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Report

Phase II study of docetaxel and epirubicin in Chinese patients with metastatic breast cancer

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The efficacy and safety of docetaxel–epirubicin chemotherapy in the treatment of metastatic breast cancer was investigated in Chinese women. Three-weekly cycles comprised epirubicin 75 mg/m^2 i.v. followed 1 h later by docetaxel 75 mg/m^2 i.v. After 3 cycles, responding patients received a further 3 cycles, followed by 3 cycles of docetaxel alone. Forty-six patients entered the study, of whom 37% had received prior adjuvant chemotherapy. Three patients withdrew due to toxicity and were not evaluable for response. There were five complete responses and 31 partial responses, giving an overall response rate of 83.7% (95% CI 72.7–94.8%). The median time to progression was 10.96 months (95% CI 7.76–12.86) and median survival was 24.2 months (95% CI 16.6–). The most common grade 3/4 adverse events were neutropenia (96% of patients) and neutropenia with fever (39%). Hepatotoxicity occurred in six patients, two being attributable to hepatitis B virus reactivation. No patients suffered grade 3/4 cardiac toxicity and there were no treatment-related mortalities. Quality of life aspects deteriorated after 3 cycles, but there was a trend towards improved emotional aspects after 9 cycles. We conclude that docetaxel–epirubicin chemotherapy is highly effective for recurrent metastatic/locoregional breast cancer, with myelosuppression being the main toxicity. [© 2002 Lippincott Williams & Wilkins.]

Key words: Docetaxel, epirubicin, metastatic/recurrent breast carcinoma.

Introduction

Anthracyclines and taxanes are two of the most active groups of cytotoxic agents used in the treatment of metastatic breast cancer. When administered as single agents, they produce objective responses in approximately 40 and 50% of patients, respectively.[1,2] Prior to the availability of taxanes, several randomized trials and a meta-analyses demonstrated that chemotherapeutic regimens containing doxorubicin were associated with improved responses and survival when compared with non-doxorubicin-containing treatment.[1] As a result, anthracycline-containing regimens have been considered as the standard initial therapy for patients with metastatic breast cancer.[3]

The cytotoxic effects of taxanes, including paclitaxel and docetaxel, are mediated principally by inhibition of mitosis. These drugs bind to tubulin, promote assembly of microtubules and then inhibit their depolymerization.[4,5] In addition, the taxanes have other biologic effects that may contribute to their antineoplastic activity.[6] With the demonstrated activity of anthracyclines and taxanes as single agents in breast cancer, their relative non-cross-resistance, partially non-overlapping toxicities and differing mechanisms of action, combination treatment with these drugs offers a potentially attractive treatment for metastatic breast cancer.

Several phase I, II and III trials using a doxorubicin–paclitaxel combination have reported high response rates in metastatic breast cancer.[7,8] However, cardiotoxicity was found to be a problem.[9,10] Subsequent reports have suggested that cardiac toxicity can be reduced by limiting the cumulative dose of doxorubicin to 360 mg/m^2,[11] allowing an interval of at least 16 h between the administration of the two drugs,[12] using the cardioprotective agent dexarazoxane immediately before therapy[13] or administering paclitaxel as a 24-h infusion with a 4-h interval between the drugs.[14]

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However, these measures are inconvenient and may require inpatient treatment.

Epirubicin, a doxorubicin analog, has been reported to have equivalent efficacy to doxorubicin. In previously treated patients with advanced breast cancer, objective response rates to standard doses ($\leqslant 90\,mg/m^2$ every 3 weeks) ranged from 16 to 50%.[15] Moreover, the major metabolite of epirubicin, epirubicinol, is less cardiotoxic than doxorubicinol and epirubicin has thus replaced doxorubicin in recent clinical trials.[15–18] The combination of taxanes and epirubicin has yielded high response rates of 42–85%.[16–24] In pharmacokinetic studies on epirubicin administered with docetaxel, there was no apparent pharmacokinetic interaction observed between the two agents. Therefore, schedules could be given more conveniently in an outpatient setting with limited cardiac toxicity.[20–25]

In a phase I trial using a dose-escalation schema consisting of epirubicin in combination with docetaxel, two doses have been recommended for phase II study: docetaxel ($75\,mg/m^2$)/epirubicin ($75\,mg/m^2$) and docetaxel ($75\,mg/m^2$)/epirubicin ($90\,mg/m^2$).[19] In view of the fact that most of the literature available on taxane–anthracycline therapy is based on populations in the West, with limited data on Chinese patients, we describe herein a prospective study of the use of combination docetaxel ($75\,mg/m^2$) and epirubicin ($75\,mg/m^2$) in Chinese patients with metastatic/recurrent metastatic breast cancer. The endpoints were objective tumor response, time to progression, toxicity and survival. Quality of life (QoL) was measured as a secondary outcome.

Patients and methods

Patient population

Patients with histologically or cytologically proven carcinoma of the breast with manifestations of metastatic or recurrent disease were considered for entry into the study. The criteria for entry into the trial were: (i) written informed consent, (ii) age between 18 and 75 years, (iii) measurable disease on clinical or radiologic grounds, and (iv) WHO performance status 0, 1 or 2. Previous therapy was allowed in the following settings: (i) previous hormonal therapy in the adjuvant/salvage setting with $\leqslant 2$ different regimens and the last therapy being $\geqslant 4$ weeks prior to study entry; (ii) previous chemotherapy in the adjuvant and/or neoadjuvant setting if completed $\geqslant 6$ months prior to entry to the present study; (iii) previous doxorubicin of cumulative dose $\leqslant 250\,mg/m^2$ (iv); previous radiotherapy given as an adjuvant to locoregional area and in a palliative setting, provided that they were given $\geqslant 4$ weeks prior to study entry. Also required were adequate hematologic function (absolute neutrophil count $\geqslant 1.5 \times 10^9/l$ and platelets $\geqslant 100 \times 10^9/l$); adequate hepatic function [total bilirubin $\leqslant 1.5 \times$ upper limit of normal (ULN), alanine (ALT) and aspartate (AST) transaminases $\leqslant 2.5 \times$ ULN or $\leqslant 3.0 \times$ ULN in the presence of liver metastases, alkaline phosphatase $\leqslant 6 \times$ ULN (unless bone metastases present in the absence of liver metastases)]; adequate renal function (serum creatinine $\leqslant 1.5 \times$ ULN); and adequate cardiac function as confirmed by echocardiography with left ventricular ejection fractions (LVEF) $\geqslant 50\%$.

Patients were excluded if they had any of the following: (i) presence of central nervous system or only bone metastases at presentation; (ii) history of a second malignancy; (iii) symptomatic peripheral neuropathy (WHO grade $\geqslant 2$); (iv) contraindications for corticosteroid therapy; (v) concomitant cardiovascular disease; (vi) previous taxane or current anticancer therapy of other modalities; (vii) inability to comply with oral medication; (viii) pregnancy or lactation; (ix) concurrent hypercalcemia or concomitant bisphosphonate therapy unless it had been initiated $\geqslant 3$ months prior to the study; (x) active infection or any other serious underlying medical condition not compatible with study entry. The Ethics Committee, Faculty of Medicine, Chinese University of Hong Kong, approved the protocol.

Treatment plan

Epirubicin $75\,mg/m^2$ was given as an i.v. injection followed 1 h later by docetaxel $75\,mg/m^2$ given as a 1–h i.v. infusion. Dexamethasone (8 mg orally twice daily) was given for 3 days beginning 1 day before each treatment. Patients were assessed twice during each 3-weekly cycle—on the day prior to treatment and on day 10. Treatment was repeated if the neutrophil count was $\geqslant 1.5 \times 10^9/l$, platelets $\geqslant 100 \times 10^9/l$ and upon recovery from all non-hematologic toxicities.

Dose reduction schema for severe toxicities

Patients who developed febrile neutropenia were given prophylactic ciprofloxacin in the subsequent cycles. For recurrent febrile neutropenia despite

prophylactic antibiotics, grade 4 thrombocytopenia and/or bleeding, or grade $\geqslant$3 non-hematologic toxicity, dose reductions were implemented: 20% of docetaxel, followed by 20% of epirubicin in subsequent cycles for persistent toxicities. After the first 10 patients were recruited into the study, administration of hematopoietic granulocyte colony stimulating factor (Novartis Pharma, Basel, Switzerland) was introduced as supportive therapy in patients who developed neutropenic fever, prior to the planned dose reduction schema. For patients who developed persistent grade 3/4 toxicity after dose reductions, further chemotherapy was withheld. All toxicities were graded according to WHO criteria.[26]

It was planned that all patients would receive 6 cycles of treatment unless there was unacceptable toxicity or progression of disease. Patients who responded could receive an additional 3 cycles of docetaxel only. Patients with stable disease but no response would stop treatment after 6 cycles. Treatment was stopped in the event of progressive disease or intolerable side effects.

Schedule for tumor evaluation and response assessment

Pretreatment investigations included a full clinical history, physical examination, renal and hepatic function tests, and a complete blood picture. Computed tomography (CT) of the thorax, abdomen and/or pelvis, chest X-ray, bone scintigraphy, abdominal ultrasonography, and other tests were performed as indicated by the clinical picture within the 4 weeks prior to the start of treatment.

In between each cycle, nadir complete blood picture with white cell differential count, renal and hepatic function tests were performed. Toxicity of treatment was scored after each course according to WHO recommendations on acute and subacute toxicity of cancer treatment.[26]

Evaluation of response by radiologic methods was carried out after 3, 6 and 9 cycles, and then every 3 months thereafter until disease progression. Classification of response was according to the WHO criteria.[26] Complete response (CR) was defined as the complete disappearance of all measurable or evaluable disease and all objective signs and symptoms of the disease with a duration of more than 30 days post-treatment. Partial response (PR) was defined as a decrease of $\geqslant$50% in cross-perpendicular dimensions of all measurable or evaluable lesions for at least 30 days. Stable disease (SD) was defined as a response less than partial response or an increase in cross-perpendicular dimensions of all measurable or evaluable lesions of $<$25%. Progressive disease (PD) was defined as an objective increase of $\geqslant$25% in all measurable or evaluable lesions. For patients with multiple metastatic sites, the response was recorded for each individual site. In cases where there was a difference in response at the various sites, the worst response grading at any metastatic site was taken as the overall response of the patient.

During each response assessment, QoL assessment, adapted and translated from a questionnaire based on work by Priestman and Baum[27] was performed. This involved linear analog self-assessment with a score of 10 on nine indices in three major aspects: (A) emotional (feeling of well-being, mood and level of anxiety), (B) physical (level of activity, ability to perform housework and social activities) and (C) symptomatic (pain, nausea and appetite). The more severe the subjective disturbances, the higher the score.

Statistical considerations

The Simon two-stage optimal design[28] for calculation of sample size was adopted. Assuming the target activity level to be 60% and lower actual level to be 20%, the stage I sample size was calculated to be 17 patients. If there were more than three responses, the study could proceed to stage II, in which the target total accrual was 46 patients.

Time to progression was calculated from the date of study entry until disease progression. Patients who received any further antitumor treatment before disease progression were censored at the date of the last tumor assessment before the start date of the antitumor treatment. Survival was assessed using the Kaplan–Meier method. Survival duration was calculated from the first day of the first course of treatment (day 1) to the time of death or last event. Patients were to receive a minimum of 3 cycles of treatment to be eligible for response assessment.

Results

Patients and treatment

From October 1997 to May 2000, 46 patients were entered into the study. The median age was 49 years (range 31–71 years). Further patient characteristics are shown in Table 1. The total number of cycles given was 305, with a median of 7.5 cycles given per patient (range 1–11). Among the

Table 1. Patient characteristics ($n=46$)

Characteristic	No. patients (%)
Prior chemotherapy	17 (37)
prior anthracycline-containing chemotherapy	3 (7)
Disease involvement	
intrathoracic metastases[a]	17 (37)
liver metastases	13 (28)
bone	11 (24)
lymph node disease	19 (41)
breast	8 (17)
chest wall disease	9 (20)
$\geqslant 2$ diseased sites	21 (46)
stage IV disease at diagnosis	10 (22)
WHO performance status, median (range)	0 (0–2)
Karnofsky performance index score, median (range)	90 (80–100)

[a]Including lung parenchymal nodules, pleural and pericardial effusions, and mediastinal lymphadenopathy.

305 cycles, 235 were of the docetaxel–epirubicin combination, while 70 were docetaxel alone. One patient had an additional 2 cycles of docetaxel after the planned 9 cycles of treatment as there was good partial response with tolerable toxicity. As a result, the number of cycles of chemotherapy that patients received ranged from 2 to 11 cycles.

Dose reductions were undertaken in 20 patients due to: recurrent neutropenic fever (11 patients), thrombocytopenia (two patients) and non-hematologic toxicities (seven patients). Among these, 15 patients had dose reduction for docetaxel alone, and five had dose reductions for both docetaxel and epirubicin. The latter was necessitated by recurrent neutropenic fever (one patient) and persistent non-hematologic toxicities (four patients).

Twenty-six patients received full-dose treatment which corresponded to 127 cycles of docetaxel–epirubicin and 32 cycles of docetaxel alone. The 20 patients who underwent dose reductions received 108 cycles of docetaxel–epirubicin and 38 cycles of docetaxel alone. A total of 36 of the cycles were given at the planned dose, 89 cycles were given with 20% docetaxel dose reductions, and 21 cycles were administered with 20% docetaxel and epirubicin dose reductions.

Response assessment

Three patients developed severe toxicities and chemotherapy was discontinued after 2 cycles in each. As a result, 43 patients were evaluable for response (Table 2). The overall response rate was 83.7% (95% CI 72.7–94.8%). The response rate of the patients who underwent full-dose cytotoxic treatment was 82.6%; that for the patients who had docetaxel dose reduction with or without epirubicin dose reduction was 85.0%. The response rate of the patients who were previously exposed to chemotherapy was 85.7% (95% CI 67.3–100%); for those who had no prior adjuvant chemotherapy, the corresponding figure was 82.6% (95% CI 67.6–97.9%).

The median time to progression was 10.96 months (95% CI 7.76–12.86 months) and median survival was 24.2 months (95% CI 16.6– months).

Toxicities

Grade 3/4 toxicities included: neutropenia (56% of cycles; 96% of patients), thrombocytopenia (1% of cycles; 7% of patients), anemia (5% of cycles; 31% of patients) and neutropenia with fever (26% of cycles; 39% of patients) (Table 3). Five patients (11%) had severe skin toxicities, including two who developed radiation-recall dermatitis over the previously irradiated chest wall after the second cycle of chemotherapy. Five patients (11%) had severe diarrhea and two (4%) had severe peripheral edema. Hepatic toxicity with raised alanine and aspartate transaminases was observed in six patients. Of these, two patients were subsequently found to have developed hepatitis B virus (HBV) reactivation: one experienced grade 3 hepatotoxicity after the third cycle of docetaxel–epirubicin chemotherapy; the other experienced grade 2 hepatotoxicity after the fourth cytotoxic treatment cycle. The other four patients experienced grade 1–2 hepatotoxicity; screening for acute infections were negative in all four cases and spontaneous resolution of hepatitis occurred without delay in chemotherapy. No patient suffered from grade 3/4 cardiac toxicity. With respect to serial monitoring of LVEF measured prior to, and after 3 and 6 cycles of docetaxel–epirubicin chemotherapy, the mean LVEF values were 73, 70 and 68%, respectively. There was no treatment-related mortality.

Three patients were not evaluable for response due to premature termination of treatment as a result of intolerable toxicities. One experienced severe malaise, one developed radiation-recall dermatitis over the previously irradiated chest wall area (see above) and one had severe infection over her axillary

Table 2. Responses to docetaxel–epirubicin combination chemotherapy

	Overall ($n=43$)	Patients with full-dose chemotherapy ($n=23$)	Patients with dose reductions ($n=20$)	Patients with prior chemotherapy ($n=14$)	Patients without prior chemotherapy ($n=29$)
CR	5 (12%)	3 (13%)	2 (10%)	0	5 (17%)
PR	31 (72%)	16 (70%)	15 (75%)	12 (86%)	19 (66%)
SD	5 (12%)	4 (17%)	1 (5%)	1 (7%)	4 (14%)
PD	2 (5%)	0	2 (10%)	1 (7%)	1 (3%)

Table 3. Toxicity profiles[a] of 46 patients (worst grade for each category)

Toxicity	Grade 1/2 [*n* (%)]	Grade 3/4 [*n* (%)]
Hematologic/infection		
neutropenia	0 (0)	44 (96)
thrombocytopenia	26 (57)	3 (7)
anemia	0 (0)	14 (30)
fever	11 (24)	18 (39)
infection	8 (17)	9 (20)
Gastrointestinal		
nausea	16 (35)	3 (7)
vomiting	16 (35)	2 (4)
stomatitis	27 (59)	1 (2)
hepatic	5 (11)	1 (2)
diarrhea	15 (33)	5 (11)
cardiac	4 (9)	0 (0)
Neurologic		
neurosensory	21 (46)	0 (0)
neuromotor	1 (2)	0 (0)
Others		
edema	14 (30)	2(4)
pleural effusion	2 (4)	0(0)
weight gain	1(2)	0(0)
fatigue	17(37)	3(7)
phlebitis	4(9)	2(4)
skin	18(39)	5(11)
myalgia	4(9)	0(0)
pain	12(26)	1(2)

[a]WHO recommendations on acute and subacute toxicity of cancer treatment.[26]

recurrent disease with poor general performance status.

QoL

Figure 1 illustrates the overall change in QoL during the course of treatment, which included the three major aspects, (A) emotional, (B) physical and (C) symptomatic, from baseline (prior to chemotherapy), and after 3, 6 and 9 cycles of the treatment. When compared with the prechemotherapy scores, all major QoL aspects deteriorated at Cycle 3. Thereafter, QoL improved, with a notable trend towards an enhancement in the emotional aspect of QoL for patients who completed the 9 cycles of treatment compared with baseline.

Discussion

To our knowledge, this is the first phase II study of docetaxel (75 mg/m^2) and epirubicin (75 mg/m^2) in Chinese patients with metastatic breast cancer. Among the 46 patients treated, the regimen resulted in an overall response rate of 83.7%, which was comparable to previous trials.[20,22,23] Dose reductions did not result in inferior responses.

In a phase III trial that compared docetaxel (75 mg/m^2) and doxorubicin (50 mg/m^2) with cyclophosphamide (600 mg/m^2) and doxorubicin (60 mg/m^2), the response rates were reported to be 60 and 47%, respectively, and the time to progression was significantly better in the docetaxel–doxorubicin arm.[29] While combination paclitaxel and doxorubicin has resulted in 20% congestive heart failure,[7–9,30] the use of docetaxel with doxorubicin did not increase the risk of cardiotoxicity inherent to anthracycline use.

As in other phase II studies using docetaxel–epirubicin combination, the main toxicity in the present study was bone marrow suppression and febrile neutropenia.[19,21–23] Of note, two studies administering docetaxel (75 mg/m^2) with epirubicin (60–110 mg/m^2) reported grade 4 neutropenia in 60–90% of the treatment cycles and neutropenic fever in up to 19% of cycles.[19,22]

Other severe but infrequent non-hematologic toxicities in the present study included skin toxicities, diarrhea, peripheral edema and fatigue; these are well documented for taxane-containing regimens. As expected, no severe cardiotoxicity was observed with this combination.

Of particular note was the occurrence of HBV reactivation (leading to grade 2/3 hepatotoxicity with raised transaminases) in two patients during chemotherapy. In this geographic area, HBV

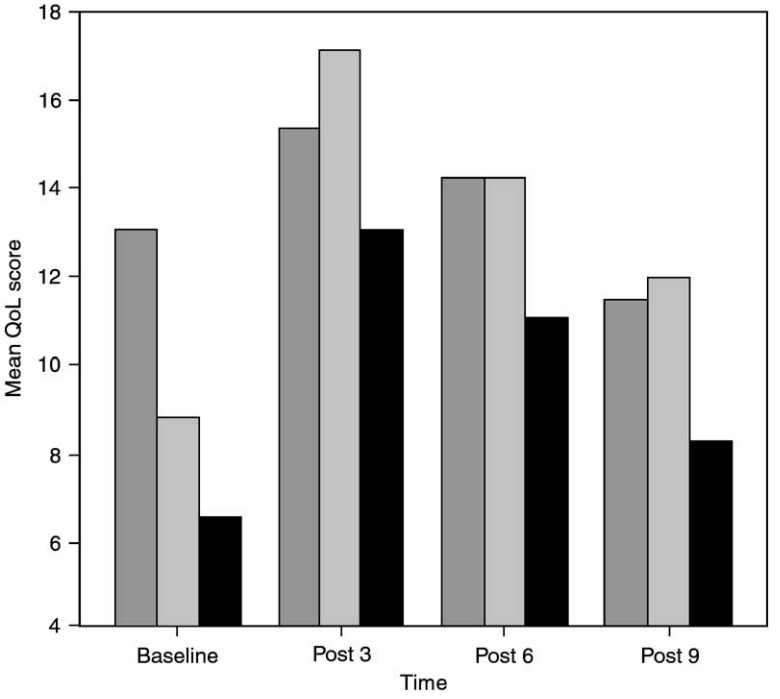

Figure 1. Quality of life assessment of all patients throughout the course of chemotherapy. Three major aspects were assessed: (A, medium bars) emotional, (B, light bars) physical and (C, dark bars) symptomatic at baseline (prior to chemotherapy), and after 3, 6 and 9 cycles of the treatment. The more severe the subjective disturbances, the higher the score.

infection is endemic, with 10% of the population being chronic carriers of the virus.[31] Patients who have chronic HBV infection are known to have increased hepatic complications during chemotherapy. This has mainly been attributed to the development of HBV reactivation.[32,33] This is a well-described and potentially fatal complication characterized by raised levels of serum viral DNA, abnormal liver function tests and clinical hepatitis of varying severity. Thus, it is routine practice in our institute to perform hepatitis B surface antigen (HBsAg) screening prior to the commencement of chemotherapy. Amongst the 46 patients in this study, five (11%) were HBsAg seropositive. Three (60%) of them developed hepatitis (one had grade 3, two had grade 2 toxicities), amongst whom two were attributable to HBV reactivation. This is in contrast to the 41 HBsAg seronegative patients, in whom only three (7%) developed hepatitis (grade 1/2). The two cases of HBV reactivation were treated with lamivudine, an antiviral agent which has been reported to result in viral response with resolution of hepatitis.[33] However, in the case with grade 3 hepatoxicity, the hepatitis resolved only after a prolonged period and chemotherapy was stopped after the third cycle.

Two patients had suspected radiation-recall dermatitis after 2 cycles of docetaxel–epirubicin chemotherapy. This had frequently been associated with the administration of anthracyclines[34] and, more recently, with taxanes including docetaxel.[34,35] The dermatitis in these two patients eventually resolved with supportive therapy after discontinuation of the cytotoxics.

Although the QoL questionnaire used in this study may appear to be quite simple and somewhat superficial, it was our intention to present a convenient assessment applicable to all patients in the trial. Previous experience gained from QoL assessment in a similar population had indicated that individuals found difficulties in responding to self-assessed QoL questionnaires that involved a large number of in-depth and complicated questions.[36] Thus, the assessment conducted in the present study aimed to provide a readily comprehensible, simple and reliable means for patients to make their own assessments of the effect of treatment on their well being. The current study revealed that QoL worsened after the third cycle of chemotherapy, after which there appeared to be some improvement. Of note, there was a notable trend towards an enhancement in the emotional aspect of QoL for patients who underwent 9 cycles of chemotherapy.

In conclusion, the present study demonstrates docetaxel–epirubicin results in a high response rate in Chinese patients with advanced breast cancer (83.7%), with a median survival of 24.2 months. The main toxicity was neutropenic fever. There was no evidence of congestive heart failure in patients treated with the regimen, and cardiac toxicity was not a dose-limiting factor. The response rate of 83.7% observed in this study is similar to those seen in previous reports based on Western populations and suggests a docetaxel-containing regimen may be superior to standard anthracycline combinations in the treatment of metastatic breast cancer.

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References

1. Honig SF. Treatment of metastatic disease: hormonal and chemotherapy. In: Harris JR, Lippman ME, Morrow M, *et al.*, eds. *Disease of the breast*. Philadelphia, PA: Lippincott-Raven 1996: 669–734.
2. van Oosterom AT, Schrijvers D, Schrijvers D. Docetaxel (Taxotere), a review of preclinical and clinical experience. Part II: clinical experience. *Anti-Cancer Drugs* 1995; **6**: 356–68.
3. Sparano JA. Compilation of phase I and II trial data of docetaxel and doxorubicin in the treatment of advanced breast cancer and other malignancies. *Semin Oncol* 1998; **25**(suppl 13): 10–5.
4. A'Hern RP, Smith IE, Ebbs SR. Chemotherapy and survival in advanced breast cancer: the inclusion of doxorubicin in Cooper type regimens. *Br J Cancer* 1993; **67**: 801–5.
5. Gueritte-Voegelein F, Guenard D, Lavelle F, *et al.* Relationships between the structure of taxol analogues and their antimitotic activity. *J Med Chem* 1991; **34**: 992–8.
6. Verschueren H, Dewit J, De Braekeleer J, *et al.* Motility and invasive potency of murine T-lymphoma cells: effect of microtubule inhibitors. *Cell Biol Int* 1994; **18**: 11–9.
7. Gianni L, Munzone E, Capri G, *et al.* Paclitaxel by 3-hour infusion in combination with bolus doxorubicin in women with untreated metastatic breast cancer: high antitumor efficacy and cardiac effects in a dose-finding and sequence-finding study. *J Clin Oncol* 1995; **13**: 2688–99.
8. Dombernowsky P, Gehl J, Boesgaard M, *et al.* Doxorubicin and paclitaxel, a highly active combination in the treatment of metastatic breast cancer. *Semin Oncol* 1996; **23**(suppl 11): 23–7.
9. Gianni L, Vigano L, Locatelli A, *et al.* Human pharmacokinetic characterization and *in vitro* study of the interaction between doxorubicin and paclitaxel in patients with breast cancer. *J Clin Oncol* 1997; **15**: 1906–15.
10. Colombo T, Gonzalez Paz O, Zucchetti M, *et al.* Paclitaxel induces significant changes in epidoxorubicin distribution in mice. *Ann Oncol* 1996; **7**: 801–5.
11. Gianni L, Capri G, Tarenzi E, *et al.* Efficacy and cardiac effects of 3-hour paclitaxel plus bolus doxorubicin in women with untreated metastatic breast carcinoma. *Proc Am Soc Clin Oncol* 1996; **15**: 116 (abstr 128).
12. Amadori D, Frassineti GL, Zoli W, *et al.* A phase I/II study of sequential doxorubicin and paclitaxel in the treatment of advanced breast cancer. *Semin Oncol* 1996; **23**(suppl 11): 16 22.
13. Swain SM. Adult multicenter trials using dexrazoxane to protect against cardiac toxicity. *Semin Oncol* 1998; **25**: 43–7.
14. Sledge Jr GW, Neuberg D, Ingle J, *et al.* Phase III trial of doxorubicin versus paclitaxel versus doxorubicin plus paclitaxel as first-line therapy for metastatic breast cancer: an intergroup trial. *Proc Am Soc Clin Oncol* 1997; **16**: 1a (abstr 2).
15. Bonadonna G, Gianni L, Santoro A, *et al.* Drugs ten years later: epirubicin. *Ann Oncol* 1993; **4**: 359–69.
16. Luck HJ, Thomssen C, duBois A, *et al.* Interim analysis of a phase II study of epirubicin and paclitaxel as first-line therapy in patients with metastatic breast cancer. *Semin Oncol* 1996; **23**(suppl 1): 33–6.
17. Catimel G, Spielmann M, Dieras V, *et al.* Phase I study of paclitaxel and epirubicin in patients with metastatic breast cancer: a preliminary report on safety. *Semin Oncol* 1996; **23**(suppl 1): 24–7.
18. Conte PF, Baldini E, Gennari A, *et al.* Dose-finding study and pharmacokinetics of epirubicin and paclitaxel over 3 hours: a regimen with high activity and low cardiotoxicity in advanced breast cancer. *J Clin Oncol* 1997; **15**: 2510–7.
19. Pagani O. Taxoids in combination with epirubicin: the search for improved outcomes in breast cancer. *Semin Oncol* 1998; **25**(suppl 12): 23–6.
20. Sessa C, Pagani O. Docetaxel and epirubicin in advanced breast cancer. *The Oncologist* 2001; **6**(suppl 3): 13–6.
21. Kouroussis C, Xydakis E, Potamianou A, *et al.* Front-line treatment of metastatic breast cancer with docetaxel and epirubicin: a multicenter dose-escalation study. The Greek Breast Cancer Cooperative Group (GBCCG). *Ann Oncol* 1999; **10**: 547–52.
22. Viens P, Roche H, Kerbrat P, *et al.* Epirubicin–docetaxel combination in first-line chemotherapy for patients with metastatic breast cancer: final results of a dose-finding and efficacy study. *Am J Clin Oncol* 2001; **24**: 328–35.
23. Mavroudis D, Alexopoulos A, Ziras N, *et al.* Front-line treatment of advanced breast cancer with docetaxel and epirubicin: a multicenter phase II study. *Ann Oncol* 2000; **11**: 1249–54.
24. Milla-Santos A, Milla L, Rallo L, Solano V. High-dose epirubicin plus docetaxel at standard dose with lenograstim support as first-line therapy in

advanced breast cancer. *Am J Clin Oncol* 2001; **24**: 138–42.
25. Esposito M, Venturini M, Vannozzi MO, *et al.* Comparative effects of paclitaxel and docetaxel on the metabolism and pharmacokinetics of epirubicin in breast cancer patients. *J Clin Oncol* 1999; **17**: 1132–40.
26. WHO. *Handbook for reporting results of cancer treatment*. Geneva: WHO 1979.
27. Priestman TJ, Baum M. Evaluation of quality of life in patients receiving treatment for advanced breast cancer. *Lancet* 1976; **i**: 899–900.
28. Simon R. How large should a phase II trial of a new drug be? *Cancer Treat Rep* 1987; **71**: 1079–85.
29. Nabholtz JM, Riva A. Taxane/anthracycline combinations: setting a new standard in breast cancer? *The Oncologist* 2001; **6**(suppl 3): 5–12.
30. Kaufman PA. Paclitaxel and anthracycline combination chemotherapy for metastatic breast cancer. *Semin Oncol* 1999; **26**(suppl 8): 39–46.
31. Lok AS, Lai CL, Wu PC, *et al.* Hepatitis B virus infection in Chinese families in Hong Kong. *Am J Epidemiol* 1987; **126**: 492–9.
32. Liang RH, Lok AS, Lai CL, *et al.* Hepatitis B infection in patients with lymphomas. *Hematol Oncol* 1990; **8**: 261–70.
33. Yeo W, Chan PK, Zhong S, *et al.* Frequency of hepatitis B virus reactivation in cancer patients undergoing cytotoxic chemotherapy: a prospective study of 626 patients with identification of risk factors. *J Med Virol* 2000; **62**: 299–307.
34. Yeo W, Leung SF, Johnson PJ. Radiation-recall dermatitis with docetaxel: establishment of a requisite radiation threshold. *Eur J Cancer* 1997; **33**: 698–9.
35. Aristizabal SA, Miller RC, Schlichtemeier AL, *et al.* Adriamycin-irradiation cutaneous complications. *Int J Radiat Oncol Biol Phys* 1977; **2**: 325–31.
36. Yeo W, Kwan WH, Teo PML, *et al.* A comparison of psychosocial impact of breast conserving therapy and total mastectomy in breast cancer patients and their partners. *Eur J Cancer* 1997; **33**(suppl 8): S60.

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