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CLINICAL TRIAL REPORT

Ixabepilone plus capecitabine for Chinese patients with metastatic breast cancer progressing after anthracycline and taxane treatment

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Abstract
Purpose Effective treatment options for patients with metastatic breast cancer pretreated with or resistant to anthracyclines and taxanes are limited. Ixabepilone has single-agent activity in these patients and has demonstrated synergy with capecitabine in this setting. This study was designed as a prospective clinical trial to evaluate the efficacy and safety of ixabepilone plus capecitabine in both anthracycline-pretreated and resistant and taxane-resistant metastatic breast cancer of Chinese women.
Patients and methods Patients with measurable disease who had anthracycline and taxanes as prior neoadjuvant, adjuvant or metastatic therapy were treated with ixabepilone at 40 mg/m^2 intravenously on day 1 of 21-day cycle plus capecitabine 2,000 mg/m^2 orally on day 1 through 14 of a 21-day cycle. The primary end point was the objective response rate. The secondary end points were time to progression, overall survival, and toxicity profiles.
Results Twenty-one patients received 146 cycles with a median of 5 cycles (range, 1–13 cycles) per patients. Fourteen patients (66.7%) had partial response, 5 patients (23.8%) had stable disease, and 2 patients (9.5%) had progressive disease. Median time to progression and duration of response were 6.2 and 6.0 months, respectively. The median overall survival was 16.7 months. Eight (38.1%) patients required dose reduction and 14 (66.7%) patients discontinued treatment for adverse effect. Grade 3/4 treatment-related events included fatigue (28.6%), peripheral sensory neuropathy (33.3%), neutropenia (61.9%), anemia (4.7%), hypokalemia (4.7%), hand and foot syndrome (19.0%) and infection (9.5%). Resolution of grade 3/4 peripheral neuropathy was reversible after a median period of 6 weeks.
Conclusion Ixabepilone plus capecitabine demonstrated a clear activity and an acceptable safety profile in Chinese patients with anthracycline-pretreated/resistant and taxane-resistant metastatic breast cancer, and the majority of patients completed 6 cycles of the therapy with manageable neuropathy toxicities.

Keywords Ixabepilone · Capecitabine · Anthracycline-pretreated · Taxane-resistant · Metastatic breast cancer · Chemotherapy

Introduction

Breast cancer is the most common malignancy among women in the developed countries and remains a leading cause of mortality in women worldwide [10]. The age-standardized rates were between 10.0 and 27.2 per 100,000 women for China (Qidong County, Shanghai, and Tianjin) and 36.2 per 100,000 women for Hong Kong. Breast cancer incidence has increased 30–40% since 2000 [22] and is projected to continue to be on the rise over the next few decades in China, including Hong Kong [20, 23]. Although impressive improvements have been achieved in the adjuvant treatment of early breast cancer, approximately 20% of patients initially diagnosed with early stage breast cancer will eventually develop metastatic breast cancer [15]. There are multiple treatment options for metastatic breast cancer including chemotherapy, endocrine therapy, and antibody therapy targeting against breast cancer-related growth

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factors. Systemic chemotherapy has also been widely applied in China for both early and metastatic breast cancer with the primary goal to prolong survival, alleviate breast cancer-related symptoms, and improve the quality of life for breast cancer patients.

Anthracyclines and taxane-based regimens have been increasingly used in China and have become the most prevalent scheme for systemic chemotherapy. Anthracyclines are the most active cytotoxic agents for metastatic breast cancer, and taxanes in combination with anthracyclines have been shown in several clinical studies to increase the response rates and time to progression (TTP), and improve the overall survival (OS) of patients with metastatic breast cancer [3, 9]. Anthracycline- and taxane-based regimens are currently active as first-line treatment for metastatic breast cancer. However, metastatic breast cancer often progresses because of primary or acquired resistance to anthracyclines and taxanes, which becomes a significant obstacle to the effective treatment of metastatic breast cancer. Besides, there are currently few treatment options for patients with metastatic breast cancer who have become resistant to anthracyclines and taxanes by failing to respond or relapsing after having received both anthracyclines and taxanes [11].

Capecitabine is a new member of the fluoropyrimidine family and is an orally administered drug that delivers fluorouracil (5-FU) selectively to the tumor. Single-agent capecitabine has been approved for treating patients with metastatic breast cancer who have failed anthracyclines and taxanes. The drug has been frequently used in these patients given its demonstrable efficacy, ease of administration and safe profile [5]. However, the objective response rate of capecitabine is only 20–28% [4, 7], suggesting the need for novel effective single agents or agents that can be combined for use with capecitabine [8]. Ixabepilone is a novel epothilone B analog which, similar to taxanes, binds to β-tubulin and stabilizes microtubules, leading to the onset of cellular death [18]. Ixabepilone has been shown efficacious in patients with metastatic breast cancer who have become resistant to multiple chemotherapeutic agents such as anthracyclines, taxanes, and capecitabine, thus demonstrating an ability to overcome common mechanisms of resistance that limit the efficacy of many other chemotherapeutic agents [6, 14]. Evaluation of combined therapy of ixabepilone and capecitabine in clinical studies indicates a good safety profile and efficacy of the combination regimen [14], which is superior to single-agent capecitabine [4, 7, 13, 17]. In the current study, we investigated the efficacy and safety of the combination therapy of ixabepilone and capecitabine in Chinese patients with metastatic breast cancer whose disease progressed after treatment with anthracyclines and taxanes. To our knowledge, this is the first clinical study evaluating the efficacy of this combination regimen in patients with metastatic breast cancer in Asia.

Patients and methods

Patients

Women who had measurable or assessable metastatic breast cancer which had been histologically confirmed were included in the current study. These women also met the following inclusion criteria: (1) women who were at least 18 years of age, (2) women who had previously received cytotoxic chemotherapy, including anthracyclines and taxanes, (3) women who had adequate renal (serum creatinine $\leq$ 2.5 mg/dl), hepatic [(aspartate aminotransferase (AST), alanine aminotransferase (ALT), or alkaline phosphatase (ALP) $\leq$ 2.5 times the upper limit of normal, and bilirubin $\leq$ 1.5 times the upper limit of normal], and cardiac [(left ventricular ejection fraction (LVEF) $\geq$ 50%)] and bone marrow functions (platelets $\geq$ 100,000/mm^3, hemoglobin $\geq$ 9 g/dl, and neutrophils $\geq$ 1,500 cells/mm^3), and (4) women whose ECOG performance status [12] was 0–2. Taxane resistance was defined as tumor recurrence within 3 months of the last dose in the metastatic setting or within 12 months in the adjuvant setting. Patients were excluded if they had brain metastases or if their motor or sensory neuropathy grade was $\geq$2 by the National Cancer Institute Common Terminology Criteria for Adverse Events version 3 (CTCAE). Other exclusion criteria included reduced hematologic or renal function, prior severe hypersensitivity to polyethoxylated castor oil-containing agent or hypersensitivity to fluoropyrimidine, known or suspected dihydropyrimidine dehydrogenase deficiency, treatment with potent cytochrome P450 3A4 inhibitors, and prior epothilone or capecitabine therapy.

Written informed consents were obtained from all patients before study and the study protocol was approved by the local institutional review board at the Cancer Hospital, Chinese Academy of Medical Sciences, Beijing, China.

Efficacy assessment

In this signal site, one group clinical trial, patients received ixabepilone at 40 mg/m^2 as a 3-h intravenous infusion on day 1 of a 21-day cycle and oral capecitabine at 2,000 mg/m^2 given in two divided doses each day on days 1–14 of a 21-day cycle, or capecitabine alone at 2,500 mg/m^2 in two divided doses each day on days 1–14 of a 21-day cycle. Treatment with single capecitabine is permitted if ixabepilone was discontinued due to adverse events. The primary end point was the objective response rate (ORR). The secondary end points included the duration of response, time to response, TTP, OS and safety of the regimen. The duration of response was defined as the time from the first documented partial response (PR) or complete response (CR) until documented progression or death. TTP was

defined as the time from the first day of treatment until the first day of progression or death. Tumor evaluation was performed every two cycles according to the modified RECIST criteria.

Safety assessment

Safety was assessed on the basis of reported adverse events and laboratory abnormalities, and adverse events were classified according to the National Cancer Institute Common Toxicity Criteria (version 3.0). Serum biochemistry was evaluated before each treatment cycle and hematology was assessed weekly and before each cycle.

Statistical design and methodology

Estimates of the median duration of response, TTP, and OS, with 95% confidence interval (CI), were calculated for each cohort using the Kaplan–Meier product-limit method. The duration of response was calculated for responding patients only. Descriptive statistics were used to summarize safety and laboratory observations.

Results

Patients' demographic data and disease characteristics

Between June 2005 and August 2006, 21 patients were enrolled into the study. Patients and tumor characteristics are summarized in Table 1. The median age of the patients was 56 years with a range from 29 to 70 years. Of the patients, 28% were positive for the human epidermal growth factor receptor (HER-2). Moreover, more than half of the patients (57.1%) were positive for the estrogen and/or progesterone receptor (ER and/or PR). In addition, the majority of patients (85.7%) had visceral disease involving the liver and/or lung and most patients had two disease sites. Furthermore, more than half of the patients (57.1%) had received one prior regimen in the metastatic setting. All patients received previous taxane and anthracycline-containing regimen as neoadjuvant, adjuvant or metastatic therapy and 80.9% of patients were taxane-resistant. Of the 21 patients enrolled, 13 patients were removed from the study due to disease progression, and seven patients were removed due to prolonged toxicity, and one patient withdrew informed consent.

Table 1 Baseline patient demographic and disease characteristics

Characteristic	Ixabepilone plus capecitabine	
	No. of patients	%
Age (years)		
Median	56	
Range	29–70	
ECOG performance status		
0	17	80.9
1	3	14.3
2	1	4.7
Hormone receptor and HER-2 status		
ER positive and/or PR positive	12	57.1
ER negative and PR negative	9	38.1
ER negative, and PR negative, and HER-2 negative	2	9.5
HER-2-positive status (IHC +++ or FISH +)	6	28.5
Visceral metastasis		
With visceral metastasis	18	85.7
Without visceral metastasis	3	14.3
Extent of disease (no. of disease sites)		
>2	18	85.7
<2	3	14.3
Prior regimens in the metastatic setting		
1	12	57.1
0	9	42.8
Prior chemotherapy		
Taxane-resistant	17	81.0
Taxanes and anthracyclines	21	100

ER estrogen receptor, *PR* progesterone receptor, *HER-2* human epidermal growth factor receptor-2, *FISH* fluorescent in situ hybridization, *IHC* immunohistochemistry

Dose delivery

Patients receiving ixabepilone and capecitabine underwent a median of five treatment cycles with a range of one to 13 cycles and a total of 146 cycles. Furthermore, 23.8% of patients received at least eight cycles of treatment. A total of nine treatment cycles (6.2%) administered after one treatment cycle were delayed. More than half of the cycles (56.2%) were administered at the planned dose of 40 mg/m^2 of ixabepilone and 2,000 mg/m^2 of capecitabine. In addition, 61.9% of patients achieved more than 75% of their planned dose intensity. The median dose intensity of ixabepilone was 13.3 mg/m^2/week (range, 8.5–13.3 mg/m^2/week). The dose of ixabepilone and capecitabine was reduced in eight patients (38.1%). Ixabepilone was discontinued in 14 patients (66.7%) and eight patients received capecitabine single-agent therapy (32 cycles) after ixabepilone was discontinued.

Efficacy

Twenty-one patients were assessed for efficacy. The objective response rate of patients was 66.7% (14/21). Fourteen patients (66.7%) showed a partial response and no complete

response was observed. Stable disease for at least 6 weeks was the best response for five patients (23.8%) (Table 2). The median time to progression for all patients was 6.2 months with a range from 1.5 to 22.5 months (Fig. 1). The median OS was 16.7 months with a range from 5.6 to 27.5 months (Fig. 2). For patients who achieved a partial response, the median duration of measurable response from the date of the first documented response was 6.0 months (range 2.5–20.7 months). Eleven patients (52.3%) showed a partial response when they were first evaluated at 6 weeks, which was further confirmed in 4–8 weeks. Among those patients who were resistant to taxanes, 75% (12/17) of patients exhibited a partial response, 18.8% (3/17) of patients had stable disease. No progressive disease was observed among these patients. Among those patients who were ER and/or PR positive, 58.3% (7/12) patients had a partial response, 25.0% (3/12) patients had stable disease, and 16.7% (2/12) patients had progressive disease. In addition, among those patients who were negative for both ER and PR, 66.7% (6/9) of patients achieved a partial response. Furthermore, among those patients who were HER-2 positive, 66.7% (4/6) of patients achieved a partial response.

Safety

Toxicity information was collected for all patients who received a total of 146 treatment cycles. These treatment-related adverse events are summarized in Table 3 and were generally manageable. All patients had at least one treatment-related adverse event. The non-hematologic toxicities were mostly grade I to III adverse events. Neutropenia was the most frequently reported hematologic adverse event; severe neutropenia (grade III/IV) was observed in 61.9% (13/21) of patients (grade III, 8 patients; grade IV, 5 patients). In addition, anemia was noted in one patient and thrombocytopenia was observed in two patients. The most notable non-hematologic toxicities included neuropathy (90.5%), fatigue (38.1%) and hand–foot syndrome (42.8%). Grade III myalgia/arthralgia/abdominal pain, peripheral neuropathy, and fatigue were observed in 9 (42.9%), 7 (38.1%), and 6 (28.6%) patients, respectively. Grade III hand–foot syndrome and nausea were noted in 4 (19.0%) and 6 (28.6%) patients, respectively. Furthermore, infection was seen in two patients.

Peripheral neuropathy was the most common and significant non-hematologic adverse event. Grade I/II neuropathy was reported in 12 (57.1%) patients, and grade III neuropathy developed in 7 (33.3%) patients. No grade IV neuropathy occurred. Peripheral neuropathy developed after a median of 3 treatment cycles (range, 1–5 cycles). Thirty-eight percent (8/21) of patients discontinued one or both drugs due to peripheral neuropathy. Most patients with persistent grade II/III peripheral neuropathy recovered after dose reduction or discontinuation of the drugs. The median time to resolution of grade III neuropathy, which was

Table 2 Objective tumor response in 21 patients with metastatic breast cancer

Response	Response assessable ($n = 21$)	
	No. of patients	%
Patient best response		
PR	14	66.7
SD	5	23.8
PD	2	9.5
Duration of response, months		
Median (range)	6.0 (2.5–20.7)	
Time to response, months		
Median (range)	6 (6–17)	

PR partial response, *PD* progressive disease, *SD* stable disease

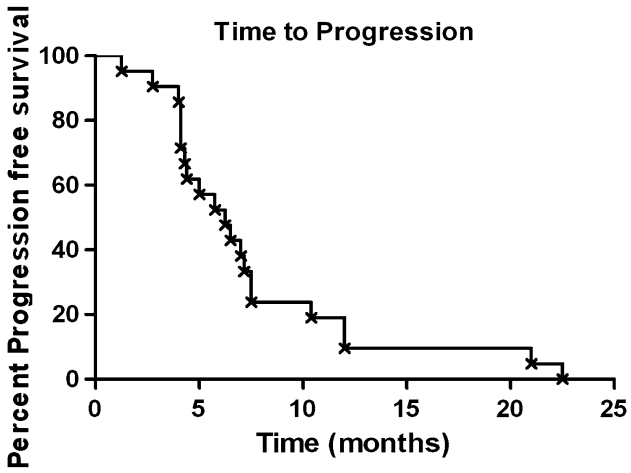

Fig. 1 Time to progression of all patients treated with ixabepilone and capecitabine

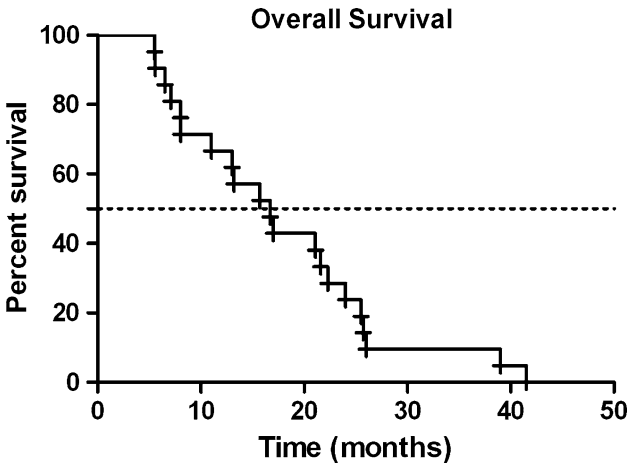

Fig. 2 Overall survival of all patients treated with ixabepilone plus capecitabine

Table 3 Treatment-related adverse events

Treatment-related toxicity	Grade 2 (n = 21)		Grade 3 (n = 21)		Grade 4 (n = 21)	
	No. of patients	%	No. of patients	%	No. of patients	%
Dermatology/skin						
Alopecia	21	100	0	0.0	0	0
Hand and foot syndrome	5	23.8	4	19.0	0	0
Pain						
Myalgia and arthralgia	12	57.1	7	33.3	0	0
Abdominal pain/cramping	1	4.8	2	9.5	0	0
Gastrointestinal tract						
Nausea	2	9.5	6	28.6	0	0
Diarrhea	4	19.0	0	0	0	0
Vomiting	2	9.50	2	9.50	0	0
Constitutional symptoms						
Fatigue	2	9.5	6	28.6	0	0
Fever	2	9.5	0	0	0	0
Peripheral neuropathy						
Neuropathy, autonomic	1	4.7	2	9.5	0	0
Neuropathy, motor	10	47.6	7	33.3	0	0
Neuropathy, sensory (paresthesia)	12	57.1	7	33.3	0	0
Arrhythmia	0	0	2	9.5	0	0
Hypersensitivity	0	0	0	0.0	1	4.8
Laboratory test						
Transaminase abnormal	1	4.8	0	0	0	0
Bilirubin elevate	1	4.8	0	0	0	0
Electrolyte disturbance (hypokalemia)	0	0.0	0	0	1	4.8
Hematologic toxicity						
Infection	0	0	2	9.5	0	0
Neutropenia	7	33.3	8	38.1	5	23.8
Anemia	2	9.5	1	4.8	0	0
Thrombocytopenia	0	0	1	4.8	0	0

defined as the time for neuropathy to return to the baseline level or grade I, was 6 weeks (range 4–16 weeks), and the median time to resolution of grade II neuropathy was 4 weeks (range 3–8 weeks).

Reasons for discontinuation of treatment included grade III neuropathy (5 patients), grade II neuropathy (3 patients) for more than 3 episodes with each episode lasing more than 2 weeks. Other reasons for discontinuing drug use were grade III cardiac arrhythmia, grade III vomiting, grade III hand and foot syndrome for more than 6 weeks. One patient developed grade IV anaphylactic shock after 10 min of ixabepilone infusion in the third treatment cycle, who, however, recovered after treatment with dexamethasone and diphenhydramine hydrochloride, and ixabepilone was discontinued. Capecitabine was discontinued in 7 patients because of grade II ($\geq$6 weeks) and III hand and foot syndrome, and grade III fatigue. One patient developed grade IV hypokalemia, and ixabepilone and capecitabine were discontinued. A total of nine treatment cycles (6.2%) administered after one treatment cycle were delayed due to grade II neuropathy, which was the most common cause of treatment delays.

Discussion

Anthracycline- and taxane-containing regimens have been increased used as the standard of care for adjuvant therapy for early stage breast cancer as well as metastatic breast cancer [2]. The majority of patients with metastatic breast cancer, however, will develop resistance to these two agents. In some other patients, these regiments have to be discontinued because of notorious side effects. Capecitabine, gemcitabine, vinorelbine, and platinum-based monotherapy

or combination therapy has been applied for these patients who were previously treated with or who became resistant to anthracyclines and taxanes. These single or combination regimens have demonstrated reasonable efficacy and safety with an overall response rate of 16–52% and a median time to progression of 2.0–5.4 months [21]. Our study has achieved a partial response rate of 66.7% and a median duration of response of 6 months. These outcomes compare favorably with those reported by Thomas et al. [16]. Most of the patients in our study were resistant to both taxanes and anthracyclines, and yet they responded favorably to ixabepilone plus capecitabine, indicating that there is no cross-resistance among ixabepilone and taxanes and the combined ixabepilone and capecitabine regimen has considerable activities against anthracycline- and taxane-resistant metastatic breast cancer.

Neutropenia is the most common hematologic toxicity in our study. Thirteen patients developed grade III/IV toxicities, including infection in one patient, but no patients discontinued their treatment due to hematologic toxicity. These toxicities were manageable and reversible, and most patients recovered by reducing drug dosage and supportive care. On the other hand, myalgia, neuropathy, fatigue, and hand and foot syndrome are the most common and significant non-hematologic toxicities in our patients. The hand and foot syndrome is a specific toxicity of capecitabine and was observed in 43% of our patients, and this incidence rate is similar to that reported by Wang et al. [19]. Neuropathy is the most frequent toxicity during ixabepilone therapy, which was observed in 90% of our patients including grade III neuropathy in 7 (33%) patients, which is higher than those reported for chemonaïve patients (1%) and patients who were treated with anthracyclines or taxanes (20%) [1, 11, 14, 17]. However, Neuropathy, which was primarily sensory, in most of these patients were effectively managed by dose reduction or treatment delays, enabling them to complete six cycles of ixabepilone, thus achieving the observed levels of efficacy.

In this study, drug discontinuation or reduction developed in 66.8% and 38.1% patients, respectively, due to toxicities. The safety profile of the ixabepilone capecitabine combination regimen in this study is similar to that previously reported and the average dose intensity (13.3 mg/m^2/week) and median cycles (5 cycles) are also similar to those by others [1, 11, 14, 17]. Although the incidence of toxicities is relatively high among the Chinese patients in our study, they are mostly mild, reversible and manageable. However, the dose of 40 mg/m^2 ixabepilone should be used cautiously in Chinese patients, especially in heavily chemotherapy-treated patients. Further clinical trials should be done to investigate an appropriate dose of ixabepilone for Chinese patients.

Conclusion

Ixabepilone plus capecitabine demonstrated clear activity and an acceptable safety profile in Chinese patients with anthracycline-pretreated/resistant and taxane-resistant metastatic breast cancer. The combination regimen provides a valuable treatment option for these patients. The toxicities and reversibility of toxicities are similar to those seen in other populations worldwide. However, more studies should be carried out to investigate a more safe and effective dosage of ixabepilone for Chinese patients.

References

1. Baselga J, Gianni L et al (2005) Predicting response to ixabepilone: genomics study in patients receiving single agent ixabepilone as neoadjuvant treatment for breast cancer. Breast Cancer Res Treat 94:S31–S32
2. Beslija S, Bonneterre J et al (2009) Third consensus on medical treatment of metastatic breast cancer. Ann Oncol 20(11):1771–1785
3. Biganzoli L, Cufer T et al (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 10961 Multicenter Phase III Trial. J Clin Oncol 20(14):3114–3121
4. Blum JL, Jones SE et al (1999) Multicenter phase II study of capecitabine in paclitaxel-refractory metastatic breast cancer. J Clin Oncol 17(2):485–493
5. Ershler WB (2006) Capecitabine monotherapy: safe and effective treatment for metastatic breast cancer. Oncologist 11(4):325–335
6. Fojo T, Menefee M (2007) Mechanisms of multidrug resistance: the potential role of microtubule-stabilizing agents. Ann Oncol 18(Suppl 5): v3–v8
7. Fumoleau P, Largillier R et al (2004) Multicentre, phase II study evaluating capecitabine monotherapy in patients with anthracycline- and taxane-pretreated metastatic breast cancer. Eur J Cancer 40(4):536–542
8. Geyer CE, Forster J et al (2006) Lapatinib plus capecitabine for HER2-positive advanced breast cancer. N Engl J Med 355(26):2733–2743
9. Jassem J, Pienkowski T et al (2009) Doxorubicin and paclitaxel versus fluorouracil, doxorubicin and cyclophosphamide as first-line therapy for women with advanced breast cancer: long-term analysis of the previously published trial. Onkologie 32(8–9):468–472
10. Kamangar F, Dores GM et al (2006) Patterns of cancer incidence, mortality, and prevalence across five continents: defining priorities to reduce cancer disparities in different geographic regions of the world. J Clin Oncol 24(14):2137–2150
11. Moreno-Aspitia A, Perez EA (2009) Anthracycline- and/or taxane-resistant breast cancer: results of a literature review to determine the clinical challenges and current treatment trends. Clin Ther 31(8):1619–1640
12. Oken MM, Creech RH et al (1982) Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 5(6):649–655
13. Reichardt P, Von Minckwitz G et al (2003) Multicenter phase II study of oral capecitabine (Xeloda(“)) in patients with metastatic breast cancer relapsing after treatment with a taxane-containing therapy. Ann Oncol 14(8):1227–1233
14. Roche H, Yelle L et al (2007) Phase II clinical trial of ixabepilone (BMS-247550), an epothilone B analog, as first-line therapy in

patients with metastatic breast cancer previously treated with anthracycline chemotherapy. J Clin Oncol 25(23):3415–3420
15. Smigal C, Jemal A et al (2006) Trends in breast cancer by race and ethnicity: update 2006. CA Cancer J Clin 56(3):168–183
16. Thomas ES (2008) Ixabepilone plus capecitabine for metastatic breast cancer progressing after anthracycline and taxane treatment. J Clin Oncol 26(13):2223
17. Thomas ES, Gomez HL et al (2007) Ixabepilone plus capecitabine for metastatic breast cancer progressing after anthracycline and taxane treatment. J Clin Oncol 25(33):5210–5217
18. Toppmeyer DL, Goodin S (2009) Ixabepilone, a new treatment option for metastatic breast cancer. Am J Clin Oncol
19. Wang T, Jiang ZF et al (2004) Single-agent Xeloda in the treatment of recurrent and metastatic breast cancer. Zhonghua Zhong Liu Za Zhi 26(6):379–381
20. Wong IO, Cowling BJ et al (2007) Age-period-cohort projections of breast cancer incidence in a rapidly transitioning Chinese population. Int J Cancer 121(7):1556–1563
21. XU B, LI K et al (2003) Gemcitabine plus cisplatin for the treatment of anthracycine2resistant advanced breast cancer. China Oncol 113:579–581
22. Yang L, Li LD et al (2006) Time trends, estimates and projects for breast cancer incidence and mortality in China. Zhonghua Zhong Liu Za Zhi 28(6):438–440
23. Yang L, Parkin DM et al (2005) Estimates of cancer incidence in China for 2000 and projections for 2005. Cancer Epidemiol Biomarkers Prev 14(1):243–250