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Clinical report

A cost–utility analysis comparing second-line chemotherapy schemes in patients with metastatic breast cancer

N Li,[1] M van Agthoven,[1] PHB Willemse[2] and CA Uyl-de Groot[1]

[1]Institute for Medical Technology Assessment/Department of Health Policy and Management, Erasmus University Rotterdam, Rotterdam, The Netherlands. [2]Department of Medical Oncology, University Hospital Groningen, Groningen, The Netherlands.

A cost–utility analysis has been performed comparing taxanes, vinorelbine and standard therapy for metastatic breast cancer considering clinical efficacy, quality-adjusted-life-years (QALYs) and costs. A decision model has been built. Clinical efficacy data were collected by literature review. Utility data and cost data were collected from previous studies and Dutch wholesale prices. Except for the MV standard therapy, VM has the lowest C/E ratio of $17 114/QALY, followed by paclitaxel ($30 270/QALY) and docetaxel ($49 739/QALY). VM yields the highest number of QALYs (0.47), compared to paclitaxel (0.35), docetaxel (0.34) and MV (0.29). Compared to the MV standard therapy, the incremental C/E of VM is $23 046/QALY, which is the lowest of all alternatives. We conclude that compared to paclitaxel, docetaxel and MV standard chemotherapy, VM is the most cost-effective second-line chemotherapy for metastatic breast cancer patients. There is a considerable variation in utility scores, depending on the methods or the data sources used. The C/E ratios were influenced most strongly by drug prices, utility and efficacy (in descending order of importance). [© 2001 Lippincott Williams & Wilkins.]

Key words: Cost–effectiveness analysis, cost–utility analysis, decision model, docetaxel, metastatic breast cancer, paclitaxel, quality-adjusted-life-years, second-line chemotherapy, vinorelbine.

Introduction

Breast cancer is the most frequent malignant disease in women in industrial countries. Although different screening strategies have increased the early diagnosis rate, and optimized adjuvant therapy has improved disease-free and overall survival, breast cancer still accounts for 12% of all cancers, 10% of all cancer deaths and 20–25% of all female cancer deaths.[1,2] In the Netherlands, approximately 10 000 women are diagnosed annually with breast cancer and more than 3000 patients die from the disease. About 20–40% of breast cancer patients will ultimately experience metastatic progress and 4–10% of patients already present with metastatic breast cancer (MBC) at diagnosis.[3] Chemotherapy plays an important role in the potential curability of MBC patients.[4] After first-line chemotherapy, the majority of MBC patients will experience relapse or progression which necessitates second-line chemotherapy.[5] In recent years, clinical trials have been performed to establish more effective second-line chemotherapy regimens.[4–16] Taxanes (taxoids), including docetaxel and paclitaxel, have proven to be effective single agents with average response rates of 47 and 27%, respectively.[9] However, paclitaxel appears to cause more neurotoxicity, while docetaxel induces more frequent and severe neutropenia, and a significantly higher fluid retention.[7–9,17,18] Currently, taxanes move rapidly to first-line and adjuvant chemotherapies. Other regimens than taxanes should therefore be identified for patients who develop progressive disease after having received first-line chemotherapy with taxanes. Vinorelbine is another active single agent in both first-line and second-line chemotherapies.[15] Recent phase II studies suggest that a combination of vinorelbine and mitomycin C (VM) might be an active and useful option for second-line chemotherapy of MBC.[19–21]

Only a few cost–utility analyses have been conducted which compared single agents including paclitaxel, docetaxel and vinorelbine.[22–25] However, in the light of current clinical therapy improvements,

Correspondence to CA Uyl-de Groot, Institute for Medical Technology Assessment, Erasmus University Rotterdam, PO Box 1738, 3000 DR Rotterdam, The Netherlands.
Tel: (+31) 10 408 85 33; Fax: (+31) 10 408 90 94;
E-mail: uyl@bmg.eur.nl

combination treatments should also be taken into account. In the current analysis, we compared the single agents paclitaxel and docetaxel, and combination therapy with vinorelbine plus mitomycin C (VM) to the current standard second-line chemotherapy [mitomycin plus vinblastine (MV)] on the basis of clinical results, costs and quality-adjusted-life-years (QALYs).

Materials and methods

Structure of the model

A decision analytic model was built for this cost–utility analysis, to compare paclitaxel, docetaxel, VM and MV. MV is currently considered to be the standard chemotherapy.[23] As input of this model, a baseline patient was defined as a female patient (aged 18–70), histologically diagnosed as having breast cancer, with at least one site of metastatic cancer and having developed progressive disease after first-line chemotherapy (which was not one of the above-mentioned regimens). The patient has a life expectancy of at least 12 weeks with standard hematological, renal and hepatic functions, and a performance status of at least 60 Karnofsky Index or $\leqslant 2$ Eastern Cooperative Oncology Group Scale. Patients with metastatic cancer in the central nervous system were excluded. Patients were also ineligible if having received a cumulative dose of doxorubicin over 550 mg/m^2[23] or epirubicin over 900 mg/m^2 which resulted in a low level of cardiac function demonstrated by left vertricular ejection fraction.

As disease courses are complicated and vary between different patients, we standardized the disease course on the basis of clinical literature and expert opinion.

The concept of the disease course for the total model is as follows (Figure 1).

(1) A baseline patient receives one of the four chemotherapies. During the interval between each cycle, acute toxicity such as nausea or vomiting could occur immediately after the administration of chemotherapy. The addition of 5-HT$_3$ antagonists or dexamethasone to the chemotherapy can control this type of toxicity.

(2) Between each cycle, acute hematological toxicity (e.g. febrile neutropenia) will be identified on the basis of laboratory tests. Colony stimulating factors including granulocyte colony stimulating factors (G-CSF) or granulocyte macrophage colony stimulating factors (GM-CSF) will be administered immediately when severe neutropenia occurs. For febrile neutropenia patients, antibacterial treatment and blood components are administered with colony stimulating factors. In order to simplify the model structure, we assumed that the patient will be hospitalized in the case of febrile neutropenia[26] and that febrile neutropenia only occurs within the first three cycles. Hypersensitivity reactions may lead to death after each cycle of treatment.

(3) After three cycles of chemotherapy, patients will be classified as complete responders, partial responders, having stable disease or having progressive disease. As complete response is rare in metastatic breast cancer and stable disease is considered to be a limited response, we combined complete response, partial response and stable disease to 'Response' in the model.[23] Progressive disease was defined as 'Non-response'. Patients with 'Response' will continue to the next treatment cycle, while chemotherapy will be terminated if patients become non-responders. Patients who respond to chemotherapy will eventually develop progressive disease, which directly leads to death.[23] Because of the variety in palliative treatments, we assumed that follow-up visits of non-response patients only comprise routine laboratory tests, X-ray, ultrasound and computed tomography (CT) scan.

(4) Cumulative toxicity associated with taxoids such as bradycardia, edema and neuropathy mostly occurs after the first three cycles. However, these side-effects are not specified in the model because of the low costs of their treatments.

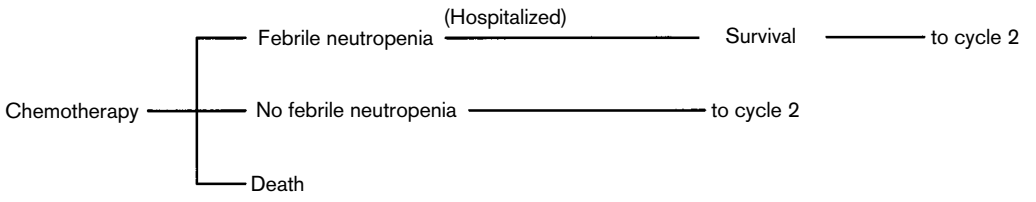

Figure 1. Model structure: outcome options for the first cycle of chemotherapy.

The model consisted of four alternatives: paclitaxel, docetaxel, VM and standard second-line chemotherapy with MV. Each alternative included chemotherapy cycle 1 to cycle 12. Acute hematological toxicity is specified within the first three cycles of the model. In case of hematological toxicity, patients are treated with hematopoietic growth factors. The model structure was then simplified by defining a 3-month interval with the outcomes 'Response', 'Non-response' and 'Death'. Non-response patients were assumed to develop progressive disease in the next interval, which leads to death in the follow-up period (Figure 2). Each treatment arm contains 18 health states reflecting different treatment regimens, treatment-associated toxicities, treatment effects and patient utilities. Probabilities of changing health states were evaluated on the basis of response rate, non-response rate and death rate.

Clinical data for the model

The data which measured the effectiveness of the chemotherapy schedules include toxicity death rate, treatment-limited death rate and chemotherapy response rate. These data were obtained by literature review. Two phase III clinical trials on paclitaxel, docetaxel and MV were cited.[27,28] Data of VM were collected from a recent phase II trial.[29] In these studies, the heterogeneity of baseline patients was evaluated by means of average age, prior treatment history, number and sites of metastatic cancer, and performance status (Table 1). In the phase III study comparing docetaxel and MV, 169 of 203 patients (83%) received docetaxel as second-line chemotherapy, 149 of 189 patients (79%) received MV as second-line chemotherapy and the remainder of the patients received either docetaxel or MV as first-line treatment.[27] Since the majority of patients received chemotherapy as second-line treatment, the pooled survival rates and progression-free survival rates were directly used as inputs for our model. In the phase III study on paclitaxel, two different doses were administered.[28] Only the data of the high-dose group (175 mg/m^2) were cited in accordance with recent agreements on the standard dose.[4–9,17] As presented in Table 1, the overall response rates of paclitaxel, docetaxel, VM and MV are 29, 33, 45 and 12%. The median times to progression are 4.2, 4.4, 6.2 and 2.6 months, respectively. The median survival times are 11.7, 11.4, 13.2 and 8.7 months, respectively.

The model time horizon is 12 months. Dose reduction was ignored by lack of detailed data. Response rates and death rates of each model arm were calculated by analyzing survival curves and progression-free survival curves. Febrile neutropenia rates were obtained from the literature. Subsequently, outcome probabilities were calculated on the basis of clinical efficacy data (Table 1) under the assumption of non-responders contributing more to death rates than responder (ratio 3:1).

Cost data for the model

This study was conducted from the hospital perspective and only direct medical costs are accounted for. All wholesale prices of cytostatics and other relevant drugs were obtained from the *Pharmaceutical Compass 1998*.[29] Costs of hospitalization and follow-up costs were collected from published studies.[26,31] The base year of the cost analysis was 1998. No discounting was applied because of the short time horizon.

Utility data for the model

QALYs and quality adjusted progression-free life years (QAPFYs) were considered as main outcome measures of the model. QALYs aim to combine expected increments in the quantity of life resulting from the treatment with the effects on quality of life in a single measure.[31] QALYs were used to evaluate the trade-off

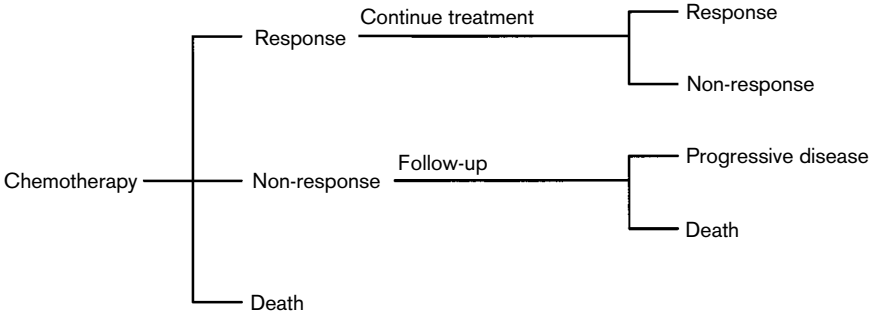

Figure 2. Model structure: outcome options for cycles 3–12.

Table 1. Heterogeneity explored among studies

	Paclitaxel (Nabholtz *et al.*, 1996)[28]	Docetaxel (Nabholtz *et al.*, 1999)[27]	VM (De Placido *et al.*, 2000)[29]	MV (Nabholtz *et al.*, 1999)[27]
Total no.	163[a]	169[a]	55	149[a]
Median age (range)	50 (25–75)	51 (30–73)	56 (26–70)	52 (32–78)
Previous treatment				
endocrine therapy (%)	73	66	76.4	68.2
radiotherapy (%)	76	–	47.3	–
Metastatic sites				
visceral (%)	72	75	61.8	73
liver (%)	45	50	–	47
Performance status				
ECOG				
0 (%)	41	–	54.5	–
1 (%)	42	–	41.8	–
2 (%)	17	–	2.0	–
Karnofsky [median (range)]	–	90 (60–100)	–	90 (60–100)
Treatment studied				
dose and schedule	175 mg/m^2 d1/3 weeks	100 mg/m^2 d1/3 weeks	VNB 30 mg/m^2 d1,8/3 weeks MMC 10 mg/m^2 d1/3 weeks	MMC 12 mg/m^2 d1/6 weeks VLB 6 mg/m^2 d1/3 weeks
median no. of cycles	6	6	5.5	4
response rate (95% CI)	29% (23–36%)	33% (26–40%)	45% (32–59%)	12% (7–17%)
median TTP (months)	4.2	4.4	6.2	2.6
median survival (months)	11.7	11.4	13.2	8.7

VNB, vinorelbine; MMC, mitomycin; VLB, vinblastine; TTP, time to progression; d1, day 1.
[a]Refers to patient numbers of the second-line chemotherapy group.

between mortality, morbidity, preferences of patients, and the willingness of patients and society to accept a shortening of life to avoid morbidity. The utility values needed to calculate QALYs were collected by literature review.[22–25,31] The utility data were linked to different health states. After balancing different utility values, we chose a 'six-country average utility' as the basic data source.[31] The, average utility for response consisted of the average of 'partial/full response' and 'stable disease'. The value of 'progressive disease' was used as 'non-response utility'. In each arm of the model, the utilities were modified with changing health states probabilities. The total number of QALYs was calculated on the basis of the calculation of life-years:

$$\mathrm{QALY}_i = \sum \mathrm{LY}_i * \mathrm{U}_i$$

U_i is the utility of each time interval and LY_i is the number of life-years of each time interval, which equals to the area under the survival curve within each time interval. LY_i is calculated by:

$$\mathrm{LY}_i = (S_i + S_j)/2 * 1/4$$

S_i is the survival rate of the current time interval. S_j is the survival rate of the previous time interval. The time interval is 3 months (0.25 years).

QAPFYs were calculated simultaneously.

Cost–utility analysis and sensitivity analysis

On the basis of the cost data, utility data and clinical data, the cost–utility ratio was calculated as follows:

$$\mathrm{C/E\ ratio} = \text{total treatment costs} / \text{total number of QALYs per patient}$$

$$\text{Incremental C/E ratio} = \Delta\ \text{costs}/\Delta\ \text{QALYs}$$

$$\Delta\ \text{Costs} = \text{costs of alternatives} - \text{costs of standard chemotherapy}$$

$$\Delta\ \text{QALYs} = \text{QALYs of alternatives} - \text{QALYs of standard chemotherapy}$$

where 'alternatives' refers to paclitaxel, docetaxel and VM, and 'standard chemotherapy' refers to MV.

The calculation of C/E ratio for progression-free life years was calculated in the same way. A one-way sensitivity analysis was performed, including changing clinical efficacy, changing treatment costs by changing dose delivery and changing utility data.

Results

The basic model results on costs and QALYs are shown in Table 2. The life-years gained were 0.76 (paclitaxel), 0.76 (docetaxel), 0.85 (VM) and 0.70 (MV). With the average utility data 0.73 (response) and 0.39 (non-response), the total numbers of QALYs were 0.35, 0.34, 0.43 and 0.29, respectively. Costs of these four regimens were $10 594 (paclitaxel), $16 911 (docetaxel), $7359 (VM), and $4037 (standard therapy MV). The C/E ratios (costs/QALYs) obtained were $30 270 (paclitaxel), $49 739 (docetaxel), $17 114 (VM) and $13 922 (MV).

VM therapy represented relatively low costs and a higher number of QALYs. Docetaxel treatment was the most expensive treatment with a much lower effectiveness than those of its two alternatives. The MV standard therapy cost the least, but it also offered the least number of life-years and progression-free life-years gained.

The incremental results with MV as the standard comparator are presented in Table 3. The VM combination therapy showed the lowest incremental C/E ratio of $23 046/QALY, followed by paclitaxel ($99 547/QALY) and docetaxel ($256 304/QALY).

Data from different trials were used for the sensitivity analysis.[13,32,33] Table 4 shows that a higher response rate of paclitaxel treatment (e.g. 37%), lead to an increase of 32% to QAPFYs. Furthermore, it resulted in an increase of treatments costs of 12% and an increase of C/E ratio in terms of costs/QALY of 13%. When overall response rates were changed to 47%, the QAPFY values increased much more than the costs, which lead to a decrease of the costs/QAPFY ratio. When half of the docetaxel dose delivery is used[33], the total costs of treatment decreased more than 40%. However, the number of QAPFYs also decreased, i.e. by 17%.

In the baseline analysis, average utility data were used as input for the model. According to previous reports, utility values varied among different treatments and methods of evaluation. In order to investigate the impact of varying utility values on the C/E ratios, utility data of different treatments[22] and data from different evaluating methods[23] for the sensitivity analysis have been selected. The results of this sensitivity analysis supported that the utility value of the health outcome had an important impact on QALYs, QAPFYs and C/E ratios, and that this value affected the ranking of the C/E ratios directly.

Discussion

Paclitaxel, docetaxel and vinorelbine have proven to be effective agents in the treatment of MBC. VM is recently reported to be a new effective regimen for second-line chemotherapy. Previous studies compared paclitaxel or docetaxel to MV therapy, and compared paclitaxel or docetaxel to single-agent vinorelbine.[22–25] Still, no direct comparison among taxanes, and the combination therapies VM and MV has been performed.

In our study, the VM regimen showed a high level of QALYs and QAPFYs, with costs being less than 20% of the costs of docetaxel treatment. De Placido *et al.* administered VM therapy with G-CSF supporting treatment immediately in grade IV neutropenia patients.[29] Therefore, they achieved a high response

Table 3. Results of incremental cost–utility analysis

Strategy	ΔOverall costs ($)	ΔQALY	ΔC/ΔE ($)
Paclitaxel versus MV	6557	0.07	99547
Docetaxel versus MV	12873	0.05	256304
VM versus MV	3322	0.14	23046

Table 2. Basic results of the model

	Paclitaxel	Docetaxel	VM	MV
Life-years gained	0.7595	0.7591	0.8466	0.7008
Progress-free life years gained	0.3950	0.4458	0.5326	0.3241
Total costs per patient	$10594	$16911	$7359	$4037
Total QALYs	0.35	0.34	0.43	0.29
Total QAPFYs	0.19	0.23	0.29	0.15
Costs/QALY	$30270	$49739	$17114	$13922

rate without febrile neutropenia recurrence. In spite of the fact that G-CSF support increases the total cost of therapy compared to docetaxel and paclitaxel treatments, the increased costs are still limited. Docetaxel and paclitaxel achieved similar levels of life-years gained. However, docetaxel reached a higher number of progression-free life-years, resulting in a high level of QAPFYs. Nevertheless, high treatment costs are still the main cost generator of taxane therapy. We chose the low-dose docetaxel treatment for the sensitivity analysis, but the cost/QAPFY was not reduced due to a decrease of QAPFYs.

Limitations of our study could originate from three aspects. Firstly, model assumptions are unavoidable in decision analyses and cost–effectiveness analyses. We assumed that all of the febrile neutropenia patients would be hospitalized.[26] This tends to be the reason for the high costs of taxane treatments, as these treatments bring along higher levels of febrile neutropenia. In contrast, we did not take the cost of cumulative toxicity treatments into account, because of the lower relative costs. In addition, we assumed that patients in follow-up are not given any additional palliative treatments. However, the costs of some palliative treatments and supportive care may be high. This assumption may therefore lead to an underestimation of treatment costs, especially for those regimens with a lower number of QALYs.

Secondly, cost–utility analyses are used mostly when the quality of a health state is taken into account. Utility is one of the main parameters for this kind of analysis. Hutton *et al.* used utility values from an oncology nurses survey, whilst bias resulting from patient proxies is probably considerable.[23] Leung *et al.* achieved the utility values by performing questionnaire interviews to both healthy volunteers and breast cancer patients, which showed no significant difference.[22] However, utility values estimated by healthy volunteers still seemed to be higher than those reported by breast cancer patients. Some studies used the time-trade-off method to evaluate utility values, while others used the standard-gamble method.[22,23–25] Utility values gained by time-trade-off are usually lower than those gained by the standard-gamble method.[34] These different methods hamper comparisons between studies. In this study, we used a standard utility value for all of the four regimens instead of using different values for different regimens. This may be another weakness of our health outcome analysis. On the other hand, we may have avoided the bias between the various utility data sources, which may impact results importantly, as shown in our sensitivity analysis.

The third possible drawback is constituted by the lack of sufficient clinical efficacy data which influence the validity of probabilities directly. We used data from

Table 4. Sensitivity analysis results

Parameters	QALYs	QAPFYs	Total costs ($)	Cost/QALYs ($)	Cost/QAPFYs ($)
Baseline results					
paclitaxel	0.35	0.19	10594	30270	55758
docetaxel	0.34	0.23	16911	49739	73526
VM	0.43	0.29	7359	17114	25376
MV	0.29	0.15	4037	13922	26913
Efficacy of treatment					
paclitaxel					
ORR 37%[31]	0.39	0.25	12713	32597	50852
ORR 47%[13]	0.39	0.33	14307	36669	43336
docetaxel					
ORR 44%[32]	NA	0.19	9902	NA	52116
Costs of treatment					
docetaxel					
dose 60 mg/m^2 [32] (with ORR 44.4%)	NA	0.19	9738	NA	51253
Utility of life-year					
paclitaxel					
RR = 0.62, NR = 0.24[22]	0.25	0.18	10594	42376	58856
docetaxel					
RR = 0.51, NR = 0.17[22]	0.21	0.14	16926	80529	120793
VM					
RR = 0.80, NR = 0.41[22]	0.47	0.31	7359	15657	23739
MV					
RR = 0.53, NR = 0.41[23]	0.26	0.13	4037	15527	31054

ORR, overall response rate; RR, response rate; NR, non-response; NA, not applicable.

Table 5. Results of different studies

Study	Response (%)	TTP (weeks)	QAPFYs	Costs ($)	Cost/QAPFYs ($)
Leung *et al.* (1999)[22]					
paclitaxel	21	16.8	0.102	7877	77225
docetaxel	30	19	0.091	13161	14436
vinorelbine	16	12	0.104	4251	40875
Hutton/Brown (1996/1997)[23]			(utility)		
paclitaxel	21	NA	0.6619	17552	NA
docetaxel	47	NA	0.6964	16897	NA
MMC+VLB	15	NA	0.608	11045	NA
Launois *et al.* (1996)[24]					
paclitaxel	28.9	18	0.283	37119	131163
docetaxel	57.1	21	0.344	37016	107605
vinorelbine	16	12.9	0.187	38021	203321
Our results					
paclitaxel	29	18	0.19	10596	55758
docetaxel	33	19	0.23	16911	73526
VNB+MMC	45.4	26.6	0.29	7359	25376
MMC+VLB	12.3	11	0.15	4037	26913

TTP, time-to-progression; MMC, mitomycin; VLB, vinblastine; VNB, vinorelbine; NA, not applicable.

two phase III trials in order to increase the validity. Nevertheless, the absence of more data is still the main reason for the difficulties in conducting this type of analysis and establishing its reproducibility.

Furthermore, the positive result of the VM regimen in our study may have resulted from the general limitations of data from phase II trials. For instance, the response rate of VM is about 45%, a high level probably resulting from the limited number of patients in this phase II study. Consequently, this high level leads to high values of life-years, QALYs and a more favourable C/E ratio.

Table 5 presents a comparison of our data to previous analyses. Some reasons for the differences among studies were described before. Furthermore, Leung *et al*. interviewed 25 healthy volunteers and 25 breast cancer patients to gather utility data.[22] This tends to be more accurate for health outcomes evaluation than the other studies, but they only took the single vinorelbine into account because of the limitation of clinical data at that time. In the UK model, utility data were cited from a previous study in oncology nurses.[23] Although oncology nurses are more familiar with the health states of breast cancer patients, they may be less able to reflect the real quality of breast cancer patients' life. In addition, they mentioned that the routine use of hematopoietic growth factors did not reflect current practice in the UK and was therefore not taken into account in their study. However, this supporting treatment has been used in many clinical trials.[4–21] Similar to the UK model, the French study used nurses as patient proxies to estimate utility values.[24] Moreover, both the UK study and the French study presented docetaxel treatment as more cost-effective than the paclitaxel regimen, which is quite different from conclusions of the Leung study and our study. The reason could be the limitation of clinical efficacy data originating from before 1997. It has to be mentioned that we used the same clinical data sources of paclitaxel,[28] docetaxel and MV[27] as Leung *et al.*, although the values of response rates were obtained in a different way (Table 5). We only used data of second-line chemotherapy patients instead of the overall data of the total group.

Summarizing, we conclude that VM represented lower treatment costs of $7359 with the highest number of QALYs of 0.43 in the second-line chemotherapy for metastatic breast cancer patients. It also yields the best incremental cost–effectiveness ratio as compared to single-agent docetaxel and paclitaxel. The high response rate reported in a single phase II study may, however, have influenced this result.

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