

CASE REPORT

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Clinical Efficacy of Vorinostat in a Patient with Leiomyosarcoma

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Abstract: Leiomyosarcoma is a heterogeneous tumor group, representing <1% of all new cancers diagnosed in United States. Treatment choice is based upon site, grade, and extent of disease. However, prognosis for metastatic or unresectable sarcoma is very poor with reported median survival of 12 months. Response to chemotherapy has been approximately 8% to 39% based upon the chemotherapeutic agent and whether used alone or in combination. Vorinostat is an orally active, potent, and competitive inhibitor of histone deacetylases approved for cutaneous T-cell lymphoma. There are limited preclinical data illustrating the activity of histone deacetylase inhibitors in sarcoma. Here is a case of a lady with leiomyosarcoma who has progressed through multiple chemotherapeutic agent who has achieved a partial response to vorinostat treatment.

Keywords: histone deacetylase inhibitor, vorinostat, leiomyosarcoma, lung metastases, soft tissue sarcoma

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Introduction

Soft tissue sarcomas are a rare heterogeneous tumor group, representing <1% (approximately 10,000 cases) of all new cancers diagnosed yearly in the United States.¹ Over 50 subtypes of malignant soft tissue sarcomas have been described in adults,² leiomyosarcomas are one of the most common.² Leiomyosarcomas are tumors of distinct smooth muscle type cells and occur intramuscularly and subcutaneously.²

Treatment choices for leiomyosarcomas are influenced by the site, grade, and extent of disease, and may include surgery, chemotherapy, and radiotherapy. Surgical resection offers the best chance of cure and is sometimes coupled with radiotherapy.³ However, metastatic or unresectable sarcoma is rarely curable with reported median survival time of approximately 12 months and 5-year survival rates of 10%–15%.⁴ Chemotherapy may have substantial benefits for patients with metastatic or unresectable sarcoma and of the agents that have been utilized to treat soft tissue sarcomas, the most common are doxorubicin, ifosfamide, and, more recently, gemcitabine, both alone and in combination with taxanes.⁵ However, repeated and/or prolonged use of these agents is prohibited by their limited efficacy and/or associated toxicity. Response rates of approximately 20%, 39%, 8%, and 16% have been reported for doxorubicin, ifosfamide, gemcitabine alone, and in combination with docetaxel, respectively.^{5–7} In addition, radiotherapy has been combined with chemotherapy as well as being used alone to treat unresectable sarcoma.³

Vorinostat (Zolinza[®], Merck Sharp & Dohme, a subsidiary of Merck & Co., Inc.), an orally active, potent, and competitive inhibitor of histone deacetylases (HDAC),⁸ was approved by the US Food and Drug Administration (FDA) in October 2006 for the treatment of cutaneous manifestations in patients with cutaneous T-cell lymphoma (CTCL) who have progressive, persistent, or recurrent disease on or following two systemic therapies.⁹ In addition to efficacy in hematologic malignancies, vorinostat has demonstrated promising efficacy in Phase I trials in a wide range of solid malignancies.¹⁰ Here we report on a female patient with leiomyosarcoma with an apparent response to vorinostat treatment after multiple previous chemotherapy treatments.

Case Report

In September 2005, a 43-year-old, asymptomatic female presented with an increasing mass (4 × 3 cm) in her left thigh which involved the subcutaneous tissue down to the muscular fascia and adductor canal. An immunohistochemical examination on the excised tumor confirmed it was positive for smooth muscle actin, heavy chain myosin, vimentin, and S100 protein. Hence, the tumor was identified as a sarcoma consistent with leiomyosarcoma. Additional biopsies performed during the patient's therapy confirmed this initial diagnosis. Once leiomyosarcoma was diagnosed the patient underwent computed tomography (CT) of the chest, abdomen, and pelvis which revealed multiple lung nodules and a tumor (2.2 cm rounded structure) in the myometrium of the left side of the uterine wall, which effaced the uterine cavity. The uterine tumor was c-kit estrogen/progesterone receptor negative; however, its origin was inconclusive. The patient initially (October 2005) received combination chemotherapy of doxorubicin (50 mg/m²), ifosfamide (2000 mg/m²), and mesna (2000 mg/m²) every 21 days for a total of 6 cycles (finishing January 2006). A partial response based upon the CT findings was achieved.

Regretfully, disease recurred 6 months later and the above treatment regimen was resumed for 4 cycles (finishing October 2006). Once more, the patient responded well until disease recurred again approximately 4 months later; when combination chemotherapy with gemcitabine (800 mg/m²) and docetaxel (75 mg/m²) was commenced. However, the patient developed Grade 4 mucositis and pancytopenia during the first cycle necessitating hospital admission and treatment was subsequently reduced to single-agent gemcitabine (1000 mg/m², once weekly for 2 weeks followed by 1 week rest). The patient responded well and received 5 single-agent gemcitabine cycles in total (finishing April 2007).

Disease again recurred approximately 4 months later and treatment with single-agent gemcitabine was resumed; however, CT showed disease progression after 2 cycles and combination chemotherapy of doxorubicin, ifosfamide, and mesna was recommenced once more. However, after 2 cycles of this combination, no response was observed. Confronted with a lack of established therapy options in this



setting, the patient was offered the opportunity to either enter a clinical trial or receive vorinostat. Vorinostat was recommended based on Phase I results in patients with refractory solid tumors.¹⁰ Vorinostat (400 mg/day) was started approximately 2 years after diagnosis (November 2007), stable disease (SD) was observed after 6 weeks and maintained. Furthermore, some shrinkage was observed at 3 months in both her liver and lung metastases. The patient experienced mild nausea initially which subsided after a couple of months. Her complete blood count and metabolic values remained within normal limits whilst receiving vorinostat.

The patient remained on vorinostat for 18 months (finishing April 2009) when she developed progressive disease and subsequently received single-agent ifosfamide, and mesna which failed to produce a response. The patient then received single-agent dacarbazine followed by single-agent paclitaxel, both of which failed to produce a response. After evaluating all of her treatment options, the patient selected doxorubicin therapy despite the cardiac risk; however, after two cycles of weekly chemotherapy, with no response, treatment was stopped. The patient then chose to enter a hospice and died approximately 3.5 years after diagnosis (July 2009).

Discussion

In common with many patients with recurrent relapsing leiomyosarcoma, our patient had exhausted all treatment options for effective chemotherapy; including first- and second-line combination chemotherapy of doxorubicin, ifosfamide, and mesna followed by combination gemcitabine and docetaxel which was stopped due to Grade 4 adverse events (AEs) and replaced with single-agent gemcitabine, followed by doxorubicin, ifosfamide, and mesna upon relapse. The best and longest duration of response, overall SD for over 1.5 years, was achieved with vorinostat (400 mg/day), with initial mild nausea which resolved, and with some metastases shrinkage. Our case is the first to report an apparent effect of vorinostat in the treatment of leiomyosarcoma. Vorinostat has been approved for the treatment of CTCL and has shown efficacy in a number of additional hematologic malignancies.^{11–17} and promising efficacy in other solid tumor types such as breast cancer, lung

cancer, and mesothelioma.^{10,18–23} In a Phase IIb study in patients with persistent, progressive, or recurrent CTCL the objective response rate with vorinostat monotherapy was 29.7%, and 32.3% of patients (with baseline pruritus scores ≥ 3) had pruritus relief.¹¹ The most common drug-related AEs were diarrhea, fatigue, nausea, and anorexia, most of which were \leq grade 2; AEs of Grade 3 and above included fatigue, pulmonary embolism, thrombocytopenia, and nausea.¹¹ In an extension study, patients who had completed ≥ 6 months of treatment in the Phase IIb study were eligible to continue vorinostat treatment, until disease progression or unacceptable toxicity.²⁴ Fifteen of the initial 74 patients entered the extension study and six of these patients continued on vorinostat therapy for more than 2 years. The most common drug-related AEs in the continuation study were diarrhea, nausea, fatigue, and alopecia and the incidence of Grade 3–4 AEs was low. To date, five patients have discontinued vorinostat and one patient continues to respond after 1445 days (4.0 years). Both the clinical trials and post-trial clinical experience have confirmed the efficacy and tolerability of vorinostat. Compared with conventional cytotoxic agents,⁵ vorinostat has a favorable tolerability profile with both short- and long-term use.^{11,24} Thus unlike the cytotoxics, vorinostat has the potential for extended use.

A variety of genetic changes have been observed in leiomyosarcoma, often including changes in *TP53* and *MDM2* expression, overexpression of cyclin-dependent kinase inhibitor 2A (*CDKN2A*; p16), and a loss of gamma-smooth muscle isoactin expression.^{25–27} These findings support a preclinical rationale for the potential clinical utility of targeted agents in the management of leiomyosarcoma. Vorinostat is a small molecule inhibitor of Class I and II HDAC enzymes, which catalyze the removal of acetyl groups from histone proteins on nucleosomes, with histone acetyltransferases (HATs) facilitating the acetylation of these proteins.²⁸ Histone hypoacetylation results in closed chromatin structures and repression of important tumor suppressor genes.²⁹ Consequently, HAT inactivation has been associated with tumorigenesis and aberrant HDAC activity has been related to the development and maintenance of human tumors, including CTCL.³⁰ In addition, HDACs have many other non-histone proteins as substrates, such



as transcription factors (p53), α -tubulin, heat shock protein 90 (Hsp90) and various signaling proteins.²⁸

There are limited preclinical data reporting the activity of HDAC inhibitors in sarcoma.^{31–39} Ecke and co-workers observed that combined 5-aza-2'-deoxycytidine (a DNA methylation inhibitor) and valproic acid (a HDAC inhibitor) efficiently prevented medulloblastoma and rhabdomyosarcoma formation in patched mutant mice.³² Nguyen and co-workers observed that the Hsp90 inhibitor 17-AAG and the HDAC inhibitor MS-275 had synergistic, antiproliferative, and proapoptotic effects on synovial sarcoma in vitro.³¹ Additionally, the HDAC inhibitors MS-275, trichostatin-A, phenylbutyrate, LAQ824, and depsipeptide, enhanced the antineoplastic action of 5-aza-2'-deoxycytidine on Ewings sarcoma cells.³³ While Sakimura and colleagues noted that depsipeptide inhibited chondrosarcoma cell growth, up-regulated the expression of aggrecan and alpha2 chain of type XI collagen (COL11A2) mRNA, and induced differentiation to a hypertrophic cell phenotype.³⁷ Two studies with vorinostat have reported growth inhibition of chondrosarcoma cells, significant inhibition of tumor growth in a xenograft model, and death of endometrial stromal sarcoma cells.^{34,36} This case, which demonstrates promising activity for vorinostat in leiomyosarcoma, represents one of the first clinical applications of an HDAC inhibitor in soft tissue sarcoma. However, this is only one case report and more studies are needed to confirm the activity and efficacy of vorinostat in leiomyosarcoma.

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Disclosure

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test subjects. If this article contains identifiable human subject(s) author(s) were required to supply signed patient consent prior to publication. Author(s) have confirmed that the published article is unique and not under consideration nor published by any other publication and that they have consent to reproduce any copyrighted material. The peer reviewers declared no conflicts of interest.

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