



Aldehyde dehydrogenase 2 genotype in tolerability of alcohol contained in paclitaxel in Japanese breast cancer patients

Toshinari Yagi¹ · Koto Fujiishi¹ · Akiko Hasegawa¹ · Tomoyuki Otsuka¹ · Tetsuhiro Yoshinami¹ · Minako Nishio¹ · Fumie Fujisawa¹ · Naotoshi Sugimoto¹ · Fumio Imamura¹

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Abstract

Background Paclitaxel (PTX) is an essential anticancer drug used to treat breast cancer. Because it contains alcohol as a solvent, it is contraindicated in many Japanese breast cancer patients when they are suspected of alcohol intolerance. Aldehyde dehydrogenase 2 (ALDH2) is one of several enzymes that catalyzes dehydrogenation of aldehydes, and plays an important role in ethanol metabolism. Deficiency of this isozyme is believed to be responsible for facial flushing and other unpleasant symptoms following ethanol intake. In this study, we examined the safety of PTX for patients with the ALDH2 GA genotype.

Methods We performed ALDH2 genotyping on 25 patients with various cancers who were suspected to be intolerant to alcohol based on an interview using a simple question. Ten patients with the ALDH2 GA genotype, including 5 breast cancer patients, underwent chemotherapy containing PTX up to 100 mg/m² (range 80–100 mg/m²), and were questioned about 16 alcohol-related symptoms at 11 timepoints to evaluate sensitivity to alcohol.

Results All patients completed the first course of planned chemotherapy with either no or grade 1 alcohol-related symptoms.

Conclusions Our study suggests that PTX up to 100 mg/m² can be used safely for patients with the ALDH2 GA genotype. To confirm the necessity of a genotyping test for ALDH2, further studies evaluating alcohol sensitivity in response to PTX among patients with the ALDH2 AA genotype are required.

Keywords Breast cancer · Paclitaxel · Alcohol · ALDH2

Introduction

Paclitaxel (PTX) is a member of the taxane drug class, which is widely used to treat patients with various types of cancers, including breast, ovarian, lung, gastric, esophageal, and head and neck cancers. This drug is used either as a monotherapy or in combination with other anticancer drugs or molecular target drugs, such as bevacizumab. In breast cancer treatment, PTX is used as an adjuvant, a neoadjuvant, and as a chemotherapeutic agent to treat metastatic cancer.

PTX (TAXOL^R) contains alcohol as a solvent. Each mL of sterile non-pyrogenic solution of this product contains 6 mg PTX, and 49.7% (v/v) dehydrated alcohol [1]. The Japanese package insert of TAXOL^R states that special

attention should be paid when PTX is used to treat patients who are sensitive to alcohol. Diagnosis of alcohol intolerance is difficult in patients when they have little or no experience drinking alcohol. For such patients, clinicians generally hesitate to prescribe PTX. Although an interview to assess alcohol intolerance is typically performed, it is difficult to select patients who are actually intolerant to alcohol based solely upon this assessment.

Aldehyde dehydrogenase 2 (ALDH2) is one of several enzymes that catalyzes dehydrogenation of aldehydes, and plays an important role in ethanol metabolism. Deficiency of this enzyme leads to elevated levels of acetaldehyde in the blood, and is believed to be responsible for facial flushing and other unpleasant symptoms following ethanol intake [2–4]. The ALDH2 locus is located on chromosome 12. An aberrant genotype of the ALDH2 locus (rs671, c.1510G > A) causes Glu504Lys substitution and results in ALDH2 deficiency. The wild genotype of the ALDH2 locus was described as ALDH2 *1, and the aberrant genotype was described as ALDH2 *2, formerly.

✉ Toshinari Yagi
yagi-to@mc.pref.osaka.jp

¹ Department of Clinical Oncology, Osaka International Cancer Institute, 3-1-69 Otemae, Chuo-ku, Osaka 541-8567, Japan

To the best of our knowledge, tolerability to alcohol contained in PTX on the basis of ALDH2 genotype has not been reported. We performed ALDH2 genotyping of 25 cancer patients who were suspected to be intolerant to alcohol based on an interview, and who were scheduled to receive chemotherapy containing PTX up to 100 mg/m². The aim of this study was to investigate sensitivity to alcohol contained in PTX when delivered up to 100 mg/m² to treat cancer patients with the ALDH2 GA genotype (heterozygous ALDH2 *1/*2).

Materials and methods

Patients

This study was conducted between April 1, 2012 and January 14, 2016 at Osaka International Cancer Institute. The eligibility criteria were as follows: patients with breast cancer, digestive tract cancer, ovarian cancer (primary peritoneal cancer), or head and neck cancer, who were suspected to be intolerant to alcohol as determined by an interview, and who required chemotherapy containing PTX up to 100 mg/m². Additional eligibility criteria included 0–2 performance status on the Eastern Cooperative Oncology Group Scale and sufficient organ function for the planned chemotherapy. Patients previously treated with PTX were excluded. Patients who were suspected to be intolerant to alcohol were selected using only one screening question regardless of their experience of actual alcohol intake: “Do you feel anxiety in drinking a glass of beer?”

Candidates for this trial were chosen through two stages. In stage 1, patients of the departments of breast endocrine surgery, gastrointestinal surgery, head and neck surgery, and gynecology who needed chemotherapy containing PTX, and were suspected to be intolerant to alcohol, were screened using the above question. In stage 2, eligibility of selected candidates was confirmed by our department (clinical oncology). Patients who met all eligibility criteria were informed of their eligibility for participation in this study. All participants signed written consent forms prior to participation.

Study design

A 2-mL peripheral blood sample was obtained for ALDH2 genotyping from each participant. ALDH2 genotyping was outsourced to SRL Inc., and performed using fluorescence correlation spectroscopy according to the manufacturer’s protocol. ALDH2 polymorphisms were classified as GG (ALDH2 *1/*1), GA (ALDH2 *1/*2), and AA (ALDH2 *2/*2) genotypes.

Patients in the GG group, who had normal ALDH2 activity, were injected with PTX for 1 h. Patients from the

GA group, who had a partially inactive form of ALDH2, were injected with PTX for 3 h in the first and second rounds of chemotherapy. After the second round of chemotherapy, the physician was able to determine the appropriate PTX injection time. Patients with the AA genotype, an inactive form of ALDH2, did not receive chemotherapy containing PTX.

PTX was used as a monotherapy or in combination with other drugs. The chemotherapy regimen was not limited, but the dose of PTX was limited to 100 mg/m². Standard anti-allergy premedications, consisting of intravenous 6.6–16.5 mg dexamethasone, intravenous 50 mg ranitidine, and intravenous 5 mg *d*-chlorpheniramine maleate (in one case, 50 mg oral diphenhydramine was used instead of *d*-chlorpheniramine maleate), were used prior to PTX infusion. Premedication drug administration was completed at least 30 min before the start of PTX infusion. All patients receiving chemotherapy were treated in the Department of Clinical Oncology during the study period. As there were no preceding studies, this study was conducted as a pilot study. We planned to evaluate at least 10 patients who received PTX-containing chemotherapy in both the GG and GA groups.

Assessments

Sixteen alcohol-related symptoms were assessed at 11 timepoints: flushing, maculopapular rash, hot flashes, pruritus, dizziness, headache, palpitation, wheezing, dyspnea, somnolence, nausea, vomiting, fatigue, euphoria, gait disturbance, and dysarthria.

These symptoms were selected by the authors from the Common Terminology Criteria for Adverse Events (CTCAE), version 4.0, and the timepoints were as follows: immediately preceding PTX infusion, and at 30 min, 1, 3, 5, 7, 9, 11, and 23 h after the start of PTX infusion, with the end of PTX infusion occurring at 3 h. Symptoms were also evaluated at the end of the second course of PTX infusion. Alcohol-related symptoms were graded according to the CTCAE, version 4.0. Breath alcohol concentration (BRAC) was measured at each timepoint using an ALCOSCENT DA-7100 digital breathalyzer (DA Tech. Co., Ltd.), which has a limit of detection of 0.03 mg/L BRAC.

We defined successful completion (SC) of chemotherapy as completion of the first course of chemotherapy on schedule with no alcohol-related symptoms of grade 3 or more. Patients with alcohol-related symptoms grade 2 or less who did not undergo the second round of chemotherapy due to alcohol-related symptoms were not classified as SC. This study was approved by the ethics committee of Osaka International Cancer Institute.

Results

ALDH2 genotyping

As no participant with the GG genotype was identified by the end of the trial, we discontinued evaluation of patients with this genotype and revised the protocol to analyze only patients with the other genotypes. During the trial period, 25 candidates were introduced to our department, and all patients were enrolled in this study. The number of patients screened by other departments for inclusion in our study is unknown.

The enrolled patients consisted of 3 males and 22 females with a median age of 64 years (range 43–79). The type of cancer was breast in 17, gastric in 4, nasopharyngeal in 2, and 1 each of esophageal and primary peritoneal cancer. The frequencies of ALDH2 genotypes of GG, GA, and AA are shown in Fig. 1.

Characteristics, alcohol-related symptoms, and rate of SC in patients with ALDH2 GA genotype

Among 14 patients with the ALDH2 GA genotype, 10 patients received PTX-containing chemotherapy according to the trial protocol. The other four patients dropped out of this trial. Three of the four refused PTX-containing chemotherapy after ALDH2 genotyping and requested different therapies, and one patient was transferred to another

hospital. Characteristics of the 10 patients who received PTX are shown in Table 1. PTX was used as a monotherapy in six patients. Three patients received PTX with bevacizumab, and one patient PTX with carboplatin. As for the five breast cancer patients, one patient was treated with PTX as a neoadjuvant chemotherapy, one patient as an adjuvant chemotherapy, and the other three patients were treated with PTX for metastatic lesions.

ALDH2 genotyping took 12–23 days. However, in most cases, genotyping was completed during a period preceding chemotherapy. Therefore, no treatment initiation delay was observed in this trial. The mean dose of PTX was 85 mg/m² (range 80–100). All patients completed the first course of planned chemotherapy without severe alcohol-related symptoms, indicating SC. Observed alcohol-related symptoms are shown in Table 2. Five patients complained of several alcohol-related symptoms after PTX injection. Patient No. 7 complained of somnolence (grade 1) just prior to PTX injection, which disappeared during PTX injection, and may have been caused by *d*-chlorpheniramine maleate, which was used as an anti-allergy premedication. Hot flashes and somnolence were the most common alcohol-related symptoms experienced by patients (40%, or, 4 of 10 patients experienced these symptoms).

Patient no. 1 complained of hot flashes at the second timepoint after PTX injection, but also felt the same symptom just prior to PTX infusion. Patients no. 3 and no. 10 complained of somnolence before and after PTX infusion. We

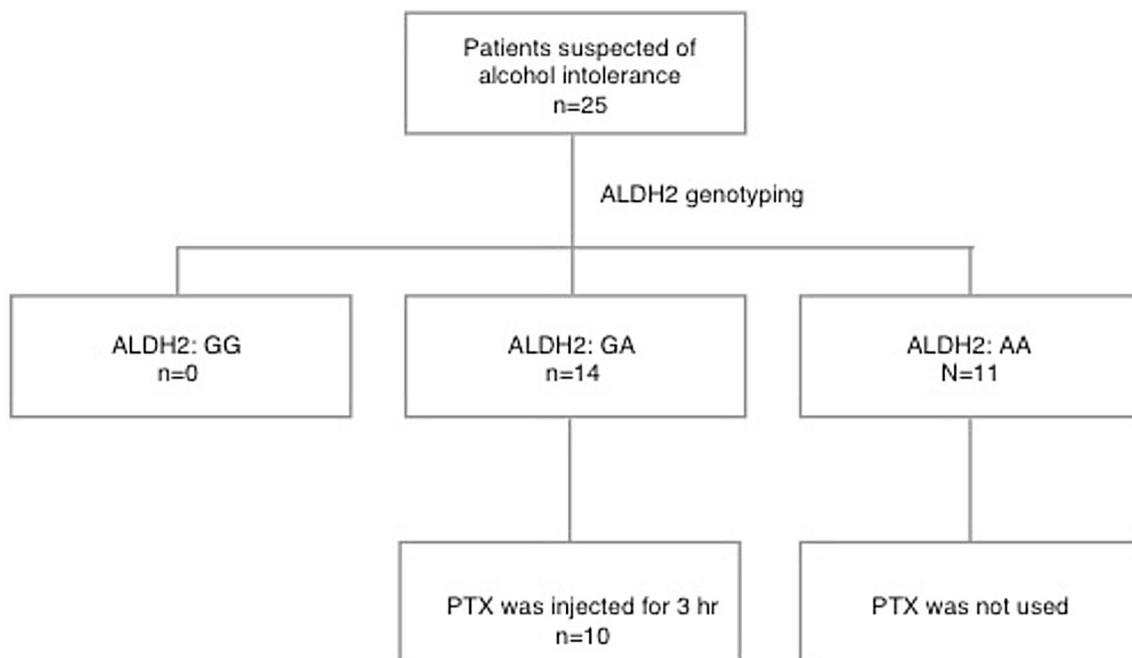


Fig. 1 Flow diagram of participants of this clinical trial. *ALDH2* aldehyde dehydrogenase 2, *PTX* paclitaxel, *n* number of patients

Table 1 Characteristics of patients with the GA genotype

Patient no.	Age	Gender	PS	Diagnosis	Protocol	PTX dose (mg/m ²)
1	65	F	2	Breast cancer	PTX + Bev	90
2	54	F	1	Gastric cancer	PTX	80
3	52	F	0	Breast cancer	PTX	80
4	64	M	1	Gastric cancer	PTX	80
5	56	F	0	Gastric cancer	PTX	80
6	78	F	2	Primary peritoneal cancer	PTX + CBDCA	80
7	76	M	0	Esophageal cancer	PTX	100
8	63	F	1	Breast cancer	PTX	80
9	64	F	0	Breast cancer	PTX + Bev	90
10	43	F	1	Breast cancer	PTX + Bev	90

PS performance status, F female, M male, PTX paclitaxel, Bev bevacizumab, CBDCA carboplatin

cannot distinguish whether these hot flashes and somnolence were caused by alcohol or by the anti-allergy premedication.

Breath alcohol concentration

BRAC was measured at 11 timepoints for each patient with the ALDH2 GA genotype (total 109 timepoints; one data point each of patients no. 9 and no. 10 was lost). All measurements were below the limit of detection of the measuring device.

Discussion

PTX (TAXOL^R) contains alcohol as a solvent. Each mL of sterile non-pyrogenic solution of this product contains 6 mg PTX, 527 mg purified cremophor^R EL (polyoxyethylated castor oil), and 49.7% (v/v) dehydrated alcohol. By comparison, beer that is commonly sold in Japan, contains 5% alcohol. Therefore, if a patient with a body surface area of 1.5 m² was treated with 100 mg/m² of PTX, the total volume of alcohol would be approximately equal to 240 mL of Japanese beer. Webster et al. described that 8 of 12 patients who received 175 mg/m² PTX for a 3-h infusion had detectable alcohol levels in post-infusion plasma [5]. To the best of our knowledge, there is only one case report of a patient who received PTX infusion developing symptoms of acute alcohol intoxication [6]. The Japanese package insert of TAXOL^R states that special attention should be paid when PTX is used for patients who are sensitive to alcohol. Moreover, anxious breast cancer patients tend to decline chemotherapy containing PTX, even if they have little experience taking alcohol. With such patients, many clinicians also hesitate to use PTX based on potential safety concerns.

Mitochondrial ALDH2 is a major enzyme responsible for oxidation of acetaldehyde derived from ethanol metabolism.

Catalytic deficiency of the ALDH2 isozyme is responsible for flushing and other vasomotor symptoms caused by increased acetaldehyde levels following alcohol intake. Individuals deficient in ALDH2 activity refrain from excessive drinking of alcohol due to these adverse reactions, leading to protection against alcoholism [7]. An aberrant genotype of the ALDH2 allele is highest in frequency in southeast China, and occurs in most areas of China, Japan, Korea, Mongolia, and Indochina, with frequencies gradually declining radially from southeast China [8]. As for ALDH2 genotype frequencies in the Japanese population, Higuchi S. et al. reported that the frequencies of GG, GA, and AA were 58, 35, and 7%, respectively [9]. Therefore, sensitivity to alcohol is common in Japan, and there is a potential risk of inducing acute alcohol intoxication by treatment with PTX. Yokohama A. et al. devised a flushing questionnaire to identify individuals with inactive ALDH2, which consists of two questions based on flushing of the face after drinking. The sensitivity and specificity of this questionnaire were both approximately 90% in Japanese subjects 40 years of age and older [10]. However, this questionnaire cannot be used for individuals who have few or no experience drinking alcohol. Thus, we used a simpler question to select participants who were suspected to be sensitive to alcohol: “Do you feel anxiety in drinking a glass of beer?” All candidates for this study selected by this simple question carried aberrant genotypes of ALDH2 (GA 56%, AA 44%), although the sensitivity and specificity of this question cannot be calculated in this study.

In this study, 10 patients with the ALDH2 GA genotype were treated with PTX up to 100 mg/m². Although 5 (50%) patients complained of several possible alcohol-related symptoms after PTX injection, every symptom was of grade 1. Three events (hot flush in patient no. 1; and somnolence in patients no. 3 and no. 10) were detected just prior to PTX infusion. As such, we cannot determine whether these symptoms were caused by alcohol or by the anti-allergy

Table 2 Alcohol-related symptoms of patients with the GA genotype

Patient no.	Just prior to PTX infusion	30 min after the start of PTX infusion	1 h later	2 h later	3 h later (at the end of PTX infusion)	5 h later	7 h later	9 h later	11 h later	23 h later	At the end of PTX infusion of the second course
1	Hot flash (1)	Hot flash (1)	Hot flash (1)	Hot flash (1)	Hot flash (1)	Hot flash (1)	Hot flash (1)	–	Nausea (1)	Flushing (1)	–
2	–	–	–	–	–	–	–	–	–	–	–
3	Somnolence (1)	Hot flash (1)	–	–	Somnolence (1)	–	–	–	–	–	–
4	–	–	–	–	–	–	–	–	–	–	–
5	–	–	–	–	–	–	–	–	–	–	–
6	–	–	–	–	–	–	–	–	–	–	–
7	Somnolence (1)	–	–	–	–	–	–	–	–	–	–
8	–	–	Somnolence (1)	Dyspnea (1)	Dyspnea (1), gait disturbance (1)	Somnolence (1), gait disturbance (1)	Somnolence (1)	Somnolence (1)	–	–	–
9	–	Somnolence (1)	Somnolence (1)	–	Fatigue (1)	–	Hot flash (1)	–	–	–	–
10	Somnolence (1)	Somnolence (1)	–	Hot flash (1), Somnolence (1)	–	–	–	–	No data	–	–

Alcohol-related symptoms (flushing, rash macula-papular, hot flashes, pruritus, dizziness, headache, palpitation, wheezing, dyspnea, somnolence, nausea, vomiting, fatigue, euphoria, gait disturbance, dysarthria)

() shows the grade of CTCAG

premedication. The results in these 10 patients suggest that patients with the ALDH2 GA genotype can tolerate alcohol contained in PTX when PTX is appropriately administered. In addition, ALDH2 genotyping is a useful tool in selecting patients who can be given PTX safely from patients with suspected alcohol intolerance.

In this study, PTX was infused into patients with the GA genotype for 3 h in the first and second courses of chemotherapy. Prolonged PTX infusion time may negatively affect PTX dose intensity. According to the trial protocol, the physician was able to determine the PTX infusion time after the second course of chemotherapy. When we followed up with these 10 patients after 2 courses of chemotherapy, we found that 9 of 10 patients could be infused with PTX for 1 h, while the other patient could be given PTX for 2 h. Considering these results, in patients with the ALDH2 GA genotype, PTX up to 100 mg/m² may be able to be infused at normal speed at the start of treatment in normal clinical situations. Some studies showed that BRAC was detectable in 44.4–56% of patients who received PTX infusion [11, 12]. In our study, BRAC was not detectable at any timepoint. A low dose of PTX and slow infusion rates may be the reason BRAC was not detected.

There are several limitations to this study. First, the sample size was not sufficient to completely confirm the safety of PTX use in patients with the aberrant ALDH2 genotype. Second, to the best of our knowledge, there is no scientifically proven assessment tool for evaluating an early alcohol intoxication state. Thus, we selected the sixteen clinical signs mentioned above from CTCAE (version 4.0), which were generally regarded as symptoms of early alcohol intoxication. Therefore, this set of items was not necessarily validated as the most suitable tool for this study. Third, we cannot completely distinguish alcohol-related symptoms from the effects of anti-allergy premedications or chemotherapy itself. Fourth, the effect of alcohol contained in PTX in patients with the ALDH2 AA genotype remains unclear. This last point is most important: if most patients with the ALDH2 AA genotype tolerate PTX up to 100 mg/m², the genotyping test itself would not be necessary. To our knowledge, there are no previous studies investigating sensitivity to alcohol contained in PTX among ALDH2 AA genotype patients. Therefore, patients with this genotype should be evaluated for their ability to tolerate alcohol during PTX treatment.

In summary, our study suggests that PTX up to 100 mg/m² can be safely used for patients with the ALDH2 GA

genotype. To confirm the necessity of a genotyping test of ALDH2, patients with ALDH2 AA genotype should be evaluated for tolerability to the alcohol contained in PTX.

Compliance with ethical standards

Conflict of interest Tetsuhiro Yoshinami received lecture fees from CHUGAI PHARMACEUTICAL CO.,LTD.

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