# Biweekly docetaxel-containing chemotherapy may be the optimal schedule

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**The dosing schedule of docetaxel may affect its clinical activity and toxicity profile. Although triweekly docetaxel has higher antitumor activity but more severe hematological toxicity, weekly docetaxel seems to have less activity or fewer adverse events. To evaluate the efficacy and toxicity of biweekly docetaxel and mitoxantrone in patients with advanced breast cancer, the regimen consisting of docetaxel (60 mg/m$^2$), and mitoxantrone (8 mg/m$^2$) was administered intravenously to 59 patients every 2 weeks. Most (54.2%) of the patients experienced objective responses. The median time to progression for the whole group was 6.8 months. The median time to progression for patients with complete or partial response was 10.3 months, but only 3.6 months for patients with stable or progressive disease ($P<0.001$). Grade III/IV adverse events of neutropenia, thrombocytopenia, anemia, febrile neutropenia, and nausea/vomiting were documented in 61.0, 6.8, 3.4, 3.4, and 3.4% of the patients, respectively. The median overall survival was 16.9 months. In conclusion, biweekly use of docetaxel and mitoxantrone is a highly effective and well-tolerated regimen for patients with advanced breast cancer. The optimal dosage of docetaxel in combination with chemotherapeutic regimen may be given every 2 weeks. *Anti-Cancer Drugs* 19:421–426 © 2008 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

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## Introduction

The hallmark of the Norton–Simon hypothesis is that the rate of tumor volume regression is proportional to the rate of tumor volume growth [1,2]. On the basis of this hypothesis, chemotherapy should be delivered at a greater dose rate to increase the cumulative cell kill, thereby achieving greater clinical benefit [1–5]. Both preclinical and clinical data support this hypothesis [2–8]. The results from the Cancer and Leukemia Group B 9840 trial comparing weekly with triweekly paclitaxel suggested that breast cancer patients treated with weekly paclitaxel had a higher overall response rate (40 versus 28%) and a longer median time to progression (TTP, 9 versus 5 months) [7]. Increased benefits from dose-dense chemotherapy are mostly in patients with specific tumor subtypes, such as hormone receptor-negative, highly proliferative, or human epidermal growth factor receptor 2 (HER2)-overexpressing tumors [3]. It is, however, not clear whether all drugs or just paclitaxel should be administered in a dose-dense fashion.

It is also unclear whether docetaxel, another taxane, should be given in a dose-dense fashion, biweekly or weekly. Biweekly use of docetaxel at 100 mg/m$^2$ in patients with breast cancer is limited by skin toxicities [9,10]. Weekly docetaxel has also been tried in advanced breast cancer (ABC) [11–13]. Only two randomized phase II trials, however, have compared weekly with triweekly docetaxel [13,14]. One trial was conducted at 10 centers in Spain and Belgium in 83 patients with ABC, and found that weekly and triweekly docetaxel had similar antitumor activities with overall response rates (ORRs) of 34 versus 33% but less severe hematological toxicity [14]. The other was done in Egypt in 30 patients and drew a similar conclusion [13]. With so small a number of patients enrolled, significant difference in antitumor activity between the two dosing schedules was not likely to be observed. Moreover, incorporation of weekly docetaxel in a combination regimen is very difficult, as combining weekly docetaxel with another drug, such as anthracyclines, gemcitabine, and vinorelbine, can result in severe toxicity [13].

A few clinical trials have evaluated the synergistic effect between docetaxel and mitoxantrone [15–17]. Alexopoulos *et al.* [17] conducted a phase II clinical trial to evaluate first-line use of docetaxel (100 mg/m$^2$) and mitoxantrone (20 mg/m$^2$) every 3 weeks in the management of 54 patients with metastatic breast cancer, and reported complete responses (CRs) in nine patients and an ORR of 61% with a 95% confidence interval (CI) of 48.1–74.1%. With the prophylactic use of granulocyte colony-stimulating factor (G-CSF), grade III/IV adverse events [mainly neutropenia (37 patients, 69%) and

0959-4973 

febrile neutropenia (16 patients, 30%)] had a relatively high incidence. Without G-CSF, the maximum-tolerated dose of this two-drug triweekly regimen was docetaxel 75 mg/m$^2$ and mitoxantrone 8 mg/m$^2$, and dose-limiting toxicities were febrile neutropenia, grade 4 neutropenia lasting more than 5 days, and grade 3 diarrhea [16]. Weekly docetaxel at 35 mg/m$^2$ and biweekly mitoxantrone at 6 mg/m$^2$, however, led to an ORR of only 40% without CR and a significant low hematological toxicity, which indicates that 35 mg/m$^2$ of docetaxel may not be a minimum effective dose [15]. Three dose levels of docetaxel (60, 75, and 100 mg/m$^2$) have been tried in breast cancer patients, and it was concluded that any of these doses may be appropriate for second-line treatment of ABC depending on the therapy goal [18]. Therefore, biweekly use of docetaxel at 60 mg/m$^2$ and mitoxantrone at 8 mg/m$^2$ may retain their high antitumor activities (compared with the weekly regimen) and low side effects (compared with the triweekly regimen).

Biweekly regimens have been successfully used in the treatment of non-Hodgkin's lymphoma, colorectal cancer, and breast cancer [19,20]. In women with early-stage breast cancer, a change in the interval of anthracycline-based and/or taxane-based chemotherapy, from every 3 weeks to every 2 weeks, improved disease-free and overall survival, and had a manageable toxicity profile [21]. Biweekly docetaxel-containing regimens have been tried in human tumors, including advanced pancreatic carcinoma, lung cancer, and breast cancer, with promising activity and an excellent safety profile [22–26]. Other reasons for choosing docetaxel and mitoxantrone for this study were their strong antitumor activities, low cost of mitoxantrone, noncross resistance of mitoxantrone with adriamycin and epirubicin, and little use of mitoxantrone in neoadjuvant and adjuvant settings. Thus, a pilot phase II study of these two drugs given biweekly to patients with ABC was conducted in our institution between June 2005 and March 2007.

## Patients and methods

### Study design

This phase II open-label study was conducted in Fudan University Cancer Hospital, China. The protocol was approved by ethics committee of our institution. Each patient was informed about the risks and benefits, and a written informed consent was obtained before enrollment. The study was conducted in compliance with Good Clinical Practice guidelines (Sixth International Conference on Harmonization and the Declaration of Helsinki).

### Eligibility criteria

Patients with histologically or cytologically confirmed breast cancer were recruited into this trial. All patients had to be female and 18 years or older with performance status of 60 or more on the Karnofsky Scale, and had to have at least a measurable lesion according to the Response Evaluation Criteria in Solid Tumors, no history of cardiac dysfunction or cardiac disease, normal white blood cell and platelet counts, adequate liver and kidney functions, and life expectancy of more than 3 months. Antitumor treatments including chemotherapy, endocrinotherapy, bio-targeted therapy, and radiation over 30 days before the administration of trial drugs were not allowed.

### Exclusion criteria

Patients were excluded from the study for any of the following reasons: (a) were pregnant or breast-feeding; (b) had known symptomatic brain or leptomeningeal involvement; (c) had no measurable lesion; (d) had severe diseases like cardiac disease, hypertension, and uncontrolled infection; (e) had allergic history to docetaxel, mitoxantrone, and their solvents; (f) were receiving or had received, in the 30 days before study screening, any treatment with experimental drugs; (g) were experiencing more than grade I symptomatic peripheral neuropathy; and (h) had a history of earlier malignancies (with the exception of excised cervical carcinoma *in situ* or nonmelanoma cell skin carcinoma).

### Treatment protocol

Docetaxel (60 mg/m$^2$) was administered intravenously in 100 ml of normal saline for 1 h on day 1. Mitoxantrone (8 mg/m$^2$) was given intravenously in 250 ml of 5% dextrose for more than 15 min on day 1. Dexamethasone (7.5 mg) was given twice daily for 3 days beginning the day before the treatment. Granisetron (3 mg) was given 30 min before chemotherapy. Primary prophylactic antibiotics or G-CSF were not permitted. Treatment was repeated every 2 weeks. Treatment could be delayed for a maximum of 7 days. Maximal number of cycles was 9.

### Dose modifications

The National Cancer Institute Common Toxicity Criteria were employed for assessment of toxicity. Doses of both docetaxel and mitoxantrone were reduced by 25% in patients who experienced grade IV neutropenia lasting for more than 7 days, febrile neutropenia lasting for more than 3 days, grade IV thrombocytopenia, grade III thrombocytopenia associated with bleeding, and other grade III to IV nonhematological toxicities (except alopecia). Patients would continue to receive the reduced dose in subsequent cycles for the remainder of the study. Two dose reductions were allowed. Patients were removed from the study if there was evidence of disease progression, presence of unacceptable toxicity, interruption of treatment for more than 1 week, informed consent was rejected, or a third dose reduction was required.

### Efficacy assessment

All measurable and evaluable lesions were assessed for efficacy at the end of cycles 3, 6, and 9, or at discontinuation of study treatment according to the Response Evaluation Criteria in Solid Tumors. After the

study, patients were followed up at 3-month intervals during the first year and at 6-month intervals from then on after completion of treatment. Target lesions were evaluated using computed tomography or MRI scans. The bone lesions, which were positive in bone scintigraphy and confirmed by bone radiography, were monitored by bone radiography, and bone scintigraphy was only employed when clinically indicated. Patients who could not complete three cycles were considered as having progressive disease (PD). Two radiologists carried out response assessment, and a third senior radiologist was called when discrepancy occurred and a consensus was reached. Efficacy was confirmed 1 month later if complete or partial response was documented. Clinical benefit was defined as patients with CR, partial response, or stable disease (SD) lasting 6 months or more.

### Statistical analysis

The primary endpoint of this trial was TTP, and the secondary endpoints included ORR, overall survival (OS), and safety profile. All statistical analyses were carried out on an intention-to-treat basis using the SPSS 12.0 software package (Chicago, Illinois, USA). TTP was calculated for all assessable patients as the interval between the date of inclusion and the date of disease progression or death. OS was calculated for all patients from the date of inclusion until death. The TTP and OS were computed according to the Kaplan–Meier method and the groups were compared using the two-sided log-rank test. After this analysis, the variables with significant correlation with TTP and OS were put in a Cox regression model to determine which was an independent prognostic factor for TTP and OS, respectively. The statistical difference was considered significant if the *P* value was less than 0.05.

## Results

### Patient characteristics

Between June 2005 and March 2007, 59 female patients with a median age of 51 years ranging from 33 to 69 years were recruited into this study (Table 1). Eight patients first presented with metastatic or locally ABC, whereas 51 patients developed metastatic diseases after radical mastectomy. In all, 91.5% (54/59) of the patients had performance status of 80 or more, 94.9% (56/59) had invasive ductal carcinoma, only three patients had lobular carcinoma, 47.5% of the patients were positive for both estrogen and progesterone receptor, 37.3% were negative for either receptors, and 30.5% were positive for HER2. The median number of organs involved was three with 37 lung metastases, 22 bone metastases, 21 liver metastases, and two brain metastases. Fifty-three patients (89.8%) were pretreated with nonmitoxantrone anthracyclines, 55.9% with vinorelbine, 23.7% with paclitaxel, 28.8% with CMF regimen, and 27.1% with capecitabine. In addition, 51 (86.4%) of the patients had primary tumor surgery, 34 (57.6%) had hormonal therapy, five (27.8%, five of 18) had herceptin treatment, 26 (44.1%) had radiotherapy. The median number of previous chemotherapy regimens was 2 (range, 0–5).

**Table 1 Baseline characteristics of patients**

| Characteristics | No. of patients | % |
|---|---|---|
| Age, years | | |
| Median | 51 | |
| Range | 33–69 | |
| Karnofsky performance score | | |
| Median | 90 | |
| Range | 70–100 | |
| Menopausal status | | |
| Premenopausal | 17 | 28.8 |
| Postmenopausal | 42 | 71.2 |
| Extent of disease | | |
| Locally advanced | 3 | 5.1 |
| Metastatic | 56 | 94.9 |
| Time from start of earlier therapy to relapse | | |
| Median, months | 17.7 | |
| Range | 0–180 | |
| Hormonal status | | |
| ER – PR – | 22 | 37.3 |
| ER + PR – | 4 | 6.8 |
| ER – PR + | 4 | 6.8 |
| ER + PR + | 28 | 47.5 |
| Unknown | 1 | 1.7 |
| HER2 status | | |
| Negative | 28 | 47.5 |
| Positive | 18 | 30.5 |
| Unknown | 13 | 22.0 |
| Number of earlier chemotherapy regimens | | |
| 0 | 2 | 3.4 |
| 1 | 15 | 25.4 |
| ≥ 2 | 42 | 71.2 |
| Number of disease sites | | |
| 1 | 6 | 10.2 |
| 2 | 21 | 35.6 |
| ≥ 3 | 32 | 54.2 |
| Hormonal therapy | 34 | 57.6 |
| Surgery | 51 | 86.4 |
| Radiotherapy | 26 | 44.1 |

ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; PR, progesterone receptor.

### Efficacy

All patients were assessable for toxicity and 58 for response status (Table 2). The one nonassessable patient was lost to follow-up after the first cycle of treatment. Objective responses were noted in 32 patients (54.2%) with one CR and 31 partial responses. Sixteen patients had SD and 11 had PD. The complete responder had one lung metastasis and a supraclavicular node metastasis. The antitumor activity in breast cancer patients pretreated with anthracyclines, vinorelbine, or paclitaxel was documented with the response rates of 50.9, 45.5, or 42.9%, respectively. Although the ORR was 27.8% (five of 18) in HER2-positive patients, it was 64.3% (18/28) in HER2-negative patients ($P = 0.037$). No statistical correlation between objective response and other clinicopathological parameters was observed.

TTP was calculated until October 2007. Median follow-up time was 14.0 months. Median TTP in all treated patients was 6.8 months (95% CI, 6.33–7.33). The median TTP for the 32 responders (10.3 months; 95%

CI, 7.49–13.19) was significantly different from that for the SD and PD patients (3.6 months; 95% CI, 1.13–6.13; $P < 0.001$), and the median TTP of patients with clinical benefit (9.1 months; 95% CI, 5.97–12.23) was significantly different from that of patients without clinical benefit (2.17 months; 95% CI, 2.03–2.31; $P < 0.001$). The TTP of the anthracycline-pretreated, vinorelbine-pretreated, or taxane-pretreated subgroups did not differ greatly from the whole study population. Twenty-seven patients died during the follow-up period with a median OS of 16.9 months (95% CI, 14.15–19.79).

### Safety

A total of 320 cycles of treatment were administered for all patients, with a per patient median of 6 (range, 1–9). Thirteen out of 59 (22.0%) patients experienced treatment delay, mostly because of hematological toxicities; of these five required dose reduction. Toxicities encountered are listed in Table 3. The most common grade III or IV adverse events were neutropenia (61.0%), thrombocytopenia (6.8%), nausea/vomiting (3.4%), febrile neutropenia (3.4%), and anemia (3.4%). Thirty-eight patients had partial alopecia and two had total alopecia. Ten patients had abnormal ECG, mostly T-wave alteration. The ECG changes were all reversed to normality when treated with traditional Chinese medicine and metoprolol. Two patients had edema in the legs.

**Table 2 Best response after chemotherapy**

| Outcome | No. of patients | % |
|---|---|---|
| Total enrolled | 59 | |
| Total treated | 59 | |
| Assessable patients | 58 | |
| Overall response | 32 | 54.2 |
| ORR 95% CI | | 40.8–67.3 |
| Best response | | |
| CR | 1 | 1.7 |
| PR | 31 | 52.5 |
| SD $\geq$ 6 months | 10 | 17.0 |
| SD $<$6 months | 6 | 10.2 |
| PD | 10 | 17.0 |
| NA | 1 | 1.7 |
| Clinical benefit[a] | 42 | 71.2 |
| Clinical benefit rate 95% CI | | 57.9–82.2 |
| Clinical benefit of sites | | |
| Liver | 21 | 66.7 |
| Bone | 22 | 77.3 |
| Lung | 37 | 75.7 |
| Lymph nodes | 50 | 72.0 |

CI, confidence interval; CR, complete response; NA, not assessable; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease.
[a]Clinical benefit is equal to CR, PR, or SD $\geq$ 6 months.

## Discussion

This is the first phase II clinical trial of biweekly docetaxel combined with mitoxantrone in women with ABC. This biweekly combination of docetaxel and mitoxantrone demonstrated high antitumor activity and was well tolerated over multiple cycles of treatment.

Biweekly use of docetaxel may be a good option to optimize its efficiency. According to the Norton–Simon hypothesis, all chemotherapeutic agents should be given in a dose-dense fashion [1–5,27]. This may, however, not be true for docetaxel. Recently published data from Eastern Cooperative Oncology Group 1199 adjuvant trial showed that triweekly but not weekly docetaxel was more effective than triweekly paclitaxel at Food and Drug Administration-approved dosages [28]. Conceivably, weekly docetaxel had less hematological effects than triweekly docetaxel, with grade III/IV neutropenia (3 versus 46%), febrile neutropenia (1 versus 16%), and infection (5 versus 13%). Our study showed that biweekly use of docetaxel and mitoxantrone had an ORR of 54.2%, which is similar to the 61% (95% CI, 48.1–74.1%) reported by Alexopoulos *et al.*, but is higher than the 40% reported by Konig *et al.* [15,17]. The median TTP of 6.8 months was shorter than the 14 months reported by

**Table 3 Treatment-related adverse events**

| | 0 | | I | | II | | III | | IV | | III/IV |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | *n* | % | *n* | % | *n* | % | *n* | % | *n* | % | % |
| Leukopenia | 5 | 8.5 | 5 | 8.5 | 13 | 22.0 | 24 | 40.7 | 12 | 20.3 | 61.0 |
| Thrombocytopenia | 46 | 78.0 | 7 | 11.9 | 2 | 3.4 | 2 | 3.4 | 2 | 3.4 | 6.8 |
| Anemia | 41 | 69.5 | 12 | 20.3 | 4 | 6.8 | 1 | 1.7 | 1 | 1.7 | 3.4 |
| FN | 57 | 96.6 | NA | | NA | | 1 | 1.7 | 1 | 1.7 | 3.4 |
| Nausea/vomiting | 31 | 52.5 | 19 | 32.2 | 7 | 11.9 | 2 | 3.4 | 0 | 0 | 3.4 |
| Fever | 55 | 93.2 | 3 | 5.1 | 1 | 1.7 | 0 | | 0 | | 0 |
| ALT elevation | 53 | 89.8 | 4 | 6.8 | 2 | 3.4 | 0 | 0 | 0 | 0 | 0 |
| AST elevation | 54 | 91.5 | 4 | 6.8 | 1 | 1.7 | 0 | 0 | 0 | 0 | 0 |
| Stomatitis | 33 | 55.9 | 20 | 33.9 | 6 | 10.2 | 0 | 0 | 0 | 0 | 0 |
| Diarrhea | 57 | 96.6 | 2 | 3.4 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Constipation | 42 | 71.2 | 14 | 23.7 | 3 | 5.1 | 0 | 0 | 0 | 0 | 0 |
| Alopecia | 19 | 32.2 | 38 | 64.4 | 2 | 3.5 | NA[a] | | NA | | |
| Fatigue | 31 | 52.5 | 19 | 32.2 | 9 | 15.3 | 0 | 0 | 0 | 0 | 0 |
| Neuropathy | 41 | 69.5 | 18 | 30.5 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Edema | 57 | 96.6 | 2 | 3.4 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

ALT, alanine aminotransferase; AST, aspartate aminotransferase; FN, febrile neutropenia; NA, not applicable.
[a]Alopecia is only graded as I or II.

**Table 4 Summary of studies using biweekly docetaxel-containing regimens**

| References | Regimen (mg/m$^2$) | Patients | Responses | G3-4 toxicity | Support |
|---|---|---|---|---|---|
| Limentani *et al.* [29] | DCT 60 NVB 45 | *N*=60, neoadjuvant | ORR, 98%; CR, 63%; pCR, 27% | Neutropenia 95%, FN 22%, mucositis 5%, pulmonary toxicity 5% | G-CSF |
| Gomez-Bernal *et al.* [30] | DCT 60 NVB 25 | *N*=48, anthracycline resistant | ORR, 46%; CR, 17% | Neutropenia 19%, FN 13%, asthenia 17%, nail toxicity 15% | G-CSF |
| Mayordomo *et al.* [31] | DCT 60 NVB 30 | *N*=41, first-line | ORR, 56%; CR, 10% | Neutropenia 34%, FN 34%, stomatitis 10%, nail toxicity 15% | No G-CSF |
| Gomez-Bernal *et al.* [32] | DCT 60 NVB 25 | *N*=49, anthracycline resistant | ORR, 45%; CR, 4% | Neutropenia 65%, FN 17% | No G-CSF |
| Von Minckwitz *et al.* [33] | ADM 50 DCT 75 | *N*=451, neoadjuvant | ORR, 75%; CR, 31.2%; pCR 7% | Neutropenia 45%, FN 3.1%, leucopenia 53.7%, alopecia 91.1%, fatigue 28.3%, loss of appetite 17.2%, nausea/vomiting 10%, diarrhea 7.6% | G-CSF |
| Von Minckwitz *et al.* [34] | ADM 50 DCT 75 | *N*=128, neoadjuvant | ORR, 68%; pCR 10% | Neutropenia 24.6%, FN 8.7%, leukopenia 35.4% | G-CSF |
| Estevez *et al.* [35] | DCT 65 G 2500 | *N*=35, neoadjuvant | ORR, 71%; CR, 23% | Neutropenia 11% | G-CSF |
| Frasci *et al.* [22] | DCT 80 CPT 100 | *N*=48, pretreated with anthracycline and paclitaxel | ORR, 64%; CR, 16% | Neutropenia 36%, thrombocytopenia 12%, fatigue 20%, diarrhea 8% | G-CSF |

ADM, doxorubicin; CPT, irinotecan; CR, complete response; DCT, docetaxel; FN, febrile neutropenia; G, gemcitabine; G-CSF, granulocyte colony-stimulating factor; NVB, vinorelbine; ORR, overall response rate; pCR, pathologic complete response.

Alexopoulos *et al.* [17], which could be accounted for by the difference in the number of lines of therapy, and the fact that as the number of applied chemotherapy regimens increased, antitumor activity decreased. Our study showed a median number of previous chemotherapy regimens used was 2, indicating most patients had received chemotherapy after recurrence before the entry into this trial, and 89.8% of patients were pretreated with adriamycin or epirubicin, therefore this regimen may be appropriate to these patients.

Biweekly docetaxel and mitoxantrone have a good safety profile. The most common adverse grade III/IV events were neutropenia in 61% of patients. The incidence of febrile neutropenia, however, was only 3.4%, which was obviously less than the 30% observed by Alexopoulos *et al.* [17] in the use of the triweekly regimen with prophylactic G-CSF as first-line chemotherapy for patients with metastatic breast cancer. Other common grade III/IV toxicities included thrombocytopenia, anemia, and nausea/vomiting, all with less than a 7% incidence of grade III/IV events. When docetaxel was combined with other drugs every 2 weeks, toxicity profile changed accordingly (Table 4) [22,29–35]. Vinorelbine-containing and irinotecan-containing regimens had more myelosuppressive and gastrointestinal toxicity, respectively (Table 4). Moreover, compared with the weekly regimen the biweekly regimen required fewer patient visits. Therefore, this is a very promising regimen in terms of both efficacy and toxicity.

It is unknown whether biweekly use of docetaxel and mitoxantrone may benefit some particular subgroups of patients. Bertheau *et al.* [36] indicated that breast cancer patients with a mutant TP53, particularly those with basal features, benefited more from biweekly use of epirubicin and cyclophosphamide. Tumors with TP53 mutation may be more sensitive to anthracyclines, and rapidly proliferating tumors may be more sensitive to cyclophosphamide-induced cell death [36]. Kummel *et al.* [3] indicated that patients with specific tumor subtypes (such as hormone receptor-negative, highly proliferative, or HER2-overexpressing tumors) may benefit more from dose-dense chemotherapy. Our data showed that HER2-negative patients might get more benefit from biweekly docetaxel-containing regimen; however, it should be further studied owing to so small a sample size.

In conclusion, the biweekly regimen of docetaxel and mitoxantrone is a highly effective and well-tolerated regimen for patients with ABC. It has the advantages of both the triweekly and weekly regimens. Further studies are needed to define the role of this regimen, optimize the dosages of the two drugs, and identify the patient population that will receive the greatest benefit from this therapy.

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