# Weekly Paclitaxel in Women with Heavily Pretreated Metastatic Breast Cancer: A Retrospective Analysis of Cases Treated at the Chang Gung Memorial Hospital

Chang-Hsien Lu[1], MD; Yung-Chang Lin[1,2], MD; Hsien-Kun Chang[1], MD

**Background:** Taxane is one of the most effective drugs used for advanced metastatic breast cancer treatment. Conventional 3-weekly regimens are widely used with significant treatment related toxicity. Recently, weekly schedules of taxane were reported to be effective and well tolerated in this patient group. We retrospectively evaluated the efficacy of weekly paclitaxel in women with metastatic breast cancer.

**Methods:** Between December 1999 and June 2004, a total of twenty-three patients with histologically confirmed and measurable pretreated metastatic breast cancer were included. The median age was 55 years (range 33~73). Their performance status was ECOG ≤ 2. All patients had received at least one regimen for metastatic disease. Paclitaxel 80 mg/m$^2$ was administered weekly for 3 weeks per 4-week cycle. WHO response criteria was used as the reference to evaluate the response to treatment.

**Results:** The response and survival of all patients were assessed. All had prior anthracycline-based chemotherapy; 14 patients (61%) had at least 3 different chemotherapy lines before this regimen. Twenty patients (87%) had at least 2 metastatic sites and 18 (78.3%) had visceral metastasis. The overall response rate was 21.7% with no complete response, while 43.5% had stable disease. The median time to progression was 121 days. Four patients (17.4%) were treated with a trastuzumab-paclitaxel combination, and 2 of them responded. The therapy was well tolerated and there were no grade III/IV toxicities observed. Only 1 patient (4.35%) dropped out because of heart failure.

**Conclusions:** Weekly paclitaxel was well tolerated and the response rate was comparable to that previously reported in heavily pretreated patients with metastatic breast cancer. Weekly paclitaxel in combination with other agents is worthy of further investigation.

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**Key words: breast cancer, metastases, chemotherapy, paclitaxel.**

Breast cancer is the second leading cancer in Taiwanese women. In the year 2002, 5339 women were newly diagnosed with breast cancer, accounting for 18% of malignancies in women. It

From the [1]Division of Hematology-Oncology, Department of Internal Medicine, Chang Gung Memorial Hospital, Taipei; [2]College of Medicine, Chang Gung University, Taoyuan.
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Correspondence to: Dr. Yung-Chang Lin, Division of Hematology-Oncology, Department of Internal Medicine, Chang Gung Memorial Hospital. 5, Fushing Street, Gueishan Shiang, Taoyuan, Taiwan 333, R.O.C. Tel.: 886-3-3281200 ext. 2513; Fax: 886-3-3283973; E-mail: yclinof@cgmh.org.tw

was also the fourth most common cause of cancer-related death in Taiwanese women in 2003.[1] Despite improvements in screening and early detection, a significant proportion of patients were diagnosed at a late stage that eventually led to recurrent metastatic disease. Treatment of metastatic breast cancer is usually disappointing despite recent advances in systemic chemotherapy. The purposes of systemic chemotherapy for metastatic breast cancer are aimed at palliating tumor-associated symptoms, improving quality of life, and prolonging survival.[2] Furthermore, those tumors resistant to first-line chemotherapy generally are less responsive to second- and third-line regimens.[3,4] Anthracycline-based regimens play an important role in the treatment of endocrine non-responsive metastatic breast cancer and remain the first line regimen in clinical practice,[5] in western countries and in Taiwan. In the early 1990s the development of a novel class of chemotherapeutic agent, taxanes, led to a new era of chemotherapy for breast cancer. Paclitaxel, an anti-tubulin agent, is effective in the treatment of metastatic breast cancer.[6] Several trials evaluating the efficacy of paclitaxel (at doses of 135 to 250 mg/m$^2$, administered by either 3- or 24-hour infusion, and used as an initial or salvage therapy) have reported an overall response rate of 21-62%.[7-10] Taxanes have moved from a second-line therapy to a front-line therapy in both adjuvant and metastatic settings in the last 5 years.[11] However, after failure from taxanes, there is no universal consensus on salvage treatment. In clinical practice, treatment should be justified individually for palliation and prolonging progression-free survivals with the least toxicity. From the perspective of costs, risk and benefits, use of sequential single agents for subsequent chemotherapy might be an alternative choice. One of these single agents, capecitabine, was recently approved for use after failure of paclitaxel therapy in metastatic breast cancer.[12]

Our previous work showed that patients with advanced breast cancer pretreated with anthracycline and paclitaxel have a 25% response rate to a 3-week schedule of docetaxel, indicating a partial cross-resistance between the two taxanes.[13] In addition, experience using paclitaxel in patients who have been exposed to anthracyclines and docetaxel is limited. Therefore, it seemed reasonable to study whether the phenomena could be seen in this patient population.

Although taxanes are active agents against breast cancer, their treatment-related toxicity is a major concern. This problem is more significant if taxanes are delivered as late line therapy, particularly in patients previously heavily treated with chemotherapy. The most frequently reported toxicities of paclitaxel are neutropenia and sensory neuropathy, particular when this drug is given every 3 weeks. Nevertheless, the question of optimal dose and schedule for delivering paclitaxel is unresolved. The introduction of weekly paclitaxel with 1-hour administration has generated much interest.[14] The rationale for this approach is based on the premise that intense dose delivery may achieve greater efficacy than the standard every- 3- weeks regimen and provide more sustained exposure of tumor cells to this cytotoxic drug.[15,16] Moreover, preclinical studies also observed that paclitaxel induced tumor cell apoptosis and anti-angiogenesis in tumors. In vitro, exposure to relatively low concentrations of paclitaxel, on the order of 0.01-0.02 μmol/L, had been shown to induce apoptosis in several different cell lines.[17-20] Lau et al. also showed that paclitaxel at low, non-tumor cell cytotoxic daily doses of 0.3 mg/kg and 6 mg/kg in mice induces anti-angiogenesis by suppression of vascular endothelial growth factor.[21] Clinically, serum levels above 0.01 μmol/L could be achieved and maintained for at least 26 hours after a dose of 100 mg/m$^2$ administered over 1 hour.[15] Metastatic breast cancer studies of weekly 1-hour paclitaxel administration (80-100 mg/m$^2$) as first-line palliative chemotherapy reported response rates of 21.5-53%.[15,22-25] Notably, patient compliance was good and there was relatively lower toxicity observed in these studies.

Since December 1999, we used weekly paclitaxel as salvage therapy for heavily prtreated metastatic breast cancer patients. A retrospective analysis of treatment outcome in these patients is reported.

## METHODS

From December 1999 to June 2004, 23 women with recurrent or metastatic breast cancer who received weekly paclitaxel were included for analysis. All data were obtained by reviewing their medical charts. Women with histologically or cytologically confirmed metastatic breast cancer and bidi-

mensionally measurable disease were included. Patients with metastasis to the brain, leptomeninges or only the bone were excluded. All patients had adequate hematologic, renal and liver function, and Zubrod performance status equal to or less than 2. Patients who had prior chemotherapy, hormone therapy, or radiation therapy for metastatic disease were included. Prior treatment with a 3-week regimen of taxane as an adjuvant or palliative treatment was allowed. Paclitaxel combined with weekly trastuzumab was allowed in patients whose Her-2/neu was 3+ by immunohistochemical staining. Patients receiving weekly paclitaxel as a second or later chemotherapy line were defined as heavily pretreated.

Paclitaxel 80 mg/m$^2$ was infused over 1 hour weekly for 3 weeks per 4-week cycle. Premedications consisted of diphenhydramine, cimetidine and dexamethasone to prevent anaphylaxis from paclitaxel. The treatment was terminated when disease progressed, unacceptable toxicity developed, the physician decided to terminatetreatment or the patient refused treatment.

The response was evaluated by physical examination, serum tumor markers, chest roentgenography, bone scan, and abdominal computerized topography scan (CT scan). Patients were re-assessed every 3 or 4 cycles of chemotherapy. Concurrent radiotherapy for symptom relief was allowed, but the radiation sites were excluded from response analysis. The primary study endpoint was the response rate and the secondary endpoints were time to progression and toxicity. A complete response (CR) was defined as disappearance of all measurable disease on conventional imaging studies. A partial response (PR) was defined as a 50% or greater decrease in the sum of the products of the largest perpendicular diameters of all measurable lesions for at least 4 weeks without progression of any lesion or appearance of new lesions. Stable disease (SD) was defined as a decrease in the size of the lesion for at least 4 weeks, which did not meet the criteria for PR, or a less than 25% increase in the size of measurable lesions. Progressive disease (PD) was defined as a 25% or greater increase in the size of one or more evaluable lesions, or the appearance of new lesions. In patients with bone disease only, the imaging-based criteria did not apply. However, if clinical symptoms improved, no new lesion appeared on the bone scan, and serum tumor markers decreased, this patient was classified as having stable disease. The time to disease progression was calculated from the date of initiating of therapy to the date of progression. The survival time was calculated from the date of starting therapy to the date of death.

## RESULTS

### Patient characteristics

From December 1999 to June 2004, 23 patients with metastatic breast cancer were enrolled for analysis. Their baseline characteristics are listed in Table 1. The median age of the patients was 55 years (range 33-73). The performance status of all patients was less than 2. Twenty patients (87%) had at least two involved organs, and 18 patients (78.3%) had visceral organ metastasis. Evaluable and measurable disease was found in 22 patients (95.7%). All patients had prior anthracycline-based chemotherapy. Eighteen had docetaxel and another 4 had paclitaxel exposure previously. Among the eighteen patients with previous docetaxel exposure, 15 received a 3

**Table 1.** Patient Characteristics (n = 23)

| | No. (%) |
|---|---|
| Age* | 55 (33-73) |
| Performance status† | |
| 0 | 0 |
| 1 | 21 (91.3) |
| 2 | 2 (8.7) |
| Number of organs involved | |
| 1 | 3 (13) |
| 2 | 12 (52.2) |
| 3 | 6 (26.1) |
| 4 | 2 (8.7) |
| Number of metastases | |
| Median | 2 |
| Site of disease | |
| Locoregional | 5 (21.7) |
| Lymph node | 8 (34.8) |
| Liver | 5 (21.7) |
| Lung | 16 (69.5) |
| Bone | 17 (73.9) |
| Visceral organ | 18 (78.3) |
| Measurable disease | 22 (95.7) |

* Median (range)

† ECOG performance status

week combination regimen with cisplatin, and the other 3 received weekly docetaxel alone. The response rate to docetaxel was 50%. Weekly paclitaxel was used for salvage in 16 patients and the median time between docetaxel exposure and weekly paclitaxel was 182 days (range 22 – 495 days). Nearly all patients had been treated with more than one chemotherapy regimen for their metastatic disease, and weekly paclitaxel was administered as at least the second line of salvage chemotherapy (range 2-8) in 20 patients (87%, Table 2).

**Course of treatment and response**

A total of 289 doses of paclitaxel were infused with a median of 11 weekly treatments per patient (range 2-33). We were able to assess all patients for response. There was no complete response and 5 patients achieved partial responses. The overall response rate was 21.7%. Among the responders, 2 were treated with the weekly paclitaxel and trastuzumab combination. The response rate to weekly paclitaxel alone was only 15.8% (3 responders among the other 19 patients). All of the responders had prior docetaxel, but none of patients pretreated with paclitaxel responded. In addition, none of the patients with later than 3rd line palliative chemotherapy responded. Stable disease was observed in 10 patients (43.5%). The disease control rate (PR + SD) was 65.2%. Eight patients had disease progression. The median time to progression was 121 days (range 21 – 345 days) and the median survival was 151 days (range 42 -681 days).

**Toxicity**

One patient (4.3%) developed grade IV neutropenia with neutropenic fever and one patient had grade II thrombocytopenia. Grade I/ II sensory neuropathy was reported in three patients. There was no dose reduction or schedule delay during the treatment course. One patient was withdrawn from the treatment after the 3rd dose of paclitaxel because of hypertensive crisis with aggravated heart failure. The toxicity was generally manageable.

**Table 2.** Prior Chemotherapy Exposure (n = 23)

| Previous chemotherapy agents | No. (%) |
|---|---|
| Anthracycline | 23 (100) |
| Docetaxel | 18 (78.3) |
| Paclitaxel | 4 (17.4) |
| Previous chemotherapy lines for metastatic disease | |
| 0 | 3 (13.1) |
| 1 | 6 (26.0) |
| 2 | 5 (21.7) |
| ≥ 3 | 9 (39.2) |

## DISCUSSION

This retrospective study demonstrated a response rate of 21.7% to weekly paclitaxel among women with heavily pretreated metastastic breast cancer. If those treated with the paclitaxel-trastuzumab combination were excluded, the response rate was 15.8%. Notably, little treatment-related toxicity was reported and the treatment was well tolerated. Disease stabilization was achieved in 43.5% of patients and the disease control rate was 65.2% in these heavily pretreated patients. The time to disease progression was 3.73 months. For such a heavily pretreated patient group, the expected response rate to further salvage chemotherapy was limited. However, our study suggested that weekly paclitaxel has some activity and, most importantly, is well tolerated.

The effect of low dose paclitaxel on breast cancer has been studied by Seidman et al. who found that 96 hours of paclitaxel infusion at a relatively low concentration (0.01 μmol/L) was cytotoxic to breast cancer cells.[25] They further suggested that frequent drug administration on a weekly schedule could extend cumulative exposure and might inhibit tumor regrowth between cycles, suppress angiogenesis, and limit the emergence of a malignant cell population resistant to chemotherapy. A phase II study conducted by the same group using a dose-dense weekly 1-hour paclitaxel infusion in metastatic breast cancer patients who had prior chemotherapy found an overall response rate of 53%, with a 10% complete response, and a median response duration of 7.5 months.[15] However, over 50% of their patents had received weekly paclitaxel as first line palliative chemotherapy for metastatic disease. Furthermore, Perez et al. reported results of a multicenter phase II trial of weekly paclitaxel in women with metastatic breast cancer showing a response rate of 21.5%, with a median time to progression of 4.7 months, and overall survival of 12.8 months in 212 women with metastatic breast cancer.[22] However, the response

rate of patients who received up to two prior chemotherapy regimens was only 15%, which was close to the response rate in this study. In the study by ten Tije et al. paclitaxel was administered with the same schedule and dosage used in this study as first line therapy for metastatic breast cancer.[23] There were 10 partial responses (43%) and 9 stable disease (38%) responses achieved in their 23 evaluable patients. The median duration of response was 194 days. Recently, Seidman et al. reported a four-arm phase III randomized trial comparing weekly and 3-week conventional 3-hour paclitaxel with or without trastuzumab in metastatic breast cancer. He found that weekly paclitaxel is superior to the 3-week regimen in term of overall response rate and time to progression. Moreover, weekly paclitaxel was associated with less hematological toxicity but more neurotoxicity.[26]

Pharmacological studies suggest a decreased clearance of taxanes in elderly breast cancer patients.[27] The safety (mild to moderate toxicity profile) and impressive response rates to weekly paclitaxel[15,22-24,28] indicate that it could be used in elderly patients. In the 5 patients (21.7%) over 65 years old in our study, weekly paclitaxel was well tolerated, and no grade 3/4 toxicity was observed throughout the course of treatment.

Our design differed from most weekly trials in that paclitaxel was administered without interruption. However, weekly administration without interruption might increase fatigue and other toxicities, particularly in such a heavily pre-treated patient population. Symptomatic myelosuppression and peripheral neuropathy were the toxicities of main concern. These toxicities seemed to be dose-dependent and were generally limited and reversible. Seidman et al.[15] reported 4 of 29 patients (14%) had grade 3/4 neutropenia, and 7 of 29 patients (24%) had grade 3 neuropathy, especially at high doses (100 mg/m$^2$/week or higher). Perez at al.[22] reported a 15% incidence of grade 3/4 hematological toxicity and a 9% incidence of grade 3 neuropathy. Wist et al.[24] also reported grade 3 neutropenia developed in 5 patients and grade 3 neuropathy in 5 of their 33 assessable patients. Nevertheless, ten Tije et al. reported that although treatment was well tolerated, 8 patients discontinued treatment because of fatigue. Grade 3 neutropenia and neuropathy occurred in 12% and 4% of patients, respectively.[23]

A break in weekly treatment might affect the dose-intensity and thus impact the efficacy of paclitaxel. A planned assessment of unscheduled treatment interruptions could be included in future trials. Furthermore, breaks in treatment should be more feasible for combination therapy including paclitaxel and other third-generation chemotherapeutic compounds such as gemcitabine.

All the patients in this study had prior anthracycline-based treatment and 78% had prior docetaxel. All the responders had prior docetaxel and less than two previous chemotherapy regimens for metastatic breast cancer. Response to weekly paclitaxel could be explained by partial cross resistance between paclitaxel and docetaxel, which we have suggested before.[13] However, none of the patients who previously received combination chemotherapy with paclitaxel and cisplatin responded. We also found a high response rate in the patients treated with combined paclitaxel and trastuzumab chemotherapy. This was not surprising since some phase II trials of weekly paclitaxel and trastuzumab reported overall response rates of 58.6-62% in women with Her-2 overexpressing metastatic breast cancer.[29-33] Therefore, in Her-2 positive patients without prior exposure to trastuzumab, a combination of paclitaxel and trastuzumab remains an interesting and effective strategy.

In conclusion, weekly paclitaxel showed a modest response and was well tolerated in heavily pretreated metastatic breast cancer patients. Furthermore, low-dose weekly paclitaxel, in light of its tolerability, might be superior to higher doses given less frequently. Weekly paclitaxel could also be combined with other chemotherapy agents, such as trastuzumab and gemcitabine. Further study is warranted to determine the best use of weekly paclitaxel-based combinations in metastatic, adjuvant, or even neoadjuvant settings.

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# 分析長庚醫院對於曾接受多次化學治療的轉移性乳癌婦女每週使用 Paclitaxel 結果之回溯研究

呂長賢[1] 林永昌[1,2] 張獻崑[1]

**背 景：** 紫杉醇類 (taxanes) 藥物是目前治療轉移性乳癌有效的藥物之一。傳統上廣泛以每三週爲週期施打的方式毒性顯著。近來，報告顯示以每週施打的方式具良好反應且病人耐受性佳。我們回溯分析本院轉移性乳癌婦女每週使用 paclitaxel 的效果。

**方 法：** 我們分析了從 1999 年 12 月到 2004 年 6 月，23 位經病理切片證實，具可測量腫瘤的轉移性乳癌病患。其平均年齡 55 歲。狀態爲 ECOG 二分以下。所有病人都接受至少一線以上的化學治療。這些病人接受每週 80 mg/m$^2$ 的 paclitaxel，連續三週，一週休息的治療。治療效果根據 WHO 定義評估。

**結 果：** 全部的病患均接受治療效果與存活評估。每個病患皆曾接受過 anthracycline 爲主的化療。其中 14 位 (61%) 在本治療前接受至少三線不同的化療。20 位病患 (87%) 有至少二個以上不同位置的轉移，18 位 (78.3%) 具內臟器官轉移。整體治療反應率爲 21.7%，但無完全反應者 (complete response)，且 43.5% 的病患病情穩定 (stable disease)。平均疾病惡化期 (median time to progression) 爲 121 日。4 位病患 (17.4%) 接受 trastuzumab 與 paclitaxel 合併治療，其中 2 人對治療有反應。病患耐受性佳，並無嚴重毒性。其中一位病患因心衰竭而中斷治療。

**結 論：** 施以每週 paclitaxel 治療曾接受多次化療的轉移性乳癌病患耐受度好且治療反應與文獻報告中，以相同方式治療者結果近似。以每週施行 paclitaxel 合併其它藥物的治療方式值得進一步探討。

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**關鍵詞：** 乳癌，轉移，化學治療，paclitaxel。

長庚紀念醫院 台北院區 [1]血液腫瘤科；[2]長庚大學 醫學院
受文日期：民國95年5月4日；接受刊載：民國95年6月16日
通訊作者：林永昌醫師，長庚紀念醫院 血液腫瘤科。桃園縣333龜山鄉復興街5號。Tel.: (03)3281200轉2513; Fax: (03)3283973; E-mail: yclinof@cgmh.org.tw