ORIGINAL RESEARCH ARTICLE

PharmacoEconomics 1996 Nov; 10 (5): 504-521
1170-7690/96/0011-0504/$09.00/0

A Cost-Utility Analysis of Second-Line Chemotherapy in Metastatic Breast Cancer

Docetaxel versus Paclitaxel versus Vinorelbine

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Summary

The aim of this study was to determine the incremental effectiveness, the incremental health-related quality of life (differences in quality-adjusted progression-free survival between treatments), the incremental cost and the incremental cost-effectiveness and cost-utility ratios, for docetaxel, paclitaxel and vinorelbine, when these drugs were used as second-line treatment in patients with metastatic breast cancer.

In the absence of comparative direct evidence of the relative efficacy of docetaxel, paclitaxel and vinorelbine in this setting, a model was designed to determine the effects of the 3 interventions on health outcome and cost. A Markov process model, based on 53 disease states, was thus constructed to evaluate the socioeconomics of the 3 treatment regimens.

The model allows assessments from the start of second-line chemotherapy until death. Costs were evaluated from the combined view of the healthcare system and the patient. Direct nonmedical and indirect costs were excluded. Consumption per episode of care was estimated by retrospective analysis of 153 medical reports from 5 different hospitals. Hospital costs were allocated values from the national accounting costs by diagnosis-related group (DRG). The content of the health states was based on the multiattribute health states classification system (MASH). Preference values were assigned by application of a standard reference lottery using 20 oncological nurses as proxies for the patients. The health-related quality-of-life score was used as a quality adjustment weighting factor to calculate quality-adjusted progression-free survival associated with the 3 different regimens.

Docetaxel reduces the time spent in progression, decreases the number of complications due to progressive disease and thereby provides better quality of life. It provides a benefit of 57 disease- and discomfort-free days compared with vinorelbine and 22 days compared with paclitaxel.

Docetaxel may be thought of as self-financing as a result of savings in hospital admissions, providing net savings of 6800 French francs (FF; 1993 values)

compared with expenditure associated with vinorelbine treatment and FF700 compared with the equivalent figures for paclitaxel.

With an annual incidence of 26 000 new cases in France and an internationally standardised incidence rate of 75.5 per 100 000, breast cancer is the most common malignancy in French women, accounting for almost 20% of all cancers in women.[1] It is also the major cause of death in women: of the 55 665 women who died from cancer in France in 1990, almost 20% (10 173) died from breast cancer.[2] Although the disease can often be controlled locally with surgery or radiotherapy, more than one-third of women with breast cancer still die from metastases.

The annual incidence of metastatic disease can be measured: the ongoing French survey of malignancy[3] reports a rate of metastases of 13% at the outset of the disease, equivalent to 3400 patients. CIRCAN, a French cancer information centre, reports a relapse rate of 50% at 10 years, 75% of which are associated with metastases.[4] The number of new cases of metastatic relapses may thus be estimated at approximately 10 000 per year. This represents a total of 13 400 new cases of metastatic malignant breast disease annually in France.

Although metastatic breast cancer is a major public health issue and is associated with high management costs, no pharmacoeconomic evaluations[5] have been undertaken in patients with this condition. Cost-effectiveness analyses have been used to determine the relative merits of different adjuvant therapies[6] in pre- and postmenopausal women, and have evaluated the utility of new adjuvant chemotherapy[7] in hormone receptor–negative women without lymph node involvement. Only 2 publications,[8,9] both examining a medical procedure (autologous bone marrow transplantation in postmenopausal women), describe stage IV (metastatic) breast cancer.

The lack of work in this field is undoubtedly the result of the paucity of available medical information. The relative merits of the different adjuvant treatments and alternative forms of therapy for the primary tumour have been evaluated systematically in many randomised trials. The same techniques have been used to standardise first-line treatment for metastatic disease, with anthracycline-based regimens predominating in France. Second-line treatment, however, remains broadly empirical. Clinicians are in the process of testing new drugs in phase II trials, either alone or in multiple combinations and/or doses, and new administration methods. The availability of new treatments, particularly docetaxel and paclitaxel, brings the promise of greater effectiveness but also higher costs. These agents also have toxicity profiles that need to be traded-off and documented.

What is the impact of these new chemotherapy treatments? Are the more effective drugs associated with more adverse effects? What is the impact of these treatments on cost? Do higher acquisition costs of treatment mean that the drugs are more likely to delay relapse because of a higher response rate and longer response time? These questions cannot be answered in terms of survival until it has been demonstrated scientifically that an increased response rate is associated with longer life. We can, however, evaluate the extent to which quality of life may differ depending on the chemotherapy regimen chosen for the same quantity of life. This is the reason for choosing a cost-utility approach in this study.

It is clear that the validity of a comparison between docetaxel and other chemotherapies is determined by the appropriateness of the choice of the reference agent(s). If the choice is not considered to be acceptable by the scientific community, no difference in efficacy, toxicity or costs will be credible. There is no problem in comparing docetaxel with the most recent compound, paclitaxel, which is the latest drug to have been registered for metastatic breast cancer. Identification of the most widely used drug is, however, not so straightforward.

In France, there are many possible reference drugs. An evaluation of practice undertaken by

ourselves[10,11] demonstrated that vinorelbine was used, either alone or in combination therapy, in 56% of second-line protocols. As the effectiveness of combinations based on vinorelbine, paclitaxel or docetaxel is not currently known, it is reasonable to compare the single drug therapies among themselves. Vinorelbine was therefore chosen as the second reference drug.

At this stage of product development, no phase III trials have compared the different treatments directly. Their respective merits and costs were therefore compared indirectly, using clinical decision analysis methods.[11,12] This type of instrument, designed to assist decision-makers manage uncertainty, is needed as it is not clear how the probabilities of clinical events interlink and because the robustness of medical data from phase II clinical trials is not known.

Methods

Therapeutic Strategies

The aim of this study was to compare the medicoeconomic consequences of different treatments that are currently acceptable for metastatic breast cancer and for which the regimens are now clearly defined. The regimens were:

- intravenous docetaxel 100 mg/m^2 repeated every 3 weeks (premedication: oral dexamethasone 8mg twice daily for 5 days);
- intravenous paclitaxel 175 mg/m^2 repeated every 3 weeks (premedication: oral dexamethasone 20mg twice daily, intravenous diphenhydramine 50mg and intravenous ranitidine 50mg);
- intravenous vinorelbine 30 mg/m^2 weekly (no premedication).

We assumed that no more than 6 courses of chemotherapy with taxoids were administered, whereas vinorelbine treatment is continued until the disease progresses.[13]

We endeavoured to follow the patient's course through the various clinical stages that characterise the natural history of the disease and its treatment for each of the 3 drugs. These were defined using 2 criteria: type of response (complete response, partial response, no change, disease progression) and the nature of toxicity.

Adverse reactions common to docetaxel, paclitaxel and vinorelbine may be either minor or major. Minor reactions were assumed to be grades 0, 1 and 2 toxic reactions of the WHO classification:[14] nausea/vomiting, alopecia, hypersensitivity reaction, infection without neutropenia. Major reactions include both febrile neutropenia leading to hospital admission and patients developing neutropenia who did not require hospitalisation.

Each cytotoxic drug also has its specific toxic reactions: skin reaction for docetaxel, arthralgia/myalgia for paclitaxel, and gastrointestinal problems (constipation) for vinorelbine. Specific toxic reactions were categorised along with the minor toxicities and were graded 0, 1 or 2. They were grouped separately when they reached or passed grade 3.

Cumulative toxicity may occur alongside acute toxicity after administration of 3 or 4 chemotherapy courses. The main problems of this type are oedema for docetaxel and neurotoxicity for paclitaxel. Vinorelbine is not associated with cumulative toxicity. Severe toxicity, common to all treatments or specific to one of the individual treatments, must be added to 'minor' toxicities which occur with all chemotherapy treatments.

The Model

Each clinical state is associated with a treatment response that carries a cost for the payer and that, for the patient, leads to either deterioration or improvement in functional capacity, measured in terms of autonomy and social participation. The contribution from each clinical state towards cost and overall treatment benefit is determined by the time spent in each of these states. We thus sought to determine the overall impact of the different treatment approaches from the start of second-line chemotherapy until death. To this end, a Markov model was constructed to simulate the course of patients following each of the treatments, in order to evaluate expected cost and benefits to the patients.

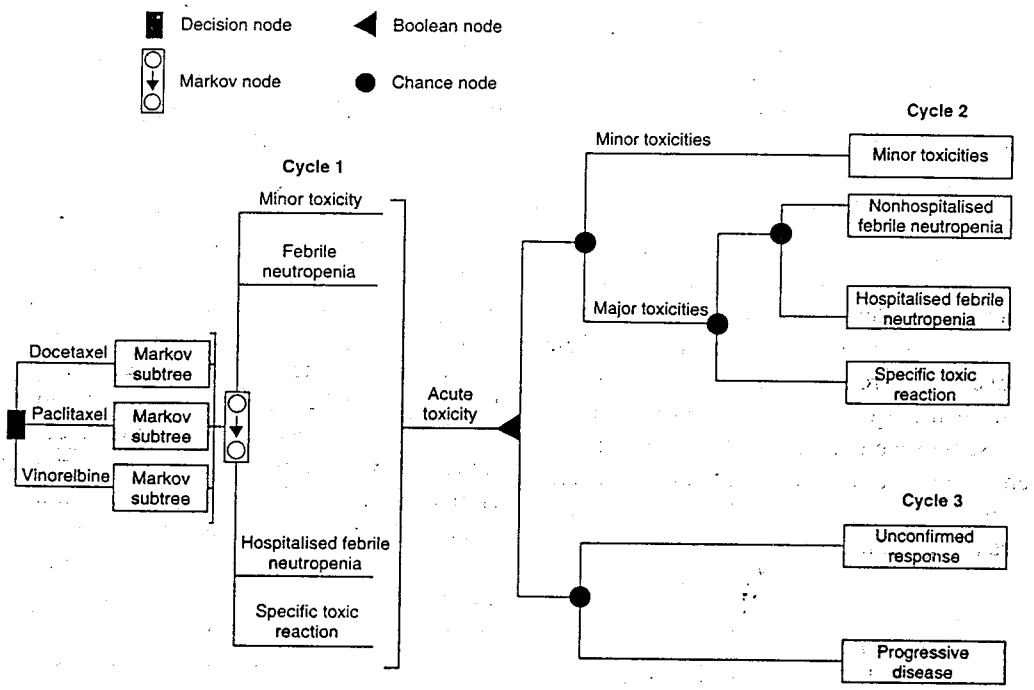

Fig. 1. Potential health states for the first 3 cycles of chemotherapy. The Markov node symbol (arrow bracket) indicates that the same subtree was used for each branch of the decision analysis. To simplify the Markov cycle tree, the overall acute toxicities were distributed over the first 2 cycles; the cumulative toxicities that appeared after cycle 3 are not shown in this figure. Specific toxic reactions were: skin reaction (docetaxel), arthralgia/myalgia (paclitaxel) and constipation (vinorelbine).

and to confirm the robustness of conclusions that may be drawn from such a comparison.

Given the complex and long-lasting therapeutic and pathological follow-up of the patients, the Markov model appeared to be particularly suited to second-line metastatic breast cancer. This kind of model provides an efficient method for capturing risk that is continuous with time and events that may occur more than once, or utilities that depend on the timing of events.[12] Using this model instead of a conventional decision tree would then give a more acute and realistic evaluation of medical care.

Markov models assume that a patient is always in one of a finite number of discrete health states, called Markov states. All events are represented as transitions from one state to another.[12] A representation of Markov process may be illustrated simply by a series of probability trees, linked between each other.[15]

In this study, the considered time interval was from the start of second-line treatment until death. This was subdivided into equal time intervals of 3 weeks, which are called cycles. Patients entered the model and were given one of the 3 treatments (docetaxel, paclitaxel or vinorelbine). Figure 1 shows, as an example, potential health states integrated in the model for the 3 first cycles of chemotherapy.

During cycle 1, different toxicities could occur before responses appear, either the usual minor toxicities resulting from this type of treatment, or major toxicities. These include febrile neutropenias that do not require hospitalisation or that threaten the patient's life and require hospitalisation, and the specific toxicities of each agent. Thus,

a patient can be in one of the following 4 health states:

- minor toxicity;
- nonhospitalised febrile neutropenia;
- hospitalised febrile neutropenia;
- specific toxic reaction.

The 4 types of toxic reaction that could occur during cycle 1 may recur in cycle 2. Patients who experienced only minor toxicity in the first cycle could continue to tolerate treatment during the second cycle. The reverse situation could, however, occur. Severe toxic reactions could develop in patients who had not experienced them previously. Also, the same severe adverse effects could recur in patients who experienced major toxicity in cycle 1. Other patients who had suffered severe toxicity during the first cycle may not do so in the next cycle, but may develop another equally severe toxic reaction of a different type. Serious adverse events may be followed later by minor toxicity.

At the end of cycle 2, a first evaluation enabled the practitioner to identify responses. Patients who were identified as unconfirmed responders or those who were stable continued treatment into the third cycle.

Chemotherapy continued into the fourth cycle for those patients who responded to the previous cycle and for patients who remained clinically stable regardless of whether they experienced cumulative toxicity (fluid retention with docetaxel, peripheral neuropathy with paclitaxel). The second evaluation took place, as in usual practice, at the beginning of the fifth cycle: either the response was confirmed, or a stabilisation of disease was observed.

Fluid retention and serious problems associated with docetaxel occasionally require treatment to be interrupted. The model was constructed in order to take this into account, although in reality, this problem largely disappears when all patients are routinely premedicated. The model was considerably simpler in the case of vinorelbine and paclitaxel. Vinorelbine has no cumulative toxic effects, while paclitaxel may cause severe neurotoxic effects. The results of the final analysis of the Bristol Myers Squibb Taxol Study Group (BMSTSG) study, presented in 1993 to the Oncologic Drugs Advisory Committee (ODAC), did not include the tolerability data.[16,17] In the intermediate results, no cases of treatment withdrawal due to neurotoxicity were reported, so it was assumed that none occurred.

If treatment was stopped because of major cumulative toxicity, chemotherapy was not resumed. Even without treatment, the patient could continue to bear the effects of cumulative toxicity and remain in the same state until these toxic effects disappear. The average time for oedema resolution is between 18 and 25 weeks, or 6 to 8 treatment cycles. The model assumed that major cumulative toxicities could appear during the fourth, fifth or sixth cycle, or would not occur at all. Patients who did not experience major toxicity, disease progression or death continued treatment until the planned end of chemotherapy. Response or stable disease could be maintained after the end of chemotherapy without treatment or toxicity, or could develop into progressive disease.

Thus, the model took into account no fewer than 53 Markov states (20 for docetaxel, 19 for paclitaxel, 14 for vinorelbine) that corresponded to the different clinical criteria: responses, toxicities and complications of the disease.

Clinical Data

The data currently available for docetaxel consist of results from the drug registration master file, i.e. pooling[18] of 3 phase II trials recently published.[19-21] For paclitaxel, we used the interim results of the BMTSG trial.[16,17] Finally, vinorelbine data were taken from the trial conducted routinely in a clinical department by Degardin et al.[13]

The pooled docetaxel data are taken from the registration dossier which included 111 pre-treated patients having received prior chemotherapy either as an adjuvant, as a first-line treatment, or both. Of these, 91 were evaluable; 90% had received previous chemotherapy for metastatic disease and 75% were considered anthracycline-resistant. Anthracycline resistance is defined as relapse within 1 year after the end of the adjuvant treatment or

Table I. Summary of clinical trial results for docetaxel, paclitaxel and vinorelbine used as second-line treatment in patients with metastatic breast cancer

Variables	Docetaxel 100 mg/m² (n = 91)	Paclitaxel 175 mg/m² (n = 117)	Vinorelbine 30 mg/m² (n = 100)
Efficacy			
Objective response (%)	57.1	28.9	16.0
Duration of response (wk)	28.0	28.0	21.0
Time to progression (wk)	21.0	18.0	12.9
Main toxicities (WHO groups 3-4) [%]			
Febrile neutropenia	17.9	2.0	3.0
Arthralgia	0	16.0	0
Severe fluid retention leading to interrupted treatment	1.9	0	0
Severe fluid retention with no interruption of the treatment	2.9	0	0
Severe neurotoxicities	0	6.0	0

Abbreviation: WHO = World Health Organization.

progression after response or no change during treatment.

The BMSTSG study[17] compared 2 dosages, 135 and 175 mg/m², in patients with metastatic breast cancer who had previously received one chemotherapy regimen either as an adjuvant or for metastatic disease, or 2 regimens, one adjuvant and one for metastatic disease. 471 patients were included, of whom 235 received the actual recommended dosage (175 mg/m² over 3 hours). At the time of the socioeconomic study, combined efficacy and tolerability data for this dosage were only available for 123 patients; these data were presented at the ODAC meeting in 1993.[16] We therefore based our model on this population. The final report has been published recently.[22] Results for the main criteria (response rate and time to progression) remained unchanged. The clinical characteristics of the 117 evaluable patients were as follows: 27% had received no prior treatment for metastatic disease and 20% were classed as anthracycline resistant (17% in the final analysis). Anthracycline resistance was defined as progressive disease under treatment or relapse within 6 months after the end of adjuvant therapy.

For vinorelbine, all patients in the Degardin clinical series[13] were anthracycline resistant. The study included 100 patients with metastatic breast cancer treated with second- or third-line chemotherapy. All patients were treated and evaluable.

The initial assumptions regarding confirmed response, median duration of response and median time to progression based on the above data, are shown in table I. As no relationship has been demonstrated between response rate and survival, the median survival time was assumed to be 12 months for each of the cytotoxic drugs.

The toxicity transition probability Pi for a period i was estimated from the observed cumulative probability between times t_o and t_j [$P(t_0,t_j)$] according to the following expression:[23,24]

$$Pi = 1 - [1 - P(t_o,t_j)]^{1/j}$$

where j is the number of time intervals i.

Probabilities of progression were calculated from the 'time to progression' for the unconfirmed responders and from the median response time for the confirmed responders, assuming progression occurs in a declining exponential fashion.[25]

The relapse rate per cycle (μ) was then converted into the transition probability per cycle (Pi) using the following equation:

$$Pi = 1 - \exp^{-\mu}$$

Measurement of Costs

All calculations were made from the point of view of the National Health Insurance and the

patients themselves, i.e. a society-based perspective restricted to the health sector. Transfer payments, direct nonmedical and indirect costs were excluded from the analysis. The direct medical costs were calculated using a standard cost method. Standard costs are defined as the product of a standard quantity and a standard price.

To evaluate the standard quantity, we conducted a retrospective study in 5 different hospitals. 153 case records from patients treated with a second-line therapy for metastatic breast cancer were examined in order to estimate the mean number of related procedures and hospital admissions. Six major classes of treatment were distinguished:

- second-line treatment;
- follow-up assessment for responders;
- management of toxicity;
- management of metastatic complications;
- third-line treatment;
- palliative end-of-life treatment.

We chose to categorise these interventions into 3 management groups depending on the clinical events which triggered them:

- the first group (treatment and follow-up) included hospitalisation and primary care associated with administration of chemotherapy and follow-up of the treatment;
- the second group (treatment-related complications) included hospitalisation and outpatient care required to manage toxic reactions;
- the third group (disease-related complications) included all care prescribed for the treatment of the complications of cancer.

87 different treatment procedures were identified in the 153 patient case records and thereafter distributed between the 6 classes.

Procedures were then classified according to the relevant charges scales: Nomenclature Générale des Actes Professionnels (NGAP),[26] Nomenclature des Actes de Biologie Médicale (NABM)[27] and Nomenclatures des Groupes Homogènes de Malades (diagnostic-related groups; DRGs).[28,29] The first 2 systems are relative value scales for community care. They describe medical services using key letters, according to consumption: C = general practitioner contact, CS = specialist contact, B = laboratory tests, Z = radiology investigation. Each key letter has a monetary value which has a variable coefficient according to the technical complexity of the procedure. To identify hospital-consumed resources, the French DRG classification[28,29] was used. The DRGs are groups of similar hospitalisations, both in terms of diseases managed[30] and the mobilisation of hospital resources. Each hospital admission is categorised into one DRG only.

Overall, the 87 clinical procedures were distributed among 39 administrative charge categories, 16 of which related to the NGAP and NABM classifications and 23 to hospital DRGs classification. The number of cases per key letter and per DRG were counted. The distribution of DRGs by treatment group showed that DRGs 254, 573 and 603 appeared only in the 'treatment-related complications' group, 12 DRGs (14, 114, 118, 213, 295, 296, 304, 336, 339, 343, 804, 806) appeared only in the group representing 'treatment of metastatic complications', whereas 8 DRGs belonged simultaneously to the 3 management groups previously defined (388, 592, 593, 571, 681, 682, 809, 816).

Outpatient medical procedures were allocated values and costs from the NGAP and NABM. In primary care, tariffs of reimbursement have been chosen as they are a relatively good reflection of the real cost. In this type of cost 1993 NGAP and NABM values have been used for the key letters: C = FF100, CS = FF140, Z = FF10.35, B = FF1.76. The hospital daily charge for each ward does not reflect the actual cost, and therefore was not used. DRGs provides the only reliable information in this field as they enable measurement of the 'per product' cost, taking into account both the nature and the severity of the illness. DRGs were allocated economic costs from the results of the most recent national cost survey.[31] This survey used analytical accounting data collected in 1993[32,33] from 22 hospitals (including 7 teaching hospitals and 3 cancer centres, 450 000 case records and 17 analytical accounting headings).

Three types of costs were available (full cost, direct total cost and direct variable medical cost)

Table II. Breakdown of diagnostic-related group (DRG) costs (1993 French francs) in patients with metastatic breast cancer (hospital setting). The 2 rows in bold type emphasise the most relevant DRGs in chemotherapy treatment

DRG code	DRG	Full cost per DRG[a]	Direct total cost per DRG[b]	Variable medical cost per DRG[c]
14	Cerebral metastases	27 298	26 129	5 634
114	Thoracic nonmajor surgery	65 792	63 683	19 765
118	Pulmonary embolism	33 509	32 221	8 701
213	Colectomy	68 287	66 081	24 837
254	Intestinal occlusion	20 991	20 145	5 124
295	Major surgery of joints	49 206	47 709	22 604
296	Nonmajor surgery in lower limbs	39 155	37 605	12 478
304	Upper limb surgery	33 458	32 123	10 822
336	Hip fracture	21 486	20 435	3 927
339	Pathological fracture	25 641	24 667	6 652
343	Metastatic medullary compression	13 171	12 644	3 198
388	Malignant breast tumour age >69 years and/or complications and/or comorbidity	22 331	21 284	4 924
571	Anaemia	20 524	19 703	6 493
573	Thrombocytopenia	21 683	21 034	7 327
592	Radiotherapy and surveillance	20 517	19 644	5 357
593	**Chemotherapy and full time hospitalisation**	**15 186**	**14 656**	**5 437**
604	Septicaemia	32 695	31 380	8 396
681	**Chemotherapy daycare hospital**	**2 809**	**2 684**	**1 352**
682	Radiotherapeutic session	1 165	957	15
804	Ambulatory treatment of respiratory tract disease without operating procedure	3 530	3 450	1 610
806	Ambulatory treatment of digestive tract disease without operating procedure	3 570	3 454	1 596
809	Ambulatory treatment of malignant tumour without operating procedure	3 745	3 663	1 992
816	Ambulatory treatment of haematopoietic diseases without operating procedure	3 308	3 229	1 668

a The full cost includes all expenses incurred by DRG, capital outlays included.

b The direct total cost reflects all costs, apart from capital outlays which are due to decisions taken which cannot be reversed.

c The direct variable medical cost reflects only those charges from variable factors which are immediately affected by choosing a given treatment: consumable, radiology, functional investigations, laboratory and other procedures, and anaesthesia. This definition therefore excludes fixed medical costs, logistics costs and capital costs.

[see table II] but the results presented in this article are based on the direct total costs estimate.They reflect all costs, apart from capital outlays, which are linked more with amortization of the hospital building than with the patient treatment cost. In order not to bias results towards docetaxel, the chosen acquisition cost for this study was set at the same level as that of paclitaxel, FF9400 per cycle (1995 launch price).

An incidence-weighted cost per treatment procedure has been calculated weighing either the NGAP tariff charges by the number of key letters counted or the direct unit costs per DRG by the number of patient admissions per DRG. These figures represent the follow-up costs for a cohort. The cohort cost was divided by the number of patients and then by the length of the observation period. The costs per day were finally multiplied by the length of the Markov cycle (21 days) to obtain the cost per patient and per cycle.

Grouping costs by clinical condition and types of treatment determines how, and at what cost, patients are managed. It enables expenditure to be predicted by clinical states according to the nature of the health interventions required and the time spent in these states. The total amount spent on healthcare as a result of the treatment can also be calculated across clinical states according to the various possible clinical events that may occur and their attendant costs: the cost of the treatment *plus*

the cost of the treatment-related complications *minus* the cost of disease-related complications averted as a result of the procedure. Two analyses are thus made possible, costs per clinical state and costs per management group.

Estimating Quality of Life

As it is very difficult in this stage of the disease to show improved survival resulting from chemotherapy, we evaluated the extent to which quality of life differed depending on the chemotherapy regimen used, for the same quantity of life.

Quality-of-life evaluation supposes that we are able to describe the hardships experienced and establish a judgment concerning the relative repercussions of the adverse events of treatment. It inevitably includes a descriptive aspect (the intensity of the physical, psychological and social effects experienced) and a normative aspect (the individual's assessment of his or her own experience).[34]

Health state descriptions were based on the Multi-Attribute Health Status Classification System (MAHS).[35] Initially, 5 generic dimensions from the MAHS classification (ambulation, dexterity, emotion, cognition and pain/activities) and 1 dimension borrowed from mark II system [36] (personal care), were selected by an expert panel on quality of life assessment (MEDTAP). They took advice from English and American clinicians and added 6 further specific dimensions (fear/anxiety, depression, energy, hair loss, pain relief and nausea) making a total of 12 dimensions. The health state descriptions for each clinical state were described by 12 dimensions with 3 to 6 intensity levels per dimension.

On this basis, the health state descriptions prepared for Great Britain and North America were translated into French and referred to 5 medical doctors and 3 oncology nurses to assess face and content validity. Changes were made concerning the number of dimensions, the number of levels by dimension, the wording of the questions and the level of functioning retained to characterise the various clinical states of the model. For instance:

- The pain dimension was rewritten, as the initial description was considered to be too complex, involving intensity, frequency, duration and the type of drug treatment.
- The depression dimension was considered to be irrelevant by clinicians and was withdrawn (the clinicians believed that depressive features could occur both in responders and in non-responders and that it was much more related to the patient's personality than to the types of treatment administered).
- The same judges were then instructed to rate the various clinical states on one of the available levels for each dimension (at this stage, some levels selected by MEDTAP were modified).
- Finally, the French health state descriptions were different in structure and content to the English version, to take into account the French specificities.

Health-related quality-of-life (HRQL) coefficients were measured via a survey of 20 nurses at 3 sites [2 hospital sites (Lille and Villejuif) and one outpatient site (Santé-Service)] using the standard gamble method.[37,38] Weighting factors obtained by this method were used to calculate expected progression-free survival adjusted for quality of life. Markov calculations were performed with the decision analysis software program SMLTREE version 2.99 (JP Hollenberg, New York, NY, USA) and on Microsoft Excel (Microsoft Co, Redmond, WA, USA).

Sensitivity Analysis

The performance of drugs at this stage of development is still highly uncertain. What happens if they fail to live up to expectations? In order to answer this question, we varied the response rates, the median time to progression, the median duration of response, the adverse event rates and costs, restricting the range of possibilities to the results of the clinical trials that have been published.

Results

Observed and Expected Costs

The model enabled the expected costs of a patient to be estimated from the start of second-line treatment until death.

Costs per Type of Treatment

Chemotherapy Treatment

Case records were analysed for 146 patients who were evaluable for response (they received at least 2 courses of chemotherapy); 7 patients were withdrawn due to early progressive disease (progression occurring before the second cycle). For the costing study, retrospective data on chemotherapy were collected only during the treatment period (mean follow-up 114.87 days). Admissions to hospital for treatment were distributed between 10 DRGs. Two of 10 DRGs [DRG 593 (chemotherapy as full-time hospitalisation) and DRG 681 (out-patient chemotherapy)] accounted for 80% of the patients treated, or 1179 admissions. The 8 other DRGs were due to admissions for disease staging, laboratory tests and implantable drug delivery systems. Out of these 1179 admissions for chemotherapy, 1044 (88.6%) were outpatients and 135 were full hospital admissions. The direct costs of these 2 management approaches were FF2684 and FF14654, respectively (table II). The mean incidence-weighted chemotherapy cost was FF5986, of which FF3509 accounted for outpatient care and FF2477 full-time hospitalisation (table III). Chemotherapy involving full-time hospitalisation cost approximately 5 times more than that involving outpatient care. As the former approach was chosen slightly less than 1 in 12 times during the series studied, the mean cost per patient treated was less than the cost of outpatient admissions which were more common.

When docetaxel or paclitaxel (which each required 1 day of hospitalisation) was substituted for the existing cytotoxic therapy, the administration of which involved both day and full-time hospitalisation, the cost of chemotherapy treatment fell from FF5986 (the incidence-weighted chemotherapy cost) to FF2684, equivalent to a gain of FF3302 (table III).

Table III. Estimate of chemotherapy treatment costs (1993 French francs)

Item	Observed cohort cost of treatment	Estimated taxoid cost of treatment
Day hospital admission (DRG 681)	3 509	2 684
Full-time hospitalisation (DRG 593)	2 477	
Subtotal 1		
Incidence-weighted chemotherapy cost	5 986	2 684
Incremental acquisition cost of taxoids		7 213
Subtotal 2		
Actual cost of chemotherapy	5 986	9 897
Cost of other DRGs	754	754
primary care procedures	160	160
transport	418	418
Subtotal 3		
Tariff costs for other care	1 332	1 332
Total 1 + 2 + 3 treatment cost	**7 318**	**11 229**

Abbreviation: DRG = diagnostic-related group.

Conversely, whereas 3 ampoules of vinorelbine (sufficient for 1 course) cost FF2187, the costs of paclitaxel and docetaxel were FF9400 per course. The incremental acquisition cost of docetaxel or paclitaxel was therefore FF7213, assuming that the cost of chemotherapy sessions with docetaxel/paclitaxel were equal. After including all the other costs (the cost of other DRGs, primary care procedures and transport), the use of taxoids increased the treatment cost from FF7318 to FF11229, i.e. an increase of FF3911 per course (table III).

Follow-Up for Responders

20 case records drawn at random from patients who responded or had stable disease were followed from the end of second-line treatment until the start of a third-line treatment. The mean observation period was 219.9 days. 99 outpatient and 18 inpatient assessments were performed during this period. Total hospital costs for the cohort were FF745 700. Outpatient costs were FF31 700, half of these were incurred because of specialist appointments. FF107 300 was spent on patients' transport. Total management

costs for the cohort were FF884 700 or FF4225 per patient per cycle.

Toxicities

Out of the 146 patients, only 93 presented with toxicity. Data were collected over 112.71 days. 381 episodes of minor toxicity were found, 237 of which were managed on a fee-for-service basis and 144 of which resulted in chemotherapy sessions being postponed. Examinations used in making this decision were counted under DRG 816 (outpatient session without operative procedure for haematopoietic organ and bone marrow disorders). Total costs of care in the cohort were FF528 616 or FF1059 per patient per cycle.

The costs of managing nonhospitalised febrile neutropenia were calculated from 17 case records of patients followed for a period of 187 days. For 13 of the 17 cases, hospitalisation was postponed. A total of FF47 421 was spent, equivalent to a cost of FF313 per patient per cycle.

The costs of patients hospitalised with neutropenia were 10 times higher than those not hospitalised. Seven cases of septicaemia were found over a follow-up period of 48 days. FF227 402 was spent on these patients, equivalent to a cost of FF14 171 per patient per cycle.

The costs of gastrointestinal toxicity in the 3 patients who were followed for a mean duration of 64 days were FF85 000. These patients were admitted to hospital with subacute intestinal obstruction. Mean costs per patient per cycle were FF9250.

Costs of other specific acute or cumulative toxicities (skin toxicity and oedema for docetaxel, arthralgia/myalgia and neuropathy for paclitaxel, and constipation for vinorelbine) were negligible, since they did not lead to any hospital admissions.

Disease Complications

The cost of complications of the disease depends on the response to treatment: disease progression is associated with a larger number of complications of cancer which, in turn, is associated with higher costs, whereas the reverse is seen in responders. This assumption, which is entirely logical, is supported by results obtained from our data. Of the 146 patients evaluable for response, 93 were in 'progressive disease', 16 were responders, 33 were stable and 4 died. The mean patient costs per cycle for complications of disease in these 3 groups were FF61 in responders and FF199 in those with stable disease, but increased to FF932 if the disease progressed.

Total Expected Costs

Total medical costs were defined either as the overall cost for each state of health multiplied by the probability of being in that state, or as the sum of costs calculated by management groups (treatment, complications of treatment, complications of the disease) weighted by their probabilities. In each case, these are projected costs, the value of which reflects all expenditure from the start of second-line chemotherapy to death.

Projected costs from the start of treatment to death, after taking into account the incremental acquisition cost of taxoids, are as follows: docetaxel FF250 400, paclitaxel FF251 100, vinorelbine FF257 200.

The basic cost of treatment and follow-up with docetaxel is higher than with vinorelbine or paclitaxel. However, this incremental cost, FF34 400 higher than vinorelbine and FF7700 higher than paclitaxel (table IV), merely reflects the cost of its improved efficacy as a larger number of responders

Table IV. Incremental cost of treatment (in 1993 French francs) with docetaxel compared with paclitaxel and vinorelbine

Costs	Docetaxel *vs* vinorelbine			Docetaxel *vs* paclitaxel		
	docetaxel	vinorelbine	incremental cost	docetaxel	paclitaxel	incremental cost
Treatment and follow-up	61 300	26 900	34 400	61 300	53 600	7 700
Treatment-related complications	20 700	22 700	−2 000	20 700	19 200	1 500
Disease-related complications	168 400	207 600	−39 200	168 400	178 300	−9 900
Total	**250 400**	**257 200**		**250 400**	**251 100**	
Net medical cost			**−6800**			**−700**

or confirmed responders remain on docetaxel treatment.

The additional costs associated with using docetaxel are compensated by large savings produced by avoiding complications due to metastases or by lowering the incidence of progression seen with the 2 reference drugs (FF39 200 lower than vinorelbine, FF9900 lower than paclitaxel). This reflects the better response rate of docetaxel compared with the other study drugs, vinorelbine and paclitaxel (57.1 *vs* 28.9 and 16%, respectively) whereas the probability of relapse (derived from the time to progression) is lower (15.9 *vs* 20.6 and 41.3%, respectively).

Using docetaxel delays progression of the disease without prolonging survival. As none of the 3 drugs had been shown to be superior in terms of longevity, the assumption of an identical median survival period of 12 months for each of these 3 drugs appears to be reasonable and conservative. By reducing the time spent in progression without extending life, docetaxel reduces the number of complications that result from progression of the cancer and the length of the third- and fourth-line salvage therapy periods. Costs are thereby reduced.

Overall, the additional costs associated with using docetaxel instead of vinorelbine are lower than the savings that it produces. Thus, the medical cost of docetaxel is negative; using it leads to savings of approximately FF6100 compared with the costs of using vinorelbine and FF700 compared with those of paclitaxel.

Table V. Classification of utilities as a function of state of health (French model)

State of health	HRQL coefficients
Before starting chemotherapy	0.86
Minor toxicities	0.76
Severe skin reactions	0.72
Severe arthralgia/myalgia	0.72
Febrile neutropenia without hospitalisation	0.66
Early progression	0.52
Gastrointestinal toxicity with hospitalisation	0.48
Febrile neutropenia with hospitalisation	0.47
Confirmed responder	0.81
with severe oedema	0.74
treatment interrupted for severe oedema	0.64
treatment interrupted for severe neuropathy	0.64
with severe neuropathy	0.57
Stable	0.75
with severe oedema	0.73
treatment interrupted for severe oedema	0.58
treatment interrupted for severe neuropathy	0.58
with severe neuropathy	0.50
Progression	0.65
treatment interrupted for severe oedema	0.58
with severe oedema	0.53
with severe neuropathy	0.50
treatment interrupted for severe neuropathy	0.45
Terminal care	0.25

Abbreviation: HRQL = health-related quality of life.

Utilities and Quality-Adjusted Disease-Free Survival

States of Health and Quality of Life

Analysis of utility according to response closely reflects the positive impact of a confirmed response (0.81) and the negative impact of stable disease (0.75), and more importantly, of progression (0.65) and early progression (0.52) [see table V].

These results clearly demonstrate the interaction between response and toxicity in a patient's view of quality of life: cumulative toxicity is tolerated better if the patient responds to therapy. If the patient develops oedema, for example, quality of life remains relatively high in a responder (0.74) or stable patient (0.73), whereas it falls to 0.58 in a patient with progressive disease. Similarly, development of neuropathy is a powerful negative factor when associated with lack of change or disease progression (0.50) whereas it is better tolerated in responders (0.57) [table V].

Expected Utility

Three subgroups of states of health were identified depending on whether they related to acute or cumulative toxicity, remission time or progression.

The remission time was calculated by simple addition of the times spent in states of health without symptoms or toxicity (TWiST) and the time during which patients were exposed the to acute or cumulative effects of toxicity. This procedure

Table VI. Quantity- and quality-of-life increment with docetaxel compared with paclitaxel and vinorelbine

Parameter	Docetaxel *vs* vinorelbine			Docetaxel *vs* paclitaxel		
	docetaxel	vinorelbine	incremental efficacy	docetaxel	paclitaxel	incremental efficacy
Progression-free survival (days)	173	99	+74	173	145	+28
Quality-adjusted progression-free survival (days)	125	68	+57	125	103	+22

calculates the number of progression-free cycles as 8.22, 6.91 and 4.7 Markov cycles for docetaxel, paclitaxel and vinorelbine, respectively. These 21-day patient cycles may be converted into progression-free survival years and progression-free survival days. Progression-free survival years are equal to the product of the progression-free cycles multiplied by the fraction of the year taken up by a 21-day cycle. Progression-free survival days are equal to the number of disease-free cycles multiplied by 21 days. This gives a value of 0.473 years or 173 days for docetaxel, 0.398 years or 145 days for paclitaxel, and 0.271 years or 99 days for vinorelbine. The progression-free survival (PFS) in days and the quality-adjusted PFS (Q-PFS) are shown in table 6.

Cost-Effectiveness Ratio

Table VII shows the effectiveness, and table VIII shows the incremental cost utility of the 3 study drugs.

Vinorelbine and paclitaxel are dominated strategies with a lower effectiveness (progression-free days both adjusted or not adjusted for quality of life) and a greater cost than docetaxel.

Sensitivity Analysis

When the least favourable values for the time to progression, median response time and response rate seen in phase II trials with docetaxel are used (table IX), docetaxel is still dominant over vinorelbine in all situations: vinorelbine is more expensive and less effective. However, if the same procedure is repeated with paclitaxel, the ranking of the 2 drugs is changed in 3 situations.

If we assume that the time to progression with docetaxel determined in current phase III clinical trials should be the lowest reported to date in phase II clinical trials, i.e. 17 weeks,[20] docetaxel would cost approximately FF6000 more than paclitaxel. However, it offers the patient 8 additional progression- and discomfort-free days at a cost of FF750 per day gained. When the median response time for docetaxel is decreased to that found in other trials,[20,21] it then loses its dominant position versus paclitaxel. It would still be more effective (an additional 19 progression- and discomfort-free days) but would no longer be less expensive, although the additional cost is modest (FF400 extra). Prolonging the paclitaxel median duration of response from 28 to 35 weeks still allows docetaxel to be more effective than paclitaxel but at a higher cost (a gain of 13 progression- and discomfort-free days at a cost of FF123 per day). In all other situations, docetaxel is dominant over paclitaxel.

Overall, the results obtained with reference to paclitaxel appear to be robust. Although the order of the different strategies can be reversed, docetaxel appears to be more effective in all cases. Moreover, while docetaxel is more expensive, the additional cost per extra unit of efficacy remains

Table VII. Total direct cost (in 1993 French francs: FF) and progression-free survival (PFS) for docetaxel, paclitaxel and vinorelbine

Strategy	Cost (FF)	Effectiveness (PFS)			Incremental cost (FF)	Incremental effect
		cycles	y	days		
Docetaxel	250 400	8.224	0.473	172.70		
Paclitaxel	251 100	6.910	0.398	145.12	+700	−1.314
Vinorelbine	257 200	4.703	0.271	98.77	+6100	−2.207

Table VIII. Total direct cost (in 1993 French francs; FF) and quality-adjusted progression-free survival (Q-PFS) for docetaxel, paclitaxel and vinorelbine

Strategy	Cost (FF)	Utility (Q-PFS)			Incremental cost (FF)	Incremental utility
		cycles	y	days		
Docetaxel	250 400	5.974	0.344	125.45		
Paclitaxel	251 100	4.921	0.283	103.34	+700	−1.053
Vinorelbine	257 200	3.243	0.187	68.11	+6100	−1.678

acceptable. If the performance of docetaxel improves [reduced incidence of febrile neutropenia from 17 to 5% and increased response time as observed in the trial conducted by Ten Bokkel et al.[19] (median duration of response of 38 weeks)], the differences between docetaxel and paclitaxel rise further in favour of docetaxel with additional savings of FF8500 and 54 additional progression- and discomfort-free days.

Discussion

To be acceptable, a modelling study must use good reference agents and unequivocal data that have been collected in such a way as to ensure quality.

Choice of Reference Agents

In this study, reference agents were selected by 2 processes: advice from an expert panel and a representative ground survey of oncology practice in French public and private institutions in the second-line treatment of breast cancer. Expert opinions correlate with observed practice. Vinorelbine is currently the most widely used drug in current French practice. This is different from the situation in other countries; mitomycin plus vinblastine is the standard treatment in this situation both in the US, Canada and the UK, whereas treatment based on fluorouracil is widely used in Germany. In France, however, as in other markets, docetaxel and paclitaxel are emerging as promising alternative therapies. Thus, the 2 treatments used in this study are clearly valid reference agents.

Data Selection

The model approach consisted of synthesising clinical and economic data derived from various sources: results from phase II trials; practice survey to define reference treatments; board of experts to select the right dosage; retrospective study identifying resources consumed during different clinical events; clinical experts group for testing the face and content validity of health state descriptions; and interviews with 20 oncology nurses as proxy respondents for the patients for measuring health states preferences. This method enabled us to foresee and anticipate the whole consequences of the disease and of each treatment. It thus clarified the decision-making process in cases of uncertainty.

Chemotherapy is usually considered to be effective when it produces a response or stability, and thus delays the progression of disease. Even if an increase in the survival period seems to be the consequence of a higher response rate, no evidence of such an assumption can be found according to the literature and the opinion of experts. Therefore, the model assumes that none of the 3 chemotherapeutic agents improves the survival capacity. As a consequence, the main end-point retained by the model is the progression-free survival time; moreover, it estimates the responders' quality of life and the management cost of all the patients from the start of the treatment until death. The model applies to a 'standard' patient representative of all the patients. Even if the model is rather complex, it is more or less a simple representation of the real situation.

The frequency of clinical events for the 3 treatments compared were drawn from the drug registration master file in 2 cases and from a clinical series in the third. In the present state of drug development, no randomised clinical trials were available. We therefore took our data from the same sources as those used by the authorities to approve the product. Selection bias may be intro-

Table IX. Sensitivity analysis of incremental benefit and cost (1993 French francs)

Parameter	Docetaxel *vs* paclitaxel		Docetaxel *vs* vinorelbine	
	difference in Q-PFS	difference in cost	difference in Q-PFS	difference in cost
Efficacy of treatment				
Docetaxel				
TTP 17wk[20]	8	+5 726	43	−329
TTP 18wk[17]	12	+3 600	47	−2 500
TTP 21wk baseline[18]	22	−700	57	−6 800
TTP 23wk[19]	28	−3 600	63	−9 650
MDR 27wk[20,21]	19	+400	35	−5 700
MDR 28wk baseline[18]	22	−700	57	−6 800
MDR 38wk[19]	54	−8 500	89	−14 600
ORR 29%[17]	19	−956	54	−7 000
ORR 48% baseline (docetaxel pooling intention-to-treat patients)	21	−780	56	−6 840
Paclitaxel				
MDR 13.3wk[39]	37	−9 800	NA	NA
MDR 28wk baseline[17]	22	−700	NA	NA
MDR 35wk[22]	13	+1 600	NA	NA
Toxicity of treatment				
Hospitalisation for docetaxel-induced neutropenia 5%	23	−2 600	58	−8 600

Abbreviations: MDR = median duration of response; NA = not applicable; ORR = objective rate of response; Q-PFS = quality-adjusted progression-free survival; TTP = median time to disease progression.

duced during recruitment and results will have to be confirmed by true randomised trials. Until publication of the phase III trials which are currently underway we can only compare the different treatments indirectly. It is important initially to check that the dosage schedules used correspond to national practices and that the populations studied have similar characteristics as far as possible.

The publications on paclitaxel refer to trials using dosages and schedules which differ greatly. Dosages range from 300 mg/m^2 over 24 hours to 135 mg/m^2 over 3 hours. The expert panel recommended paclitaxel as a reference product at a dosage of 175 mg/m^2 over 3 hours by 6 votes out of 9; this was confirmed by regulatory authorities and usual practice. With docetaxel, the situation was easier since all studies were performed with the same dosage: 100 mg/m^2 as a 1-hour infusion.

Initially we thought we could select patients based on the number of chemotherapy courses administered, including only true second-line chemotherapy. In practice this criterion proved to be difficult as almost all trials included patients who had received either one adjuvant chemotherapy or a first-line therapy, or both. We finally used the criteria pre-treated and not pre-treated to select the clinical trials used in this study. Three studies complying with these criteria could have been used (Dieras et al.,[39] Seidman et al.[40] and the BMSTSG study[16,17]). The Dieras et al. study compared paclitaxel to mitomycin and was rejected because of the small size of the population in the paclitaxel arm. the study conducted by Seidman et al.[40] corresponds to third-line chemotherapy, therefore the BMSTSG study[16,17] was chosen.

Several differences were found concerning the patient population. Firstly, the percentage of patients who received no prior chemotherapy for metastatic disease was higher in the BMSTSG study[16,17] (27 *vs* 10%) than in the pooled data on docetaxel. Secondly, the criteria for definition of response were less strict in the BMSTSG study[16,17] than in the docetaxel dossier[18] (assessable + measurable *vs* bidimensionally measurable). Thirdly, the definition

of anthracycline resistance was different. Therefore, the compared populations were not completely consistent: the number of patients who were resistant to anthracycline was lower in the BMSTSG study[16,17] (20%) than in the pooled docetaxel trials (75%).[18] As the difference between trial populations was not in favour of docetaxel, this finding only strengthens the conclusions derived from the model.

Evaluation of Quality of Life

Nursing staff were responsible for the subjective evaluation of patients' quality of life depending on their state of health. This decision was made for 3 reasons.

1. The European cultural setting is very different from that in the US. The relationship between doctor and patient is still very asymmetrical: doctors endeavour to protect their patients and rarely present them with difficult treatment dilemmas. As a result we felt that it was impossible to use the standard gamble method, describing the possibility of survival without complications or the probability of death with heavily treated patients. Indeed, to date only one study[41] in France has used this method and it seemed premature to apply this directly to patients.

2. Of all healthcare professionals, nurses appear to us to be the closest to the patients; they are as involved with the repercussions of cancer on patients' quality of life as with their clinical consequences.

3. Nurses' professional experience enables them to have an informed opinion on all states of health that a patient with cancer may experience. Patients themselves experience only one state of health at a time.

The validity of information collected relating to quality of life by everyone acting on behalf and in place of the patient is debatable.[42,43] In general, individuals who are chosen to speak for patients provide precise information on changes that may be observed in the patients' quality of life, although they find it far more difficult to determine the psychological repercussions of these changes. In any event, they tend to underestimate the complaints of the patients they represent. We would note, however, that this underestimate tends to disappear as the disease worsens. The solution chosen is not perfect, although at the time it appeared to us to be the only one possible. We are now, however, working by questioning patients directly.

Evaluation of Costs

As second-line treatments are usually administered in hospital, the study methods used to evaluate hospital costs are particularly important. In the current overall budget system, the day cost is still widely used, but it covers extremely different situations. This prevents differentiation between admissions related to the treatment itself and those that it helps to avoid by delaying the progression and complications due to the cancer.

Calculations of variable costs by procedure are too detailed to be used simultaneously in several institutions. Patients who develop febrile neutropenia between treatment courses, or who develop disease complications after treatment, are often admitted to a different hospital from the one in which they received their chemotherapy. At present there is only one cost evaluation method that takes this into account: cost evaluation by DRGs. This method was used in our model. Cost evaluation by DRGs seems to be the only method used for expenditures that are to be linked between different hospital stays.

This study took into account all of costs associated with the treatments administered to the patients, not just the acquisition cost of the drugs, which enabled us to assess the direct incremental cost of treatments. It highlighted both the clinical and economic superiority of docetaxel over paclitaxel and vinorelbine.

Conclusion

Using docetaxel brings a net benefit of 57 progression- and discomfort-free days compared with using vinorelbine, and 22 such days compared with using paclitaxel.

Therefore not only is docetaxel self-financing because of saved hospital admissions, but it produces net savings of FF6800 compared with vinorelbine and FF700 compared with the equivalent figures for paclitaxel. It also has a better cost-effectiveness ratio than the reference agents. The 2 competing treatment strategies are inferior to docetaxel, since overall, they are less effective than docetaxel, whereas the projected costs per patient treated are higher.

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