP = 33.5 days</td>
</tr>
<tr>
<td>Phase II (Bradley D, et al)</td>
<td>Hormone-refractory metastatic prostate cancer</td>
<td>27</td>
<td>400 mg daily</td>
<td>SD = 7%; no PSA decline of &gt;50 was observed; TTP = 2.8 mos; OS = 11.7 mos</td>
</tr>
<tr>
<td>Phase II (Traynor AM, et al)</td>
<td>Stage IIIB with pleural or pericardial effusion, stage IV, or recurrent NSCLC</td>
<td>14</td>
<td>400 mg daily in a 21-day cycle</td>
<td>SD = 57%; TTP = 2.3 mos; OS = 7.1 mos</td>
</tr>
<tr>
<td>Phase II (Galanis E, et al)</td>
<td>Recurrent glioblastoma</td>
<td>66</td>
<td>200 mg twice daily for 14 days followed by 1 week-rest</td>
<td>ORR = 3%; PFSR at 6 mos = 15.2%; TTP = 1.9 mos; OS = 5.7 mos</td>
</tr>
<tr>
<td>Phase II (Luu TH, et al)</td>
<td>Metastatic breast cancer</td>
<td>14</td>
<td>200 mg twice daily for 14 days followed by 1 week-rest</td>
<td>SD = 2%; TTP = 2.6 mos; OS = 24 mos</td>
</tr>
</tbody>
</table>

**Abbreviations:** CR, complete response; CTCL, cutaneous T-cell lymphoma; NSCLC, nonsmall cell lung cancer; ORR, objective response rate; PFSR, progression-free survival rate; PR, partial response; PRu, unconfirmed PR; SD, stable disease; TTP, median time to progression.
and nausea. The efficacy of vorinostat was also evaluated in Japanese patients with malignant lymphoma (follicular lymphoma, mantle cell lymphoma, diffuse large B-cell lymphoma, and CTCL). Ten patients were enrolled in this study, and 100 mg or 200 mg was given twice daily for 14 consecutive days followed by a 1-week rest. The objective response rate was 40% and there were three unconfirmed complete responses and one partial response. In a recent, larger Phase II trial of vorinostat in patients with relapsed or refractory indolent non-Hodgkin’s lymphoma and mantle cell lymphoma, 35 patients given 200 mg twice daily on days 1–14 of a 21-day cycle showed an objective response rate of 29% including five complete responses and five partial responses. Vorinostat is thus thought to have modest activity against hematological malignancies.

**Solid tumors**

The efficacy of vorinostat has also been investigated in patients with solid tumors. In a Phase II trial in patients with recurrent and/or metastatic head and neck cancer, 12 patients were given oral vorinostat 400 mg once daily. Three patients had stable disease for periods ranging from 9 to 26 weeks, but no confirmed partial response or complete response was observed. Drug-related toxicities of grades 3 or 4 were thrombocytopenia (n = 3), anorexia (n = 2), and dehydration (n = 2). In another Phase II trial in patients with recurrent or persistent epithelial ovarian or primary peritoneal carcinoma, 27 patients were enrolled and given a 400 mg daily oral dose of vorinostat until disease progression or unacceptable toxicity. Two patients survived progression-free for over 6 months and one partial response was observed. The grade 4 toxicities were leucopenia (one patient) and neutropenia (one patient). Grade 3 toxicities were constitutional (11%), gastrointestinal (11%), neutropenia, metabolic abnormalities, thrombocytopenia (7%), neurologic complaints, and pain (4%). The efficacy of vorinostat was also investigated in 16 patients with relapsed or refractory breast cancer, nonsmall cell lung cancer, or colorectal cancer. The patients were given 200, 300, or 400 mg by mouth twice daily for 14 days followed by a 7-day rest until disease progression or intolerable toxicity. Eight patients had stable disease, but there were no confirmed responses. The median time to progression was 33.5 days. The most common drug-related adverse events were anorexia (81%), fatigue (62%), nausea (62%), diarrhea (56%), vomiting (56%), thrombocytopenia (50%), and weight loss (50%). Grade 4 toxicities included thrombocytopenia (50%), anemia (12%), asthenia (12%), and nausea (12%). The most recent trial enrolled 27 patients with metastatic hormone-refractory prostate cancer who were given 400 mg vorinostat by mouth daily. Median time to progression and overall survival were 2.8 and 11.7 months. The most common adverse events were fatigue (81%), nausea (74%), anorexia (59%), vomiting (33%), diarrhea (33%), and weight loss (26%). Other Phase II studies of the effectiveness of vorinostat against solid tumors included patients with relapsed nonsmall cell lung cancer, glioblastoma, and metastatic breast cancer, and rarely showed objective responses.

**Combination therapies using vorinostat**

Clinical trials revealed that vorinostat is a promising agent to treat CTCL and some other hematological malignancies, but its efficacy against solid tumors is disappointing. Combination therapies using vorinostat and other agents have therefore been investigated, and their results are summarized in Table 2. The agent with which vorinostat was most often combined in clinical trials was 5-fluorouracil. The rationale for this is that vorinostat could overcome resistance to fluorouracil by downregulating thymidylate synthase, which is associated with resistance to fluorouracil. In one Phase I/II clinical trial in which vorinostat was combined with 5-fluorouracil and leucovorin to treat patients with metastatic colorectal cancer, two of 10 patients achieved significant disease stabilization for 4 and 6 months. Better results were obtained in another trial using the combination of vorinostat, 5-fluorouracil, and leucovorin. Twenty-one of 38 patients with fluorouracil-refractory colorectal cancer had stable disease, and one had a partial response. The combination of vorinostat, 5-fluorouracil, leucovorin, and oxaliplatin was also investigated in a Phase I trial in colorectal cancer patients. Twenty-one patients were enrolled, but no patient developed an objective response. Stable disease was confirmed in five patients. Thus, the efficacy of the combination of vorinostat and 5-fluorouracil seems to be limited.

The combination of vorinostat, carboplatin, and paclitaxel was studied in two clinical trials. Enhancement of cisplatin activity by increased platinum adduct formation of the more open DNA configuration induced by HDAC inhibition and enhancement of taxane activity by alterations in α-tubulin acetylation that are due to the inhibition of HDAC6 are thought to be the mechanisms by which the combination acts. In a Phase I trial, 28 patients with advanced solid malignancies were treated with this combination therapy. The results were encouraging. In the 25 patients evaluable for response, stable disease occurred in seven patients and partial responses...
occurred in 10 patients with nonsmall cell lung cancer and one with head and neck cancer. Given the results of this trial, a Phase II clinical trial of the combination was conducted.\textsuperscript{91} Patients with previously untreated stage IIIb or IV nonsmall cell lung cancer were treated with carboplatin and paclitaxel combined with either vorinostat or a placebo. In 94 evaluable patients, the confirmed response rate was 34% with vorinostat and 12.5% with placebo. One patient in the vorinostat arm had a complete response. A favorable trend toward improvement in median progression-free survival (6.0 months versus 4.1 months) and overall survival (13.0 months versus 9.7 months) was also observed in the vorinostat arm. The one-year overall survival rates were 51% for the vorinostat-treated group and 33% for the placebo-treated group. These studies provide a rationale for combining vorinostat, carboplatin, and paclitaxel and assessing the efficacy of the combination in other malignancies treated with carboplatin and paclitaxel.

Inducing endoplasmic reticulum stress and protein ubiquitination has recently emerged as a novel approach to the treatment of malignancies.\textsuperscript{92} The combination of vorinostat and bortezomib, a proteasome inhibitor, induces endoplasmic reticulum stress. Vorinostat inhibits HDAC6, and inhibition of HDAC6 has been shown to induce hyperacetylation of heat shock protein 90, thereby abrogating its ATP-binding activity and disrupting its chaperone function.\textsuperscript{63,64} Combining vorinostat with bortezomib therefore enhances endoplasmic reticulum stress and accumulation of ubiquitinated proteins. This combination has also been shown not only to cause accumulation of ubiquitinated proteins, but also to enhance histone acetylation synergistically.\textsuperscript{93} Because the combination affects protein ubiquitination and histone acetylation, which are universal mechanisms of protein homeostasis and control of gene transcription, the molecular consequences of the combination are diverse. The combination reportedly inhibits the RK and Akt pathways,\textsuperscript{94} diminishes expression of Bcr/Abl and cyclin D1, cleavage of p21CIP1, and phosphorylation of the retinoblastoma protein,\textsuperscript{95} and induces apoptosis.\textsuperscript{94–97} The result of a Phase I trial using this combination is promising.\textsuperscript{98} Twenty-three patients with relapsed and/or refractory multiple myeloma were enrolled in the study. The objective response rate was 42%, including three partial responses among nine patients who were refractory to bortezomib. The median time to progression was 4 months. Because of its unique mechanism of action, the combination of vorinostat and bortezomib may be a novel approach to the treatment of malignancies. Clinical trials using this combination against other types of cancer are expected.

It has been reported that HDACs are involved in the regulation of steroid hormone receptor-mediated cell signaling and that inhibition of HDACs impairs the development of tamoxifen resistance.\textsuperscript{99} In breast cancer patients resistant to hormone therapy, the combination of vorinostat and bortezomib has been shown to enhance endoplasmic reticulum stress and protein ubiquitination synergistically.\textsuperscript{100,101} The combination reportedly enhances the efficacy of the combination in other malignancies treated with vorinostat and paclitaxel.

### Table 2: Results of clinical trials testing vorinostat in combination with other anticancer agents in various types of cancer

<table>
<thead>
<tr>
<th>Trail</th>
<th>Disease</th>
<th>No of evaluable patients</th>
<th>Combined drug(s)</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase III (Wilson PM, et al\textsuperscript{90})</td>
<td>Metastatic colorectal cancer</td>
<td>10</td>
<td>5-FU/LV</td>
<td>SD = 20%</td>
</tr>
<tr>
<td>Phase I (Fakih MG, et al\textsuperscript{78})</td>
<td>FU-refractory colorectal cancer</td>
<td>38</td>
<td>5-FU/LV</td>
<td>PR = 2.6%; SD = 55.3%</td>
</tr>
<tr>
<td>Phase I (Fakih MG, et al\textsuperscript{79})</td>
<td>Refractory metastatic colorectal cancer</td>
<td>21</td>
<td>5-FU/LV and oxaliplatin</td>
<td>SD = 23.8%</td>
</tr>
<tr>
<td>Phase I (Ramalingam SS, et al\textsuperscript{99})</td>
<td>NSCLC, head and neck cancer, bladder cancer, mesothelioma, and others</td>
<td>25</td>
<td>Carboplatin and paclitaxel</td>
<td>PR = 44%; SD = 28%</td>
</tr>
<tr>
<td>Phase II (Ramalingam SS, et al\textsuperscript{80})</td>
<td>Stage IIIb or IV NSCLC</td>
<td>94</td>
<td>Carboplatin and paclitaxel</td>
<td>Confirmed response rate (34% vs 12.5%); PFS = 6.0 mos vs 4.1 mos; OS = 13 mos vs 9.7 mos (vorinostat vs placebo)</td>
</tr>
<tr>
<td>Phase II (Badros A, et al\textsuperscript{81})</td>
<td>Relapsed and/or refractory multiple myeloma</td>
<td>23</td>
<td>Bortezomib</td>
<td>PR = 42%; TTP = 4 mos</td>
</tr>
<tr>
<td>Phase II (Munster PN, et al\textsuperscript{82})</td>
<td>Refractory breast cancer</td>
<td>43</td>
<td>Tamoxifen</td>
<td>ORR = 19%; clinical benefit rate (response or stable disease &gt;24 weeks) = 40%; DOR = 10.3 mos</td>
</tr>
<tr>
<td>Phase I (Stathis A, et al\textsuperscript{83})</td>
<td>Advanced solid tumors or non-Hodgkin’s lymphomas</td>
<td>38</td>
<td>Decitabine</td>
<td>SD = 29%</td>
</tr>
</tbody>
</table>

**Abbreviations:** 5-FU, 5-fluorouracil; DOR, median duration of response; LV, leucovorin; NSCLC, nonsmall cell lung cancer; ORR, objective response rate; PFS, median progression-free survival; PR, partial response; SD, stable disease; TTP, median time to progression.
and tamoxifen was investigated with encouraging results. In 43 patients treated, an objective response rate of 19%, a clinical benefit rate of 40%, and a median duration of response of 10.3 months were observed.\textsuperscript{100}

Combining decitabine, a demethylating agent, and vorinostat was shown to result in the re-expression of tumor suppressor genes.\textsuperscript{101} When the combination of vorinostat and decitabine was examined in patients with advanced solid tumors or non-Hodgkin lymphoma, 29% of treated patients showed stable disease.\textsuperscript{102}

Thus, some combination therapies using vorinostat have promising anticancer activity. Further clinical trials with these combinations and with combinations of vorinostat and other anticancer agents with other mechanisms of action are required in order to establish novel effective treatment strategies against advanced malignancies.

**Summary**

Vorinostat, a histone deacetylase inhibitor, is a novel promising anticancer agent approved in Japan in July 2011 for the treatment of CTCL. Because it affects the principal mechanisms of gene expression by causing acetylated histones and acetylated nonhistone proteins to accumulate rather than by merely inhibiting specific signal transduction pathways, as many currently used anticancer agents do, its effects are diverse and potentially effective in many types of malignancies that are refractory to currently available treatment modalities. Although the efficacy of vorinostat alone in patients with advanced solid tumor is unfortunately limited, some recent studies have reported a favorable response to vorinostat in combination with other anticancer agents. Future basic research and clinical trials of vorinostat should focus on more effective combinations of vorinostat with other drugs.

**Disclosure**

The author reports no conflicts of interest in this work.

**References**


73. Crump M, Coiffier B, Jacobsen ED, et al. Phase II trial of oral vorinos-
95. Yu C, Rahmani M, Conrad D, Subler M, Dent P, Grant S. The pro-