

# Randomized Phase II trial of paclitaxel plus valproic acid vs paclitaxel alone as second-line therapy for patients with advanced gastric cancer

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**Abstract:** The standard regimen of second-line chemotherapy for patients with unresectable gastric cancer has not been established. However, weekly paclitaxel (wPTX) has become the preferable second-line chemotherapy in Japan. Histone deacetylase (HDAC) inhibitors have been shown to have antiproliferative activity through cell-cycle arrest, differentiation, and apoptosis in gastric cancer cells. One HDAC inhibitor, valproic acid (VPA), also inhibits tumor growth by inducing apoptosis, and enhances the efficacy of paclitaxel in a mouse xenograft model of gastric cancer. wPTX plus VPA as a second-line chemotherapy is expected to improve survival in gastric cancer patients. A multicenter randomized Phase II study was conducted to compare the effects of wPTX plus VPA and wPTX alone. A total of 66 patients participated in this study. The primary end point of the study was overall survival, and secondary end points were progression-free survival, response rate, and assessment of peripheral neuropathy.

**Keywords:** valproic acid, paclitaxel, second-line therapy, advanced gastric cancer

## Introduction

Gastric cancer remains one of the leading causes of cancer death in the world. For patients with unresectable advanced or recurrent gastric cancer worldwide, the combination of fluoropyrimidine and platinum is standard first-line chemotherapy.<sup>1</sup> Several randomized studies have revealed the survival benefit of second-line chemotherapy compared with best supportive care alone; however, median survival was less than 6 months.<sup>2-4</sup> Therefore, a more active regimen for second-line treatment is expected.

Although numerous clinical studies have considered the efficacy of molecularly targeted agents combined with conventional chemotherapy, efficacy in gastric cancer has been demonstrated only by trastuzumab as a first-line and ramucirumab as a second-line treatment.<sup>5,6</sup> Other candidates for molecularly targeted therapy are needed.

Histone deacetylase (HDAC) inhibitors have antiproliferative effects through cell-cycle arrest, differentiation, and apoptosis in various cancer cell types, including gastric cancer cells.<sup>7-9</sup> Accordingly, the combination of an HDAC inhibitor with conventional chemotherapy is expected to have a synergistic effect, because the mechanism of action of the combination varies from those of conventional chemotherapeutic regimens. Valproic acid (VPA), which has long been used clinically for the treatment of epilepsy and bipolar disorder without significant toxic effects, is now also used to prevent migraines. VPA inhibits both class I and II HDACs,<sup>10</sup> and affects tumor growth by inducing p21<sup>WAF1</sup>.<sup>11,12</sup> However, some reports suggest that HDAC inhibitors also enhance the acetylation of nonhistone proteins in relation with apoptosis.<sup>13-15</sup> Yagi et al reported that VPA induced dynamic modulation of histone H3 and  $\alpha$ -tubulin

acetylation in relation with an anticancer effect and the enhancement of paclitaxel (PTX) in the gastric cancer cell line.<sup>16</sup> The efficacy of VPA in human malignancy is unclear; however, combination therapy with radiotherapy revealed good prognosis in glioblastoma patients.<sup>17</sup> Therefore, VPA in combination with PTX is expected to be a promising therapy for gastric cancer.

Weekly PTX (wPTX) administration of 80 mg/m<sup>2</sup> is one treatment option for patients with gastric cancer in the second-line setting.<sup>18</sup> A recent randomized Phase III trial comparing PTX and irinotecan as second-line chemotherapy for gastric cancer found no significant difference in overall survival (OS) between the two groups. Third-line chemotherapy was administered to 89.8% of the participants in the PTX group and to 72.1% of those in the irinotecan group. Median OS was 9.5 months for PTX treatment and 8.4 months for irinotecan treatment, respectively. However, wPTX was associated with a good toxicity profile compared with irinotecan.<sup>19</sup>

Therefore, we planned a multicenter randomized Phase II study to investigate additional benefits of VPA as a molecularly targeting agent with wPTX in second-line or third-line chemotherapy.

## Protocol design of the study

### Purpose

The aim of this study was to compare the effects of wPTX alone and in combination with VPA (V-PTX) in patients with previously treated advanced gastric cancer.

### End points

The primary end point was OS rate, defined as the time from randomization to death from any cause. Secondary end points were progression-free survival rate, defined as time from randomization to radiographic progression, and response rate and assessment of peripheral neuropathy in each therapeutic course. OS rate and progression-free survival rate were estimated according to the Kaplan–Meier method. Response rate was evaluated every two courses during the study and classified based on Response Evaluation Criteria in Solid Tumors version 1.1. Toxicities including peripheral neuropathy were graded according to National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0.

### Eligibility criteria

Patients over 20 years of age diagnosed with histologically confirmed metastatic or recurrent gastric carcinoma that was unresponsive to first-line or second-line therapy (progressive disease confirmed by imaging studies) were eligible to

participate in the study. Other inclusion criteria were Eastern Cooperative Oncology Group performance status of 0–2, an interval of at least 4 weeks from the previous treatment, no prior chemotherapy with taxanes, adequate bone marrow, hepatic, and renal functions, and willingness to provide written informed consent.

Exclusion criteria were pregnancy, a history of allergy to Cremophor EL; intestinal pneumonia, lung fibrosis, and severe COPD; coexistence of another malignant neoplasm; psychological disease or brain metastasis; and other severe medical conditions.

## Treatment methods

PTX (80 mg/m<sup>2</sup>) was administered intravenously on days 1, 8, and 15, every 4 weeks. Thirty minutes before PTX administration, patients were premedicated with histamine receptor-1 and -2 blockers and dexamethasone for prophylaxis of allergic reactions. VPA was administered orally at a dose of 15 mg/kg/day divided into two daily doses. In this way, the serum value reached a concentration of 50–100 µg/mL, which is near the concentration required for VPA to act as an HDAC inhibitor (0.4–0.7 mM, 66.4–116.2 µg/mL).<sup>20</sup>

## Study design

The study was a prospective, multicenter, randomized Phase II clinical trial. As of 2012, participating institutions included 18 specialized centers. The protocol was approved by the independent ethics committee or institutional review board of each participating institution. This trial was conducted in accordance with the Declaration of Helsinki. All patients provided written informed consent before study entry.

After checking eligibility, patients were randomly assigned at a 1:1 ratio to receive VPA or not. Random assignment was carried out at the data center using a minimization method with the following adjustment factors: Eastern Cooperative Oncology Group performance status (0–1 vs 2), prior chemotherapy (first-line vs second-line), and measurable lesions (presence vs absence). Neither investigators nor patients were blinded to the allocated treatment.

## Statistics

The reported median OS in advanced gastric cancer patients treated with wPTX as second-line chemotherapy was 5 and 6.9 months, respectively.<sup>18,21</sup> For an exploratory study, if the median OS times for V-PTX and PTX therapy were 5 and 8 months, respectively, then 31 patients per treatment arm would be required to detect a difference with 80% power at a 5% significance level using a one-sided log-rank test of quality-of-survival curves. Assuming a dropout rate of 5%,

the number of patients per treatment group was set at 33, with a total sample size of at least 66 patients.

## Protocol registration

The study protocol was registered with the UMIN (University hospital Medical Information Network) Clinical Trials Registry (UMIN000005887) on August 1, 2011.

## Participating institutions

Departments of the following 18 centers in the Hokuriku region of Japan participated in the trial: Kanazawa University Hospital, Kurobe City Hospital, Toyama Rosai Hospital, Yatsuo General Hospital, Toyama Prefectural Central Hospital, Toyama City Hospital, Takaoka City Hospital, Keiju General Hospital, Kanazawa Medical University Hospital, Ishikawa Prefectural Central Hospital, Asanogawa General Hospital, Keiju Kanazawa Hospital, JCHO Kanazawa Hospital, Kanazawa Medical Center Hospital, Kanazawa Red Cross Hospital, Central Hospital of Matto Ishikawa, Houju Memorial Hospital, and Fukui University Hospital.

## Disclosure

The authors report no conflicts of interest in this work.

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