

Efficacy and Tolerability of Weekly Paclitaxel in Combination with High-dose Toremifene Citrate in Patients with Metastatic Breast Cancer

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Abstract

Toremifene citrate is expected to prevent drug resistance in cancer patients by inhibiting p-glycoprotein activity. The safety and efficacy of combination therapy with high-dose toremifene citrate and paclitaxel were investigated. Between December 2003 and June 2004, 15 women with a mean age of 53 years old with metastatic breast cancer were enrolled. The administration schedule was 80mg/m² of paclitaxel given on Days 1, 8, and 15, and 120mg/day of toremifene citrate orally administered starting on Day 18. On Days 32 and 39, paclitaxel was concurrently administered again. Toxicities, response rate, and time to treatment failure were assessed. All patients had been treated with endocrine or chemotherapy. Grade 3 leukopenia occurred in 2 patients on the administration of paclitaxel alone, and grade 3 febrile neutropenia occurred in 1 patient given the combination therapy. There was no grade 3 or greater non-hematological toxicity. There was no complete response and 1 partial response, producing a response rate of 6.7%. Median time to treatment failure was 2.7 months. Combination therapy of paclitaxel and toremifene was safe and well tolerated with minimal toxicity. Further clinical trials targeting patients with functional p-glycoprotein are warranted.

KEYWORDS: toremifene, paclitaxel, p-glycoprotein, metastatic breast cancer

Original Article

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Toremifene citrate is expected to prevent drug resistance in cancer patients by inhibiting p-glycoprotein activity. The safety and efficacy of combination therapy with high-dose toremifene citrate and paclitaxel were investigated. Between December 2003 and June 2004, 15 women with a mean age of 53 years old with metastatic breast cancer were enrolled. The administration schedule was 80 mg/m² of paclitaxel given on Days 1, 8, and 15, and 120 mg/day of toremifene citrate orally administered starting on Day 18. On Days 32 and 39, paclitaxel was concurrently administered again. Toxicities, response rate, and time to treatment failure were assessed. All patients had been treated with endocrine or chemotherapy. Grade 3 leukopenia occurred in 2 patients on the administration of paclitaxel alone, and grade 3 febrile neutropenia occurred in 1 patient given the combination therapy. There was no grade 3 or greater non-hematological toxicity. There was no complete response and 1 partial response, producing a response rate of 6.7%. Median time to treatment failure was 2.7 months. Combination therapy of paclitaxel and toremifene was safe and well tolerated with minimal toxicity. Further clinical trials targeting patients with functional p-glycoprotein are warranted.

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Metastatic breast cancer is considered incurable and optimal palliation and prolongation of life rather than curative intent are the main goals of treatment [1, 2]. Anthracycline-containing regimens have been the most effective against this disease [3] and

until recently, there was no standard treatment for patients with metastatic breast cancer in whom an anthracycline-containing regimen was ineffective. However, taxanes have proved to be equally as efficacious as anthracycline [4], and anthracycline and taxanes are now considered the most active chemotherapeutic agents for metastatic breast cancer [5]. Taxanes have also demonstrated significant activity as second- and third-line agents in the treatment of meta-

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static breast cancer [4, 6]. However, tumors initially sensitive to agents often acquire a multidrug resistance (MDR) phenotype, which is characterized by cross resistance to drugs to which the tumor has not been exposed [7]. A number of mechanisms have been identified for the resistance to chemotherapeutic agents. As one form of resistance, p-glycoprotein encoded by *MDR1* as an energy-dependent drug efflux pump can acquire resistance to structurally unrelated compounds simultaneously [8]. Toremifene citrate was developed in the 1980s, as a safe, less toxic, and non-steroidal triphenylethylene antiestrogen and became widely used in the treatment of postmenopausal breast cancer [9–11]. Toremifene citrate was an affinity substrate for the p-glycoprotein capable of interfering with the transport catalyzed by the p-glycoprotein [12]. Toremifene citrate in combination with paclitaxel is expected to be effective against breast cancer, however, both agents are mainly degraded via the same pathway by the hepatic enzyme cytochrome P450 [13, 14] and their combination in treatment might induce an increase in plasma concentrations or severe side effects. We designed this prospective study to assess whether high-dose toremifene citrate in addition to paclitaxel would be safe for or beneficial to patients with metastatic breast cancer.

Patients and Methods

Patients and Eligibility criteria. Patients with metastatic breast cancer were considered for enrollment. Eligibility criteria were as follows: 1) age of 80 years or younger; 2) Eastern Cooperative Oncology Group (ECOG) performance status of 2 or less; 3) recovery from the toxic effects of previous therapy; 4) adequate bone marrow, liver and renal function; 5) without severe cardiac disease; and 6) more than 3 months predictive survival. Eligibility was independent of estrogen receptor status. Previous treatments including taxanes were not considered in the eligibility criteria. This study was performed at the Shikoku Cancer Center. The protocol was approved by the institutional review board of Shikoku Cancer Center and was carried out in accordance with the Helsinki Declaration. All patients gave their written informed consent before entry and the participants' identification codes were used for unequivocal

identification of the patients. Patients were excluded if they had a high risk of a poor outcome because of concomitant nonmalignant disease, an active double cancer, and any other reason for which the investigator judged the patient to be unsuited for inclusion or unable to cooperate in the study.

Study design. Paclitaxel was administered intravenously on day 1, 8, 15, 32 and 39 and oral toremifene was administered daily from day 18. Paclitaxel was administered by intravenous infusion for 1.5 h at a dose of 80 mg/m² and toremifene was administered at 120 mg/body once every day (Fig. 1). This study was stopped on day 39, after which, paclitaxel was administered weekly for 3 consecutive weeks, followed by an one-week rest period and toremifene was concurrently administered orally every day. Prophylactic colony-stimulating factor (G-CSF) was used to determine whether neutropenic complications had occurred in a previous cycle.

Given the lack of appropriate pharmacological data, many questions remain about the use of toremifene for reversal of MDR including optimal dose and optimal schedule. In an *in vitro* experiment, a toremifene concentration of more than 2 μM reversed resistance, but this phenomenon was shown to be highly influenced by serum proteins *in vivo* [15]. In patients receiving toremifene to reverse doxorubicin resistance, it must be assumed that toremifene was extensively protein bound (>95%) and that toremifene concentrations in the order of >10 μM were required to overcome the effects of protein binding in plasma [15]. On the basis of pharmacological studies [16, 17], a dose of 120 mg per day was enough to maintain the plasma concentration necessary to reverse drug resistance. In addition, the time required to achieve a steady-state plasma concentration of toremifene and its metabolites was more than 2 weeks [18]. The present regimen was designed with these data in mind.

Safety evaluation. On the day before the

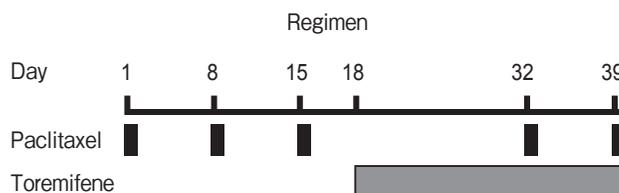


Fig. 1 Treatment schedule of weekly paclitaxel and toremifene.

administration of paclitaxel, laboratory tests were performed as follows; complete blood cell counts, differential white blood cell count, serum glutamic oxaloacetic transaminase, serum glutamic pyruvic transaminase, lactate dehydrogenase, gamma-glutamyl transpeptidase, cholinesterase, total cholesterol, electrolytes, total bilirubin, direct bilirubin, alkaline phosphatase, leucine aminopeptidase, total protein, albumin, albumin/globulin ratio, blood urea nitrogen, triglyceride, zinc sulfate turbidity test, thymol turbidity test, carcinoembryonic antigen, carbohydrate antigen 15-3, urinalysis and creatinine clearance. Doctors also interviewed patients to take a history of adverse events and physical examination. Toxicities were evaluated according to National Cancer Institute-Common Toxicity Criteria (NCI-CTC) version 2.0. The primary end point was the incidence of adverse events.

Evaluation of response. The objective response to chemotherapy was evaluated by the General Rules for Clinical and Pathological Recording of Breast Cancer (The Japanese Breast Cancer Society, 14th edition). Response assessment was performed every 1 or 2 months by serial clinical, radiographic, or computed tomographic measurement. A complete response (CR) was defined as the disappearance of all evidence of cancer for at least 4 weeks, and a partial response (PR) was defined as less than a complete response, but more than a 50% reduction of tumor volume for at least 4 weeks, without any evidence of new lesions or progression. No change (NC)

was defined as less than a 50% reduction or less than a 25% increase with no new lesions. Progressive disease (PD) was defined as more than a 25% increase in a solitary lesion or the appearance of new lesions. Stable disease (SD) was defined as neither sufficient shrinkage to qualify for PR nor a sufficient increase to qualify for PD for more than 6 months. We also defined the disease control rate as the sum of CR, PR and SD to evaluate the potential benefits of this treatment.

Time to treatment failure. Time to treatment failure was calculated by the Kaplan-Meier method from the day of the initiation of the concurrent administration of toremifene and paclitaxel until the date of progression, death (any cause) or withdrawal owing to an adverse event, or patient refusal. StatView 5.0 software (SAS Institute, Inc., Cary, NC, USA) was used throughout this study.

Results

This study was carried out between December, 2003, and June, 2004, and enrolled a total of fifteen women who had metastatic breast cancer. Characteristics of patients are listed in Table 1. There were 15 women with an average age of 53.0 years. Thirteen patients had a performance status of 2 or less. Two patients had a performance status of 3, because of metastasis to vertebrae which obliged them to be bedridden however, they were considered capable of tolerating the treatment. Frequent metastatic tumor

Table 1 Patient characteristics

Total patients		15 women	
Age (range)		53.0 ± 12.8 (33–77) yrs.	
Performance status	0	8	
	1	2	
	2	3	
	3	2	
Menopausal state	Premenopausal	6	
	Postmenopausal	9	
Prior treatment	Anthracycline	14	
	Taxane	11	(Paclitaxel: 9, Docetaxel: 9)
	5-FU	10	
	Endocrine	14	
Metastatic site	Bone	11	
	Lung	8	
	Liver	10	
	Locoregional	7	
	Others	6	

sites included the bone in 11 patients, the liver in 10 patients and the lung in 8 patients and metastases to 3 or more sites were observed in 7 patients. A total of 11 patients (73%) had received prior taxane therapy. Two patients had received paclitaxel, 2 patients (1 in a neoadjuvant setting) had received docetaxel, and 7 patients (1 who received docetaxel in a neoadjuvant setting) had received both. There was no patient who had received taxane therapy in an adjuvant setting. Characteristics of primary lesions are shown in Table 2. Twelve patients had recurrent disease; 10 of these after a curative operation and 2 patients after neoadjuvant chemotherapy and a curative operation. Three patients had metastatic disease on first arrival; 2 had received chemotherapy and surgery because their quality of life was impaired, and 1 patient received only chemotherapy. Eleven patients tested positive for estrogen receptors. No patients showed strong HER2 expression.

Table 2 Characteristics of initial tumor

Initial tumor site	Right	6
	Left	8
Initial stage	Bilateral	1
	I	1
	II	6
	III	4
	IV	3
Estrogen receptor	Unknown	1
	Positive	11
HER2 (IHC)	Negative	4
	0, 1+	13
	2+	2

A total of 112 accomplished combination treatment cycles (median 7.5, range 1–25) were administered.

Non-hematological toxicities are listed in Table 3A. There were no patients with grade 3 or greater toxicity. Frequent toxic symptoms included nausea, vomiting, alopecia, myalgia, arthralgia, and flushing. During the combination therapy, vaginal discharge was found in 3 patients. Hematological toxicities are noted in Table 3B. Only 1 patient (6.7%) had grade 3 febrile neutropenia. According to the lipid effects, hypercholesterolemia was improved but hyperglycemia worsened. Overall the therapy was generally well tolerated and there were no toxicity-associated deaths.

Table 4 summarizes the results of chemotherapy. Of all patients, 1 partially responded and the response rate was 6.7%. Ten patients (66.7%) showed no change and 4 of them (26.7%) were stabilized for 6 months or more. The disease control rate summarizes complete responses, partial responses and stable disease, thereby accounting for the overall benefit from treatment, and was 33.3% (5 of 15 patients). Four patients (26.7%) had progressive disease. Fig. 2 shows Kaplan-Meier estimates of time to treatment failure. Median time to treatment failure was 2.7 months.

Discussion

Toremifene citrate has been shown to be an affinity substrate for the p-glycoprotein [12] and has chemosensitizing activity in MDR-positive cells at concen-

Table 3A Non-hematological toxicities

	Before entry		Paclitaxel		Paclitaxel + toremifene	
	G1	G2	G1	G2	G1	G2
Nausea/vomiting	1	0	5	0	6	1
Stomatitis	0	0	2	0	3	1
Alopecia	6	4	8	6	2	13
Sensory neuropathy (Numbness)	10	0	11	0	11	1
Myalgia/Arthralgia	2	0	3	0	5	1
Flushing	0	0	14	0	13	0
Fatigue	3	0	8	0	7	2
Taste disturbance	1	0	3	0	3	0
Edema	0	3	3	3	2	3
Lethargy	0	0	3	0	3	0
Vaginal discharge	0	0	0	0	0	3
Cough	4	0	4	0	4	0

Table 3B Hematological toxicities

	Before entry				Paclitaxel				Paclitaxel + toremifene			
	G1	2	3	4	G1	2	3	4	G1	2	3	4
Leukopenia	0	0	0	0	4	5	2	0	3	2	1	0
Hemoglobin decreased	3	1	0	0	7	2	0	0	4	4	0	0
Febrile neutropenia	0	0	0	0	0	0	0	0	0	0	1	0
Glutamic oxaloacetic transaminase increased	3	1	0	0	6	0	0	0	2	1	0	0
Glutamic pyruvic transaminase increased	3	0	0	0	7	0	0	0	3	1	0	0
Bilirubin increased	1	0	0	0	0	0	0	0	0	0	0	0
Gamma-glutamyl transpeptidase increased	3	0	1	0	4	2	0	0	0	5	0	0
Alkaline phosphatase increased	6	1	0	0	9	0	0	0	4	1	0	0
Hypoalbuminemia	2	0	0	0	4	0	0	0	6	0	0	0
Hypercholesterolemia	7	0	0	0	7	0	0	0	4	0	0	0
Hypertriglyceridemia	5	0	0	0	6	0	0	0	7	0	0	0
Proteinuria	2	0	0	0	5	0	0	0	3	0	0	0
Hematuria	3	0	0	0	4	0	0	0	2	0	0	0

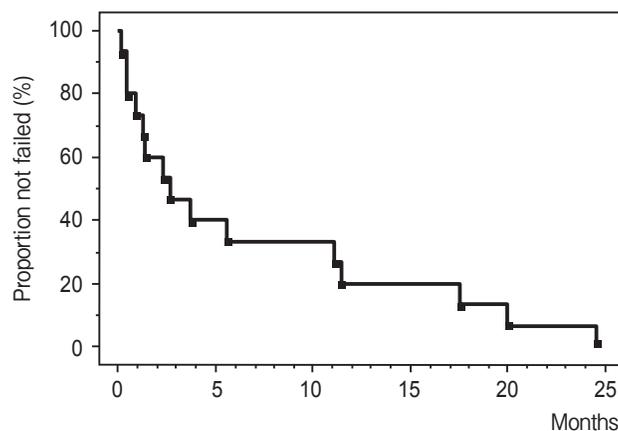
Table 4 Summary of efficacy results: response rate

Tumor response	No. of patients (%)
CR	0 (0%)
PR	1 (6.7%)
NC	≥ 6 months 4 (26.7%)
	< 6 months 6 (40%)
DCR	5 (33.3%)
PD	4 (26.7%)

CR, complete response; PR, partial response; NC, no change; DCR, disease control rate; PD, progression disease.

trations that are achieved in humans with minimal toxicity, although the mechanism underlying the modulation of multidrug resistance is unknown [19–22]. The development of MDR is one of the major mechanisms by which cancer becomes refractory to chemotherapeutic agents [21] and mechanisms of the MDR phenotype may involve p-glycoprotein expression, topoisomerases, and multidrug resistance-associated protein [7]. P-glycoprotein is overexpressed in approximately 40% of breast cancers and is associated with resistance to drugs of plant or bacterial origin [7]. In addition, drug resistance may arise with high baseline levels or increased expression levels of p-glycoprotein as a consequence of treatment [23]. A meta-analysis by Trock BJ *et al.* showed that patients are twice as likely to be MDR-positive following treatment, suggesting that treatment increased the expression of p-glycoprotein [7, 23].

A major problem with many reversing agents is

**Fig. 2** Kaplan-Meier curve for time to treatment failure.

that they can significantly alter the pharmacokinetics of the cytotoxic agents with which they are coadministered and increase the toxicity of the regimen [23, 24]. Valspodar and elacridar were developed as p-glycoprotein inhibitors in clinical trials [25]. These inhibitors modified the pharmacokinetic parameters of chemotherapeutic agents, which suggests that p-glycoprotein inhibition mediates the metabolism of anti-cancer drugs. However, Dofequidar fumarate, a new p-glycoprotein inhibitor, was shown to improve the progression-free survival of metastatic breast cancer patients, but it did not modify the area under the curve (AUC) of doxorubicin in a study by Saeki *et al.* [26]. Toremifene is extensively metabolized by CYP3A4 and to a minor extent, by other hepatic

isozymes [14]. Paclitaxel was also metabolized by cytochrome P450 enzymes of the CYP3A and CYP2C subfamilies in hepatic metabolism [13]. The coadministration of these agents with a common metabolic pathway may appear to influence drug concentration and increase adverse effects. Some p-glycoprotein inhibitors have been shown to modulate the pharmacokinetic parameters of chemotherapeutic agents in pre-clinical and clinical studies, and these inhibitors often enhanced toxicity as evidenced by an increase in the AUC of anti-cancer agents. However, concerning drug resistance, the concurrent use of chemotherapeutic and endocrine agents may be reasonable.

Weekly paclitaxel therapy was well-tolerated, with favorable safety and efficacy [27]. In previously published reports on weekly paclitaxel treatment (80–100 mg/m² per week) [28, 29], the toxicity was mild and consisted mainly of neutropenia and neuropathy. Severe adverse events included 14–18% grade 3–4 neutropenia, and 4–24% severe neuropathy. Myalgia and arthralgia were common but rarely severe. Toremifene has been also considered to be a promising agent with no serious side effects for use in breast cancer treatment [30, 31]. In phase III trials of standard or high-dose regimen comparisons, adverse events in patients who received 60-mg/day standard doses occurred in less than 20% of the patients [32], and frequent adverse events included hot flashes, sweating, nausea and/or vomiting, vaginal discharge, dizziness, edema, vaginal bleeding, liver function abnormalities, ocular changes and thromboembolic or cardiac events [32–34]. With high doses of toremifene (200 or 240 mg) in phase III studies, there was a trend toward more nausea, reversible corneal keratopathy, clinically insignificant serum glutamic oxaloacetic transaminase elevations, and hypercalcemia compared with tamoxifen [33, 34]. Toremifene appeared equally tolerated at high (up to 240 mg) and low (60 mg) dosage with the exception of a significantly higher incidence of nausea at high dosage in one study [19, 35]. In Japan, high-dose toremifene at 120 mg/day is approved for the treatment of patients refractory to tamoxifen or other agents. In a phase II study by Asaishi *et al.*, adverse events occurred in 5.1% of patients and included nausea, vertigo, and abnormal liver function [36]. It is noted that in our study compared with other studies, most patients were treated heavily with prior chemotherapy. They had

already complained of various symptoms or had abnormal laboratory data reflecting side effects. Although this study was conducted over a relatively short period, all patients tolerated the treatment well. Only 1 patient (6.7%) had grade 3 neutropenia and for this patient, the administration of paclitaxel was often postponed until neutropenia improved and the treatment was continued with prophylaxis G-CSF. In the follow-up study, 1 patient complained of grade 3 sensory neuropathy and declined to continue the therapy. No other patients experienced severe adverse events and continued to receive the therapy until tumor progression. Actually, some studies showed an increase in hematological toxicities by the addition of a p-glycoprotein modulator [25]. In our study, pharmacokinetics interactions between toremifene and paclitaxel were under the investigation, but the dose reduction may be needed, depending on the analysis.

The benefits of chemoendocrine therapy compared to hormonal therapy or chemotherapy remains unclear. As for the adjuvant chemoendocrine therapy, a study of the SWOG 8814 trial showed that the sequential use of tamoxifen with cyclophosphamide, doxorubicin, and 5-fluorouracil in postmenopausal women with hormone receptor-positive, node-positive breast cancer resulted in better disease-free survival compared to their concurrent use [37]. In advanced or metastatic breast cancer, combining hormonal therapy with chemotherapy was considered to have a potential benefit through additive or synergistic cytotoxicity in hormone receptor-positive breast cancer [38]. But previous studies show no survival advantage for the addition of hormonal therapy to chemotherapy compared to sequential therapy [38]. In our study, because most patients receiving previous various therapies acquired multidrug resistance, chemosensitizing activity rather than additive or synergistic cytotoxicity would be expected.

Paclitaxel is an effective agent in the treatment of metastatic breast cancer and administration schedules of weekly paclitaxel by 1-hour infusion at doses ranging from 80 to 100 mg/m² has achieved overall response rates of 50–68% [39]. In pretreated patients with metastatic breast cancer, response rates were in the range of 22–53% with a median time to progression of 5–6 months [29]. On the other hand, in a large phase III study of toremifene therapy for advanced breast cancer, response rates in the high-

dose toremifene arms were 22.6% in the North American Trial [35] and 28.7% in the Eastern European Trial [40], with a median time to progression from 5.5 to 6.1 months. Furthermore, high-dose toremifene therapy (120 to 240 mg/day) in a phase II study in patients with advanced breast cancer refractory to tamoxifen therapy achieved a 0 to 14% objective response rate, and a 19 to 44% disease stabilization during toremifene treatment with a median duration of disease stabilization of more than 2 months [19]. In a Japanese phase II study, Asaishi *et al.* reported that 120 mg of toremifene daily achieved an objective response rate of 14% and disease stabilization of 19% in patients with tamoxifen-refractory breast cancer [19, 36]. In our study, most of the patients had already been exposed and become refractory to various chemotherapeutic or endocrine agents. Notably, our study included 11 (73%) patients exposed to taxanes. In this disadvantageous state, objective response and disease stabilization were observed in 1 (6.7%) and 4 (26.7%) patients, respectively. Overcoming drug resistance is highly suspected beyond our expectations.

In conclusion, the results of this study demonstrate the tolerability and effectiveness of paclitaxel combined with toremifene in patients with metastatic breast cancer. Only 1 patient partially responded in terms of the suspected release of drug resistance. This result is promising in patients previously exposed to multi-drug therapy. In addition in deteriorated patients, this therapy is safe and tolerant as salvage chemotherapy. However, this study was small and did not require p-glycoprotein expression for inclusion. We believe that further clinical trials targeting patients with a functional p-glycoprotein are warranted.

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References

- Hortobagyi GN: Treatment of breast cancer. *N Engl J Med* (1998) 339: 974–984.
- Greenberg PAC, Hortobagyi GN, Smith TL, Ziegler LD, Frye DK and Buzdar AU: Long-term follow-up of patients with complete remission following combination chemotherapy for metastatic breast cancer. *J Clin Oncol* (1996) 14: 2197–2205.
- Fossati R, Confalonieri C, Torri V, Ghislandi E, Penna A, Pistotti V, Tinazzi A and Liberati A: Cytotoxic and hormonal treatment for metastatic breast cancer: a systematic review of published randomized involving 31,510 women. *J Clin Oncol* (1998) 16: 3439–3460.
- Nabholtz JMA, Reese DM, Lindsay MA and Riva A: Docetaxel in the treatment of breast cancer: an update on recent studies. *Semin Oncol* (2002) 29 (Suppl 12): 28–34.
- Leonessa F and Clarke R: ATP-binding cassette transporters and drug resistance in breast cancer. *Endocr Relat Cancer* (2003) 10: 43–73.
- Seidman AD, Reichman BS, Crown JPA, Yao TJ, Currie V, Hakes TB, Hudis CA, Gilewski TA, Baselga J, Forsythe P, Lepore J, Marks L, Fain K, Souhara M, Onetto N, Arbuck S and Norton L: Paclitaxel as second and subsequent therapy for metastatic breast cancer: activity independent of prior anthracycline response. *J Clin Oncol* (1995) 13: 1152–1159.
- Trock BJ, Leonessa F and Clarke R: Multidrug resistance in breast cancer: a meta-analysis of MDR1/gp170 expression and its possible functional significance. *J Natl Cancer Inst* (1997) 89: 917–931.
- Dexter DW, Reddy RK, Geles KG, Bansal S, Myint MA, Rogakto A, Leighton JC and Goldstein LJ: Quantitative reverse transcriptase-polymerase chain reaction measured expression of *MDR1* and *MRP* in primary breast carcinoma. *Clin Cancer Res* (1998) 4: 1533–1542.
- Kallio S, Kangas L, Blanco G, Johansson R, Karjalainen A, Perila M, Pippo I, Sundquist H, Sodervall M and Toivola R: A new triphenylethylene compound, Fc-1157a. I. Hormonal effects. *Cancer Chemother Pharmacol* (1986) 17: 103–108.
- Kangas L, Nieminen AL, Blanco G, Gronroos M, Kallio S, Karjalainen A, Perila M, Sodervall M and Toivola R: A new triphenylethylene compound, Fc-1157a. II. Antitumor effects. *Cancer Chemother Pharmacol* (1986) 17: 109–113.
- Kangas L: Review of the pharmacological properties of toremifene. *J Steroid Biochem* (1990) 36: 191–195.
- Rao US, Fine RL and Scarborough GA: Antiestrogens and steroid hormones: substrates of the human p-glycoprotein. *Biochem Pharmacol* (1994) 48: 287–292.
- Sonnichsen DS and Relling MV: Clinical pharmacokinetics of paclitaxel. *Clin Pharmacokinet* (1994) 27: 256–269.
- Berthou F, Dreano Y, Belloc C, Kangas L, Gautier JC and Beaune P: Involvement of cytochrome P450 3A enzyme family in the major metabolic pathways of toremifene in human liver microsomes. *Biochem Pharmacol* (1994) 47: 1883–1895.
- Wurz GT, Emshoff VD, DeGregorio MW and Wiebe VJ: Targeting chemosensitizing doses of toremifene based on protein binding. *Cancer Chemother Pharmacol* (1993) 31: 412–414.
- Tominaga T, Hayashi K, Hayasaka A, Asaishi K, Abe R, Kimishima I, Izuo M, Iino Y, Yokoe T, Abe O, Enomoto K, Fujiwara K, Watanabe H, Yamaguchi S, Fukuda M, Yoshida M, Miura S, Miyazaki I, Noguchi M, Senoo T, Sonoo H, Monden Y, Morimoto T, Nomura Y and Tashiro H: Phase I study of NK622 (toremifene citrate). *Jpn J Cancer Chemother* (1992) 19: 2363–2372 (in Japanese).
- Shiba E, Watanabe T, Taguchi T, Tsukamoto F and Noguchi S: Plasma concentrations of toremifene citrate and N-desmethyltoremifene in postmenopausal patients with breast cancer. *Jpn J Cancer Chemother* (2000) 27: 245–249 (in Japanese).
- Wiebe VJ, Benz CC, Shemano I, Cadman TB and DeGregorio MW: Pharmacokinetics of toremifene and its metabolites in

- patients with advanced breast cancer. *Cancer Chemother Pharmacol* (1990) 25: 247–251.
19. Wiseman LR and Goa KL: Toremifene. A review of its pharmacological properties and clinical efficacy in the management of advanced breast cancer. *Drugs* (1997) 54: 141–160.
 20. DeGregorio MW, Ford JM, Benz CC and Wiebe VJ: Toremifene: Pharmacologic and pharmacokinetic basis of reversing multidrug resistance. *J Clin Oncol* (1989) 7: 1359–1364.
 21. Wiebe V, Koester S, Lindberg M, Emshoff V, Baker J, Wurz G and DeGregorio M: Toremifene and its metabolites enhance doxorubicin accumulation in estrogen receptor negative multidrug resistant human breast cancer cells. *Invest New Drugs* (1992) 10: 63–71.
 22. Baker WJ, Maenpaa JU, Wurz GT, Koester SK, Seymour RC, Emshoff VD, Wiebe VJ and DeGregorio MW: Toremifene enhances cell cycle block and growth inhibition by vinblastine in multidrug resistant human breast cancer cells. *Oncol Res* (1993) 5: 207–212.
 23. Clarke R, Leonessa F and Trock B: Multidrug resistance/p-glycoprotein and breast cancer: review and meta-analysis. *Semin Oncol* (2005) 32 (Suppl 7): S9–15.
 24. Tolcher AW, Cowan KH, Solomon D, Ognibene F, Goldspiel B, Chang R, Noone MH, Denicoff AM, Barnes CS, Gossard MR, Fetsch PA, Berg SL, Balis FM, Venzon DJ and O'Shaughnessy JA: Phase I crossover study of paclitaxel with r-verapamil in patients with metastatic breast cancer. *J Clin Oncol* (1996) 14: 1173–1184.
 25. Sandor V, Fojo T and Bates SE: Future perspectives for the development of P-glycoprotein modulators. *Drug Resist Updat* (1998) 1: 190–200.
 26. Saeki T, Nomizu T, Toi M, Ito Y, Noguchi S, Kobayashi T, Asaga T, Minami H, Yamamoto N, Aogi K, Ikeda T, Ohashi Y, Sato W and Tsuruo T: Dofequider fumarate (MS-209) in combination with cyclophosphamide, doxorubicin, and fluorouracil for patients with advanced or recurrent breast cancer. *J Clin Oncol* (2007) 25: 411–417.
 27. Seidman AD, Hudis CA, Albanell J, Tong W, Tepler I, Currie V, Moynahan ME, Theodoulou M, Gollub M, Baselga J and Norton L: Dose-dense therapy with weekly 1-hour paclitaxel infusions in the treatment of metastatic breast cancer. *J Clin Oncol* (1998) 16: 3353–3361.
 28. Seidman AD: Single-agent paclitaxel in the treatment breast cancer: phase I and II development. *Semin Oncol* (1999) 26 (suppl 8): 14–20.
 29. Eniu A, Palmieri FM and Perez EA: Weekly administration of docetaxel and paclitaxel in metastatic or advanced breast cancer. *Oncologist* (2005) 10: 665–685.
 30. Pyrhonen SO: Phase III studies of toremifene in metastatic breast cancer. *Breast Cancer Res Treat (Suppl)* (1990) 16: S41–46.
 31. Robinson SP, Parker CJ and Jordan VC: Preclinical studies with toremifene as an antitumor agent. *Breast Cancer Res Treat (Suppl)* (1990) 16: S9–17.
 32. Gams R: Phase III trials of toremifene vs tamoxifen. *Oncology (Williston Park)* (1997) 11 (Suppl 4): 23–28.
 33. Vogel CL: Phase II and III clinical trials of toremifene for metastatic breast cancer. *Oncology (Williston Park)* (1998) 12 (Suppl 5): 9–13.
 34. Gershanovich M, Hayes DF, Ellmen J and Vuorinen J: High-dose toremifene vs tamoxifen in postmenopausal advanced breast cancer. *Oncology (Williston Park)* (1997) 11 (Suppl 4): 29–36.
 35. Hayes DF, Van Zyl JA, Hacking A, Goedhals L, Bezwoda WR, Mailliard JA, Jones SE, Vogel CL, Berris RF, Shemano I and Schoenfelder J: Randomised comparison of tamoxifen and two separate doses of toremifene in postmenopausal patients with metastatic breast cancer. *J Clin Oncol* (1995) 13: 2556–2566.
 36. Asaishi K, Tominaga T, Abe O, Izuo M and Nomura Y: Efficacy and safety of high dose NK 622 (toremifene citrate) in tamoxifen failed patients with breast cancer. *Gan to Kagaku Ryoho (Jpn J Cancer Chemother)* (1993) 20: 91–99 (in Japanese).
 37. Sledge GW Jr, Hu P, Falkson G, Tormey D and Abeloff M: Comparison of chemotherapy with chemohormonal therapy as first-line therapy for metastatic hormone-sensitive breast cancer: an eastern cooperative oncology group study. *J Clin Oncol* (2000) 18: 262–266.
 38. Albain KS, Green SJ, Ravdin PM, Cobau CD, Levine EG, Ingle JN, Pritchard KI, Schneider DJ, Abeloff MD, Norton L, Henderson IC, Lew D, Livingston RB, Martino S and Osborne CK: Adjuvant chemohormonal therapy for primary breast cancer should be sequential instead of concurrent: initial results from intergroup trial 0100 (SWOG-8814). *Proc Am Soc Clin Oncol* (2002) 21: 143a.
 39. Perez EA, Vogel CL, Irwin DH, Kirshner JJ and Patel R: Multicenter phase II trial of weekly paclitaxel in women with metastatic breast cancer. *J Clin Oncol* (2001) 19: 4216–4223.
 40. Gershanovich M, Garin A, Baltina D, Kurvet A, Kangas L and Ellmen J: A phase III comparison of two toremifene doses to tamoxifen in postmenopausal women with advanced breast cancer. Eastern European Study Group. *Breast Cancer Res Treat* (1997) 45: 251–262.