Cancer Chemother Pharmacol (2010) 66:89–94
DOI 10.1007/s00280-009-1137-z

ORIGINAL ARTICLE

Phase I study of combination therapy with weekly paclitaxel and cyclophosphamide for advanced or recurrent breast cancer

Norikazu Masuda · Takahiro Nakayama · Jun Yamamura · Shunji Kamigaki · Tetsuya Taguchi · Mai Hatta · Junichi Sakamoto

Received: 26 May 2009 / Accepted: 8 September 2009 / Published online: 19 September 2009

Abstract
Purpose Although anthracycline is a key agent in breast cancer treatment, its use is associated with the risk of cardiotoxicity. Recently, the value of combination therapy with docetaxel and cyclophosphamide was reported. Because the characteristics of paclitaxel differ on weekly versus tri-weekly administration, such as in the induction of apoptosis and anti-angiogenic activity, establishment of a treatment regimen with a combination of paclitaxel and cyclophosphamide (PC) is warranted. We initiated a phase I study to determine the maximum tolerated dose (MTD) and recommended dose (RD) of combination therapy with PC for advanced or recurrent breast cancer.
Patients and methods Eligible patients had advanced or recurrent breast cancer. Paclitaxel was given intravenously on days 1, 8, and 15 of every 3-week course, and cyclophosphamide on day 1, over a total of four courses. Paclitaxel was given at 80 mg/m^2 for level 1 and 100 mg/m^2 for level 2, and cyclophosphamide at 600 mg/m^2 in both cases. Onset of dose-limiting toxicity was evaluated during the first course, and tolerability throughout the four courses.
Results Four patients were enrolled in each of levels 1 and 2 from October 2006 to November 2007. The main toxicities were grade 3 neutropenia in four patients (50%) and sensory neuropathy in one (12.5%). An MTD was not attained, as neither a hematologic toxicity of grade 4 nor a non-hematologic toxicity of grade 3 or higher was observed during the first course at level 1 or 2. Response rate amongst assessable patients (one in level 1, two in level 2) was 66.7%.
Conclusions Safety was well tolerated throughout the four courses at level 2, and this dosage level was therefore regarded as the RD.

Keywords Breast cancer · Combination chemotherapy · Weekly paclitaxel · Cyclophosphamide · Phase I

N. Masuda (✉) · J. Yamamura
Breast Oncology Group, Department of Surgery,
Osaka National Hospital, 2-1-14, Honenzaka,
Chuo-ku, Osaka, Osaka 540-0006, Japan
e-mail: nmasuda@alpha.ocn.ne.jp

T. Nakayama · T. Taguchi
Department of Breast and Endocrine Surgery,
Graduate School of Medicine, Osaka University, Suita, Japan

S. Kamigaki
Department of Surgery, Sakai Municipal Hospital,
Sakai, Japan

M. Hatta · J. Sakamoto
Social Life Science, Young Leaders' Program,
Graduate School of Medicine, Nagoya University,
Nagoya, Japan

Introduction

Anthracycline-containing regimens such as doxorubicin and cyclophosphamide (AC); cyclophosphamide, doxorubicin, and 5-fluorouracil (CAF); and 5-fluorouracil, epirubicin, and cyclophosphamide (FEC), for breast cancer patients are highly active and widely used as primary systemic anticancer therapy, in either the adjuvant or neoadjuvant setting, and can reduce the risk of recurrence and death compared with non-anthracycline-containing regimens [1]. Results have shown, however, that anthracycline drugs show increasing cardiotoxicity as the total cumulative dose increases, and are associated with the risk of congestive heart failure (CHF). With regard to epirubicin, for example, the minimum cumulative dose level associated with cardiotoxicity may lower with increasing

age, when given in the treatment of breast cancer [2]. Further, it has been suggested that the incidence of CHF is higher in patients treated with anthracycline-containing regimens, even at 10 years after the end of treatment, as compared with patients who do not receive anthracyclines, indicating the potential negative effects of these drugs on long-term cardiac safety [3]. New combination regimens for the treatment of breast cancer that include alternatives to anthracyclines but maintain clinical efficacy are therefore required. In this regard, combined taxane plus cyclophosphamide therapy may be useful for avoiding the cardiotoxicity of anthracyclines.

Taxanes, including paclitaxel, are among the most active agents for the treatment of metastatic breast cancer [4–8] and are increasingly used in the adjuvant setting in high-risk patients. For metastatic breast cancer, regimens containing taxanes have similar efficacy to those with anthracyclines. Anthracyclines and taxanes have therefore been viewed as standard treatment in first-line chemotherapy in metastatic or recurrent breast cancer [9–11]. With regard to dosing, weekly administration of paclitaxel conferred a significantly better prognosis than conventional tri-weekly treatment [12–14].

Interestingly, Jones et al. [15] reported in 2006 that the combination of docetaxel and cyclophosphamide as adjuvant chemotherapy in patients with operable breast cancer resulted in a significantly higher disease-free survival (DFS) rate than standard adjuvant chemotherapy using a combination of doxorubicin and cyclophosphamide. We previously confirmed the tolerability of this combined regimen in a conducted a phase I trial of docetaxel plus cyclophosphamide in Japanese patients with breast cancer [16], and expected that combined therapy with paclitaxel will provide comparable efficacy.

Although many dose-finding studies of paclitaxel plus cyclophosphamide in breast cancer have been reported, all were conducted at high dose levels in combination with granulocyte colony-stimulating factor (G-CSF); no report to date has focused on an optimal dose level of paclitaxel and cyclophosphamide (PC) when administered without concomitant G-CSF [17–20]. Here, we investigated the maximum tolerable dose (MTD) of weekly paclitaxel plus three-weekly cyclophosphamide therapy for advanced or recurrent breast cancer, as well as the recommended dose (RD) for a forthcoming phase II trial.

Patients and methods

This was a multicenter, phase I, dose-finding study conducted by the Kinki Multidisciplinary Breast Oncology Group (KMBOG). The institutional review board at each center approved the protocol, and the study was conducted in accordance with the Good Clinical Practice Guidelines (Sixth International Conference on Harmonization and the Declaration of Helsinki). All patients provided written informed consent.

Women aged 20–75 years with either advanced breast cancer defined as stage IIIA–B or axillary lymph nodes metastases $\geq$4, or recurrent breast cancer were eligible for enrollment. Invasive ductal carcinoma was definitively diagnosed on the basis of histological examination of surgical specimens. The main inclusion criteria were ECOG performance status 0–1; normal cardiac (absence of serious arrhythmia and serious ischemic change on ECG), renal (serum creatinine <1.5 mg/dL), hepatic (aspartate aminotransferase and alanine aminotransferase $\leq$100 IU/L; bilirubin <1.5 mg/dL), and hematologic (white blood cell count $\geq$3,000/mm^3; neutrophils $\geq$1,500/mm^3; platelets $\geq$100,000/mm^3; hemoglobin $\geq$8.0 g/dL) function confirmed by pre-study examination; and, for recurrent breast cancer patients, life expectancy $\geq$3 months. Inclusion was not dependent on the presence or absence of measurable lesions.

In all patients, cyclophosphamide 600 mg/m^2 was administered intravenously (iv) on day 1 of each 3-week cycle, while paclitaxel was administered iv as a 60-min infusion at a dose of either 80 mg/m^2 (level 1) or 100 mg/m^2 (level 2) on days 1, 8, and 15 (Table 1). The doses were

Table 1 Treatment schedule and dose-escalation scheme

Course		1			2			3			4		
Day		1	8	15	22	29	36	43	50	57	64	71	78
Paclitaxel		↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓
Cyclophosphamide		↓			↓			↓			↓		
Level	Paclitaxel (mg/m^2)		Cyclophosphamide (mg/m^2)										
0	80		500										
1	80		600										
2	100		600										

the same for four or more courses of treatment. This maximum dose was selected on the basis of a phase I trial conducted in Japan [21] in which paclitaxel was administered weekly over 1 h for 6 weeks followed by a 1-week break. In this trial the dose of paclitaxel was escalated from 80 to 120 mg/m^2 in the absence of dose-limiting toxicity. Although no dose-limiting toxicity was seen, peripheral neuropathy developed in all six patients who received 120 mg/(m^2 week), and four patients discontinued treatment. Based on this prior trial, a maximum dose of weekly paclitaxel at 100 mg/(m^2 week) was therefore established for the present phase I study.

During the first course, dose-limiting toxicities (DLTs) were checked. Tolerability was evaluated over the four courses of treatment. Premedication prior to each paclitaxel administration was mandatory and consisted of iv dexamethasone 16 mg, oral diphenhydramine hydrochloride 50 mg, and iv ranitidine 50 mg. If no hypersensitivity reaction occurred after the first administration of paclitaxel, the dexamethasone dose was reduced to 8 mg from the second week, and if no hypersensitivity reaction occurred during the second week it was further reduced to 4 mg thereafter.

Three patients were to start at dose level 1. Thereafter, the decision regarding dose-escalation to level 2 was based on the occurrence of DLTs. A DLT was defined as grade 4 leukopenia/neutropenia lasting >4 days, fever associated with grade 3 or 4 neutropenia or infection, grade 4 thrombocytopenia, grade 3 or 4 non-hematologic toxicity (excluding nausea/vomiting, anorexia, and fatigue), and any other event that could be classified as a DLT at the discretion of the data and safety monitoring committee. If none of the three patients in a cohort experienced a DLT, three patients were to be treated at the next dose level. If one of the three patients experienced a DLT, three additional patients were to be treated at the same dose level. If no further DLTs occurred, three patients were to be treated at the next dose level. If a DLT occurred in two or more of a cohort of six patients, or two or more of a cohort of three patients, that dose level was to be defined as the maximum tolerated dose (MTD) and the previous dose level was to be defined as the RD.

Toxicities were graded using the third version of the National Cancer Institute Common Toxicity Criteria (CTCAE v3.0). Details of all toxicities and laboratory abnormalities and their relationship to study treatment were recorded on patient report forms. In patients with measurable lesions, objective response to treatment was assessed according to RECIST criteria.

Results

Eight women were enrolled from October 2006 to November 2007; four patients were evaluated in each of levels 1 and 2 due to the simultaneous registration of the third and fourth patients in each level. Baseline characteristics are summarized in Table 2. There were five patients with advanced breast cancer and three with recurrent breast cancer. Six of the eight patients had received previous chemotherapy with anthracycline-containing regimens. Measurable lesions were noted in three patients. All patients were administered four or more courses without a dose reduction in PC.

Table 2 Patient characteristics ($n = 8$)

Median age (range)	59.5 (48–70)
ECOG performance status	
0	8
Status of disease	
Advanced	
Lymph node ≧4	3
Stage IIIA or IIIB	2
Recurrent	3
Prior chemotherapy	
None	2
Yes	6
Estrogen receptor status	
Positive	5
Negative	3
Progesterone receptor status	
Positive	6
Negative	2
HER2/neu status	
Positive	3
Negative	5

Table 3 shows all toxicities during the first course of therapy. No patient in level 1 or 2 experienced grade 4 hemotoxicity or grade 3 or 4 non-hematologic toxicity, the MTD was not reached at the maximum prespecified dose of paclitaxel as outlined in the protocol. During the first course of treatment, grade 3 neutropenia was experienced in four patients (50.0%). No allergies, skin or nail changes, vomiting, or hemorrhagic cystitis were reported during the first course. In subsequent courses, grade 2 peripheral neuropathy was noted in one patient in the level 2 group during the fourth course of treatment. Dose reduction was not needed in any individual. In one patient in level 2, treatment was delayed for 2 weeks during the fourth course of treatment.

Three patients were included in the evaluation of efficacy (level 1, $n = 1$; level 2, $n = 2$). Response to treatment was rated as 'progressive disease' in one patient in level 1, and 'complete response' and 'partial response' in one patient each in level 2 (response rate 66.7%).

Table 3 Adverse events during the first course of therapy

	Level 1 group ($n = 4$)			Level 2 group ($n = 4$)		
	Grade 1	Grade 2	Grade 3	Grade 1	Grade 2	Grade 3
Leukopenia	1	2	1		4	
Neutropenia		2	2		2	2
Anemia	2	1		1		
Thrombocytopenia	1					
AST	1			2		
ALT	1			3		
Blood urea nitrogen	1					
Creatinine increased				1		
Fatigue	1			1		
Neuropathy: sensory				1		
Nausea	1			1		
Anorexia				1		

AST Aspartate aminotransferase, *ALT* alanine aminotransferase

Discussion

Here, we successfully investigated the MTD of combination therapy with paclitaxel given weekly plus cyclophosphamide for advanced or recurrent breast cancer, as well as the RD for a forthcoming phase II trial. This therapy was administered to eight eligible patients, including five in the adjuvant setting. Although the MTD was not reached at the maximum prespecified dose of paclitaxel, we confirmed that this therapy can be safely administered for ≥4 courses. Based on the results, level 2 (paclitaxel 100 mg/m^2 plus cyclophosphamide 600 mg/m^2) was established as the RD for the phase II trial.

Paclitaxel is an important drug in the treatment of breast cancer. Effective schedules of paclitaxel treatment include a tri-weekly schedule and a weekly schedule. The results of CALGB 9840 [13] indicate that a weekly paclitaxel schedule is more effective than a tri-weekly schedule, resulting in a significantly ($P = 0.0004$) higher response rate (42 vs. 29%; OR 1.75), longer median time to progression [9 vs. 5 months; adjusted hazard ratio (HR) 1.43; $P < 0.0001$], and longer median survival (24 vs. 12 months; adjusted HR 1.28; $P = 0.0092$). Further, Sparano et al. [12] reported in the ECOG1199 trial a significant lengthening of overall survival (OR 1.32; $P = 0.01$) and DFS (OR 1.27; $P = 0.006$) for a weekly over a tri-weekly paclitaxel regimen. With the tri-weekly paclitaxel group as the control, comparison of the weekly paclitaxel, tri-weekly docetaxel, and weekly docetaxel groups showed the weekly paclitaxel group had the most favorable improvement in overall survival and DFS.

Here, we examined PC as an anthracycline-sparing regimen. Presently, the CALGB40101 trial [22], which is comparing anthracycline and dose-dense paclitaxel, is currently underway and will address whether there is a necessity for anthracycline. The results of this trial should therefore clarify the necessity and optimal number of dosing courses for chemotherapy.

In preclinical studies, low dose levels of paclitaxel exerted not only a direct cytocidal effect, but also induced apoptosis of tumor cells and suppressed neovascularization. Further, these effects appeared to be enhanced by frequent exposure of tumor cells to the drug [23–27]. The utility of weekly paclitaxel treatment has therefore been endorsed in both clinical and preclinical studies, and this drug is now considered a standard therapy in breast cancer. Previous studies have shown that the safe and effective dose of weekly paclitaxel for breast cancer is 80–100 mg/m^2 [13, 14, 28]. Based on this, we introduced 80 mg/m^2 as the starting dose for paclitaxel and increased the dose up to 100 mg/m^2.

For ethical reasons, phase I trials are usually performed with patients who have advanced or recurrent cancer, and are not usually conducted in the adjuvant setting. In the present study, however, five of the eight subjects received weekly paclitaxel plus cyclophosphamide as adjuvant chemotherapy. The inclusion of these patients was based on the following three reasons. First, adjuvant chemotherapy for breast cancer usually uses a regimen containing an anthracycline that is sequentially or concomitantly combined with a taxane. In Japan, four courses of FEC followed by weekly paclitaxel for 12 weeks are safely administered as standard therapy in an outpatient setting. The patients receiving adjuvant therapy in this study were administered FEC and PC as a sequential regimen. Although the total dosing of cyclophosphamide in this FEC-PC sequential regimen is 4.4 g/m^2, secondary leukemia and secondary carcinoma are not usually seen. The regimen tested in this study of weekly paclitaxel plus cyclophosphamide was therefore based on these established treatment principles. Second, we previously conducted a phase I trial of docetaxel plus

cyclophosphamide as adjuvant chemotherapy and confirmed its tolerability [16]. Third, no drug interactions between PC leading to severe toxicities have been noted in previous clinical studies involving patients with breast cancer [17–19].

In conclusion, this study showed that combined weekly paclitaxel plus cyclophosphamide therapy can be administered safely to patients with advance or recurrent breast cancer for $\geq$4 courses. From these results, the RD for a forthcoming phase II trial was established as paclitaxel 100 mg/m^2 on days 1, 8, and 15 plus cyclophosphamide 600 mg/m^2 on day 1, of a 3-week cycle. Antitumor efficacy in the three patients with measurable lesions was favorable, with a response rate of 66.7%. These results warrant further investigation into this combination therapy regimen of paclitaxel plus cyclophosphamide for the treatment of advanced or recurrent breast cancer.

Acknowledgments This work was supported in part by the nonprofit organization (NPO) "Epidemiological and Clinical Research Information Network (ECRIN)." We wish to thank all the patients who participated in the KMBOG clinical trial.

References

1. Early Breast Cancer Trialists' Collaborative Group (1998) Polychemotherapy for early breast cancer: an overview of the randomized trials. Lancet 352:930–942
2. Ryberg M, Nielsen D, Cortese G, Nielsen G, Skovsgaard T, Andersen PK (2008) New insight into epirubicin cardiac toxicity: competing risks analysis of 1097 breast cancer patients. J Natl Cancer Inst 100:1058–1067
3. Giordano SH (2006) 2006 ASCO annual meeting (abstract #521)
4. Nabholtz JM, Gelmon K, Bontenbal M, Spielmann M, Catimel G, Conte P, Klaassen U, Namer M, Bonneterre J, Fumoleau P, Winograd B (1996) Multicenter, randomized comparative study of two doses of paclitaxel in patients with metastatic breast cancer. J Clin Oncol 14:1858–1867
5. Biganzoli L, Cufer T, Bruning P, Coleman R, Duchateau L, Calvert AH, Gamucci T, Twelves C, Fargeot P, Epelbaum R, Lohrisch C, Piccart MJ (2002) Doxorubicin and paclitaxel versus doxorubicin and cyclophosphamide as first-line chemotherapy in metastatic breast cancer: the European Organization for Research and Treatment of Cancer 10967 multicenter phase III trial. J Clin Oncol 20:3114–3121
6. Jassem J, Pienkowski T, Pluzanska A, Jelic S, Gorbunova V, Mrsic-Krmpotic Z, Berzins J, Nagykalnai T, Wigler N, Renard J, Munier S, Weil C, Central and Eastern Europe, Israel Paclitaxel Breast Cancer Study Group (2001) Doxorubicin and paclitaxel versus fluorouracil, doxorubicin, and cyclophosphamide as first-line therapy for women with metastatic breast cancer: final results of a randomized phase III multicenter trial. J Clin Oncol 19:1707–1715
7. Smith RE, Brown AM, Mamounas EP, Anderson SJ, Lembersky BC, Atkins JH, Shibata HR, Baez L, DeFusco PA, Davila E, Tipping SJ, Bearden JD, Thirlwell MP (1999) Randomized trial of 3-hour versus 24-hour infusion of high-dose paclitaxel in patients with metastatic or locally advanced breast cancer: National Surgical Adjuvant Breast and Bowel Project Protocol B-26. J Clin Oncol 17:3403–3411
8. Jones SE, Erban J, Overmoyer B, Budd GT, Hutchins L, Lower E, Laufman L, Sundaram S, Urba WJ, Pritchard KI, Mennel R, Richards D, Olsen S, Meyers ML, Ravdin PM (2005) Randomized phase III study of docetaxel compared with paclitaxel in metastatic breast cancer. J Clin Oncol 23:5542–5551
9. Chan S, Friedrichs K, Noel D, Pintér T, Van Belle S, Vorobiof D, Duarte R, Gil Gil M, Bodrogi I, Murray E, Yelle L, von Minckwitz G, Korec S, Simmonds P, Buzzi F, González Mancha R, Richardson G, Walpole E, Ronzoni M, Murawsky M, Alakl M, Riva A, Crown J, 303 Study Group (1999) Prospective randomized trial of docetaxel versus doxorubicin in patients with metastatic breast cancer. J Clin Oncol 17:2341–2354
10. Sledge GW, Neuberg D, Bernardo P, Ingle JN, Martino S, Rowinsky EK, Wood WC (2003) Phase III trial of doxorubicin, paclitaxel, and the combination of doxorubicin and paclitaxel as front-line chemotherapy for metastatic breast cancer: an intergroup trial (E1193). J Clin Oncol 21:588–592
11. Bishop JF, Dewar J, Toner GC, Smith J, Tattersall MH, Olver IN, Ackland S, Kennedy I, Goldstein D, Gurney H, Walpole E, Levi J, Stephenson J, Canetta R (1999) Initial paclitaxel improves outcome compared with CMFP combination chemotherapy as front-line therapy in untreated metastatic breast cancer. J Clin Oncol 17:2355–2364
12. Sparano JA, Wang M, Martino S, Jones V, Perez EA, Saphner T, Wolff AC, Sledge GW Jr, Wood WC, Davidson NE (2008) Weekly paclitaxel in the adjuvant treatment of breast cancer. N Engl J Med 358:1663–1671
13. Seidman AD, Berry D, Cirrincione C, Harris L, Muss H, Marcom PK, Gipson G, Burstein H, Lake D, Shapiro CL, Ungaro P, Norton L, Winer E, Hudis C (2008) Randomized phase III trial of weekly compared with every-3-weeks paclitaxel for metastatic breast cancer, with trastuzumab for all HER-2 overexpressors and random assignment to trastuzumab or not in HER-2 nonoverexpressors: final results of Cancer and Leukemia Group B protocol 9840. J Clin Oncol 26:1642–1649
14. Verrill MW, Lee J, Cameron DA (2007) Anglo-Celtic IV: first results of a UK National Research Network randomized phase III pharmacogenetic trial of weekly versus 3 weekly paclitaxel in patients with locally advanced or metastatic breast cancer (ABC). In: 2007 ASCO annual meeting (abstract #LBA1005)
15. Jones SE, Savin MA, Holmes FA, O'Shaughnessy JA, Blum JL, Vukelja S, McIntyre KJ, Pippen JE, Bordelon JH, Kirby R, Sandbach J, Hyman WJ, Khandelwal P, Negron AG, Richards DA, Anthony SP, Mennel RG, Boehm KA, Meyer WG, Asmar L (2006) Phase III trial comparing doxorubicin plus cyclophosphamide with docetaxel plus cyclophosphamide as adjuvant therapy for operable breast cancer. J Clin Oncol 24:5381–5387
16. Matsunami N, Masuda N, Morimoto T, Nakayama T, Nomura T, Ishitobi M, Kamigaki S, Yamamura J, Tsukamoto F, Ohashi Y, Taguchi T, Tsujinaka T (2008) Feasibility study of combination therapy with docetaxel and cyclophosphamide for breast cancer in Japan (in Japanese). In: 16th Annual meeting of the Japanese breast cancer society (abstract #O-217)
17. Pagani O, Sessa C, Martinelli G, Cerny T, de Jong J, Goldhirsch A, Zimatore M, Cavalli F (1997) Dose-finding study of paclitaxel and cyclophosphamide in advanced breast cancer. Ann Oncol 8:655–661
18. Tolcher AW, Cowan KH, Noone MH, Denicoff AM, Kohler DR, Goldspiel BR, Barnes CS, McCabe M, Gossard MR, Zujewski J, O'Shaughnessy JA (1996) Phase I study of paclitaxel in combination with cyclophosphamide and granulocyte colony-stimulating factor in metastatic breast cancer patients. J Clin Oncol 14:95–102
19. Kennedy MJ, Zahurak ML, Donehower RC, Noe DA, Sartorius S, Chen TL, Bowling K, Rowinsky EK (1996) Phase I and pharmacologic study of sequences of paclitaxel and

cyclophosphamide supported by granulocyte colony-stimulating factor in women with previously treated metastatic breast cancer. J Clin Oncol 14:783–791
20. Sessa C, Pagani O, Martinelli G, Cerny T, de Jong J, Goldhirsch A, Zimatore M, Cavalli F (1997) Dose-finding study of paclitaxel and cyclophosphamide in women with advanced breast cancer. Semin Oncol 24(suppl 17):S17–52–S17–57
21. Nokihara H, Tamura T, Matsumoto Y (2002) Weekly paclitaxel in solid tumor, a phase I trial. 43rd The Japan Lung Cancer Society annual meeting (abstract #E-13). Jpn J Lung Cancer 42:395 (in Japanese)
22. Shulman L (2009) Phase III randomized study of adjuvant cyclophosphamide and doxorubicin versus single-agent paclitaxel in women with operable breast cancer and 0–3 positive axillary lymph nodes. http://www.cancer.gov/search/viewclinicaltrials.aspx?version=healthprofessional&cdrid=69444. Accessed 26 Aug 2009
23. Milross CG, Mason KA, Hunter NR, Chung WK, Peters LJ, Milas L (1996) Relationship of mitotic arrest and apoptosis to antitumor effect of paclitaxel. J Natl Cancer Inst 88:1308–1314
24. Belotti D, Vergani V, Drudis T, Borsotti P, Pitelli MR, Viale G, Giavazzi R, Taraboletti G (1996) The microtubule-affecting drug paclitaxel has antiangiogenic activity. Clin Cancer Res 2:1843–1849
25. Symmans WF, Volm MD, Shapiro RL, Perkins AB, Kim AY, Demaria S, Yee HT, McMullen H, Oratz R, Klein P, Formenti SC, Muggia F (2000) Paclitaxel-induced apoptosis and mitotic arrest assessed by serial fine-needle aspiration: implications for early prediction of breast cancer response to neoadjuvant treatment. Clin Cancer Res 6:4610–4617
26. Griffon-Etienne G, Boucher Y, Brekken C, Suit HD, Jain RK (1999) Taxane-induced apoptosis decompresses blood vessels and lowers interstitial fluid pressure in solid tumors: clinical implications. Cancer Res 59:3776–3782
27. Milas L, Hunter NR, Mason KA, Milross CG, Saito Y, Peters LJ (1995) Role of reoxygenation in induction of enhancement of tumor radioresponse by paclitaxel. Cancer Res 55:3564–3568
28. Eniu A, Palmieri FM, Perez EA (2005) Weekly administration of docetaxel and paclitaxel in metastatic or advanced breast cancer. Oncologist 10:665–685