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Economic evaluation of new drugs

Cost–utility model comparing docetaxel and paclitaxel in advanced breast cancer patients

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Relevant data from direct comparisons in clinical trials are not available for economic evaluations of docetaxel and paclitaxel in the management of metastatic breast cancer. A modified Markov model is used to estimate the incremental cost in US$ per quality-adjusted life-year (QALY) for docetaxel versus paclitaxel in managing metastatic breast cancer patients in the US. The model incorporates the latest available clinical trial data (response rates of 47.8% for docetaxel and 25% for paclitaxel, chemotherapy-specific toxicities, time to progression, and 1-year survival) from studies against other comparators. Medical care resources were estimated by US oncologists and costed using US data sources. Utility scores were obtained from 29 US oncology nurses. The base case and subsequent sensitivity analyses show that docetaxel management of advanced breast cancer is more costly per patient but yields higher health benefits than paclitaxel therapy. The cost per QALY gained by docetaxel is $8615, and ranges between $3943 and $9416 in sensitivity analyses. These results confirm those of an earlier model using preliminary data and compare favorably with other cost–utility results in this patient group. [© 1998 Lippincott Williams & Wilkins.]

Key words: Breast cancer, quality of life, cost–utility, taxoid.

Introduction

Breast cancer is the most common neoplasm affecting women in the Western world and to improve its management and outcomes, several new chemotherapy's have been introduced over the past few years. New breast cancer chemotherapy's are developed in order to improve patients' outcomes, but generally add to current management costs through both acquisition of the drug and the management of toxicities related to it. From agents available within the last 5 years, taxoids (paclitaxel and docetaxel) have the advantage of decreased cardiotoxicity in comparison with doxorubicin and appear to be the most active single agents in the treatment of advanced breast cancer.

Paclitaxel functions by promoting microtubulin assembly and stabilization, ultimately leading to mitotic arrest.[1] It requires premedication and prolonged infusion (generally 3 h) to decrease the likelihood of hypersensitivity.[2] The immediate dose-limiting factor is myelosuppression, although neutropenia is generally brief. The agent's major cumulative toxicity that curtails use is peripheral neurotoxicity. In phase II studies with paclitaxel in minimally pre-treated women, response rates have ranged from 32 to 63%.[3–10] These studies suggested a schedule dependency and an appearance that the highest response rates were seen with longer infusion times (24 h). In pretreated patients, many having received anthracycline, the response rates reported range from 19 to 48%.[11–20] Currently paclitaxel is combined with other agents, e.g. doxorubicin, in metastatic breast cancer patients who have never received chemotherapy and results in a 48–83% response rate.[21]

Docetaxel also affects the microtubulin.[2] Dose-limiting factors include myelosuppression in the short term, and longer term edema and neurologic toxicities.[22,23] In phase II studies of docetaxel the reported response rates range from 52% at 75 mg/m^2 to 68% at 100 mg/m^2 in minimally pretreated patients.[24–28] In patients previously treated with anthracyclines, phase II studies have reported response rates ranging from 32 to 58%.[29–35] Docetaxel is also being tested in combination with other agents.[36]

In a phase III trial, Paridaens *et al.*[37] reported a 25% response rate for paclitaxel when given to anthra-

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cycline naïve patients. Chan *et al.*[38] reported phase III overall response rate of 47% in women who had failed previous alkylating chemotherapy and had progressive metastatic disease.

The intermediate clinical outcomes of taxoid treatments show improvement in response rates and time to progression, but evidence of effect on survival and quality of life is not yet available from controlled clinical trials. Access to chemotherapy depends, in many instances, on whether health care systems or payers are willing to cover such treatments which may be perceived as expensive and offering little benefit. Particularly at a time of continued pressure to contain health expenditures, the adoption of new treatments may be met with considerable barriers. One way to overcome these barriers is to conduct formal economic analysis to measure the additional cost for a therapy in relation to the benefits gained. Costs include the resources used in administering treatment, in managing side effects and adverse events, and in providing supportive care as well as the direct drug costs of chemotherapy. In a disease such as advanced breast cancer it is important to have an outcome measure which includes the impact on patients' quality of life, which may be of more significance than gains in survival. The most appropriate measure is 'utility', which measures the patients' preferences between health outcomes with different combinations of quality of life and survival.[39,40] The utility measure offers a generalized outcome indicator which allows comparison between treatments for different patient groups as well as comparison of different treatments for the same patient group. Cost-utility analysis is therefore the preferred economic evaluation approach.[41]

Although it is possible to conduct cost-utility analysis within a clinical trial it has not yet been done in advanced breast cancer. The alternative is to use a decision modeling approach drawing the best available information from different sources to estimate the clinical and economic impact of a treatment on a target population.[42] Models are not meant to replace clinical trials, but can be used to extrapolate from clinical trial data; to provide interim information when trial results are awaited; and to help plan future trials.[43,44] Supplementary sources of information are typically databases, observational studies and expert opinion. The impact of assumptions used in the modeling process can be tested through the use of sensitivity analysis.

Previous economic analyses of taxoid treatment for advanced breast cancer have used cost-utility analysis in a modeling framework.[45,46] Similar approaches were used by other researchers in studies of bone marrow transplantation for advanced metastataic breast cancer patients[47] and of endocrine therapies in less advanced disease.[48] This paper reports the findings of a model-based comparison of docetaxel and paclitaxel in metastatic breast cancer patients, using the most recently available response rates and time to disease progression data. These are supplemented by utilities obtained from oncology nurses and resource cost data from the US. The findings may help decision makers considering the use of a taxoid in managing breast cancer patients.

Methods

Model description

The model presented here compares docetaxel and paclitaxel chemotherapy in advanced metastatic breast cancer patients, and is an adaptation of the model reported by Hutton *et al.*[46] The previous model has been updated to incorporate the most recent phase III clinical trial data available. The model estimates the differences in costs of direct medical resource utilization and patient outcomes in terms of quality of life and survival for breast cancer patients receiving docetaxel or paclitaxel after failing previous chemotherapy. The two taxoids have not been compared in head-to-head trials; however, in order to compare them directly, we have used data from trials in which each is compared with the anthracycline, doxorubicin used at a dose of 75 mg/m^2.

The model is a modified Markov process that begins with the first cycle of docetaxel or paclitaxel and follows patients through 3-week cycles until death within 3 years. Patients may experience immediate and/or intercurrent toxicities during the first two cycles of chemotherapy (Figure 1). Nausea and vomiting, diarrhea, and stomatitis are assumed to occur among all chemotherapy patients, and, because there is no difference between the therapies, are not considered as differentiating factors in this model. Infections and febrile neutropenia may occur during the first two cycles with the potential for hospitalization and/or i.v. antibiotics, and, ultimately, death. Patients continuing therapy move to cycle 3 and hence to cycle 4.

During the fourth cycle (Figure 2) one of three responses to therapy is confirmed: complete plus partial response, stable disease or no response (progressive disease). Chemotherapy is continued for those with response or stable disease for seven cycles for docetaxel patients and six cycles for paclitaxel patients, based upon trial data. Patients remain in the

response or stable disease states (Figure 3) until moving to progressive disease. The last cycle of progressive disease is considered terminal disease. The length of time spent in terminal disease is not different between treatments. The time in progressive disease is shorter for those patients with a longer time to progression (TTP) as there is no difference in long-term (up to 3 years) survival between treatment arms. TTP is calculated from the first cycle of chemotherapy and patients remain in stable disease or complete/partial response until reaching the average TTP as reported in the clinical results.

Cumulative toxicities may occur from cycle 4 until the end of chemotherapy and the impact of these toxicities, in terms of quality of life deficits, may continue throughout the first year. The occurrence of severe edema, severe peripheral neuropathy, painful skin conditions and cardiac toxicity (leading to discontinuation) is included. Other toxicities were considered not to differ between the two regimens and, therefore, were not included. Within the model, patients die due to progressive disease, infection/febrile neutropenia or cumulative toxicity. The medical resources and patient utilities associated with chemotherapy, related toxicities and disease stage are applied at the appropriate points in the model.

Model parameter values

The probabilities of model events (Table 1) are obtained primarily from the latest available clinical

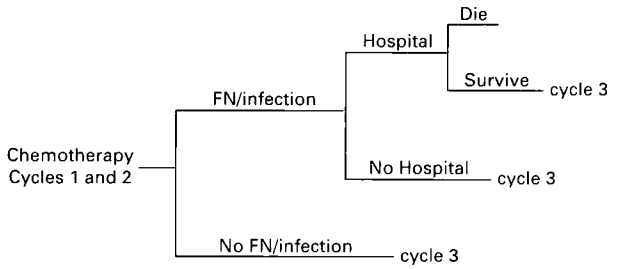

Figure 1.

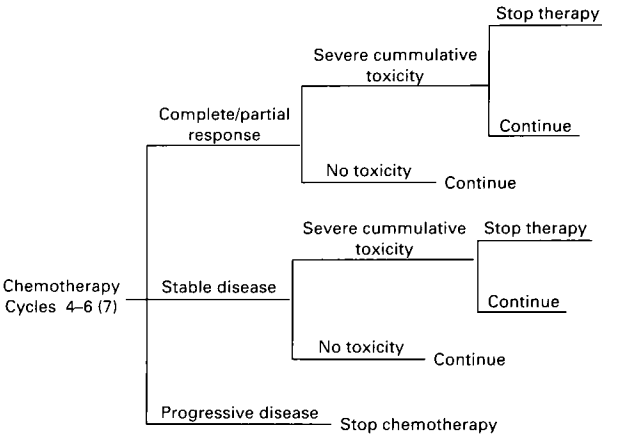

Figure 2.

Table 1. Probability of events in metastatic breast cancer model

Parameter	Docetaxel[a]	Paclitaxel[b]
Overall response rate (ITT), base case (%)	47.8	25
Evaluable patient response rate (%)	52	25
Progressive disease, base case (%)	12.4	31
Time to progression, base case (weeks)	26	16[c]
Mortality at 12 months (%)	35	35[c]
Infection with hospitalization and/or i.v. antibiotic, base case (sensitivity analyses) (%)	2.5	4 (2.5–8)[d]
Febrile neutropenia (FN) with hospitalization and/or i.v. antibiotic, base case (%)	5.7	7
FN without hospitalization, base case (sensitivity analyses) (%)	10.7	10 (5–15)[d]
Death associated with infection or FN (%)	1.2	0
Severe neurotoxicity (%)	8	9
Severe edema (%)	5	0
Discontinue with cardiac toxicity (%)	0.6	0.6[d]
Severe skin conditions (%)	1.9	5
Time to response (weeks)	9[e]	9[e]
Cycles of chemotherapy	7	6

[a]Chan *et al.*[38] applies to all docetaxel parameters not otherwise labeled.
[b]Paridaens *et al.*[37] applies to all paclitaxel parameters not otherwise labeled.
[c]Paridaens *et al.*[37] reports progression-free survival.
[d]Estimated base case and/or range of values where data were not reported. Generally paclitaxel assumed equal to docetaxel if data not available.
[e]Model is designed so responses are identified in the fourth 3-week cycle and is the same for each regimen.
ITT, intent to treat.

data.[37,38] The chemotherapy doses tested in the model are 100 mg/m^2 for docetaxel and 200 mg/m^2 for paclitaxel. The patients were assumed to have a body mass of 1.66 m^2 in computing the number of vials needed per cycle of chemotherapy. The patient responses are based upon patients receiving docetaxel therapy after failing an alkylating chemotherapy or for anthracycline-naive advanced breast cancer patients (paclitaxel). Patient populations for the two taxoid trials differed. Thirty percent of paclitaxel patients had received adjuvant chemotherapy and 70% had no prior chemotherapy, whereas 100% docetaxel patients had prior chemotherapy. Moreover, definitions for fefrile neutropenia, infections and cumulative toxicities may have differed. Where the paclitaxel trial did not report the necessary model values, we assumed there was no difference from docetaxel and/or used a range of values (Table 1).

Medical care resources included in the analysis are physician and nurse time, chemotherapeutic agents, antibiotic regimens, and in-patient or out-patient management of infections and febrile neutropenia, progressive and terminal disease palliative medication, monitoring tests and hospital days. The combination of resources (treatment patterns) used in each stage of the model were estimated by three US oncologists with considerable experience in managing metastatic breast cancer patients (see examples of treatment patterns in Hutton *et al.*[46]). For managing infections or febrile neutropenia reported as having hospitalization and/or i.v. antibiotics, we assumed that 80% were treated in the hospital setting and, of those, 75% had i.v. antibiotics. The balance of 20% of the patients received i.v. antibiotics at home or in the out-patient setting. No costs for prophylactic use of granulocyte colony stimulating factor (G-CSF) were included in the base case analysis; however, sensitivity analysis included an estimate of G-CSF costs. The difference in resource use between the treatment groups depends only upon the chemotherapeutic regimen, occurrence of events (e.g. febrile neutropenia and severe edema) or the length of time in a health state (e.g. stable disease and progressive disease).

US costs were obtained from Medicare, or private third-party payers, and the Redbook. Unit costs used in the analysis (Table 2) were obtained for 1997, or inflated as necessary. The model does not attempt to capture all of the costs associated with managing metastatic breast cancer, but only the differences in resource use between the two treatment groups.

Utilities are a measure of preference between health states. Because it was not possible to obtain utility ratings from metastatic breast cancer patients, the utilities for the model were obtained from 29 US oncology nurses at two large oncology centers. The scores (ranging between 1.0 for perfect health and 0 for death) were obtained using the standard gamble methodology recommended by Furlong *et al.*[49] Descriptions of the health states relevant to the model were constructed with input from clinical experts. Each health state includes measures of well-being, social and physical functioning. An example of a health state is shown in Table 3. The nurses, as proxy patients, compared their preferences for the health states to best possible health and to death. The US nurse respondents had worked in oncology an average of 7 years, 71% in out-patient settings only and had a mean age of 39 years. In addition to US nurses, 25–30 nurses from each of Germany, Italy, Netherlands, Spain and the UK also estimated patient preferences. The health states were translated and back-translated to assure comparability, and the resulting utilities were highly consistent across all countries. The average utilities from US nurses and nurses from all six countries are shown (Table 4), and in general the

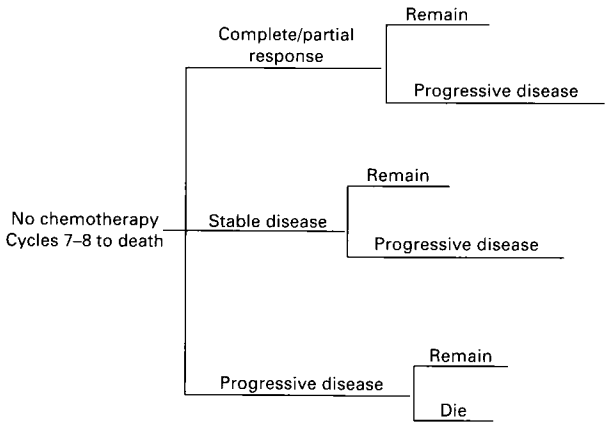

Figure 3.

Table 2. US costs for metastatic breast cancer model, 1997

Resource	$
Physician visit	57
General blood chemistry	14
Hospital day	995
i.v. antibiotic home treatment	125
Ciprofloxacin (daily 1000 mg)	60
Paclitaxel 200 mg/m^2 (332 mg)	
3–17 ml vials	1826
1–5 ml vial	182
Docetaxel 100 mg/m^2 (166 mg)	
2–80 mg vials	2062
1–20 mg viall	258

average scores for all nurses are lower than the US-specific scores. The average utilities are used in a sensitivity analysis.

Analyses

A cost-utility analysis was conducted comparing the alternative treatment regimens such that the difference in the per patient costs of the therapies under comparison is divided by the difference in per patient utility aggregated over the survival period for the therapies and yields the cost for the incremental utility gained [quality-adjusted life-year (QALY)]. The base case analysis uses the overall response rates from the trials for each taxoid. Sensitivity analyses vary parameter values to use the response rate for docetaxel evaluable patients, decreased toxicity rates related to paclitaxel, decreased TTP for docetaxel, changed utilities to the average of six countries, manufacturer's list prices for docetaxel and paclitaxel, and decreased prices for paclitaxel.

Table 3. Health state representing stable disease and peripheral edema

Walks and lifts with *some* limitations; *moderately* vigorous activities require help.
Eats, bathes, dresses and uses the toilet normally.
Limitations in the use of hands or fingers, does *not* require help of another person.
Energy level is *low. Occasional* disruption of normal social and work activities.
Somewhat fearful and anxious. *Somewhat* depressed. *Somewhat* pessimistic about the future. Loss of hair on head.
Able to think clearly and solve day to day problems.
Frequently moderate pain; discomfort relieved by oral medicine. Occasional nausea and vomiting and sores in mouth.

Results

A Markov modeling technique is used to compare docetaxel and paclitaxel through the use of data from trials against other comparators. The analysis shows that docetaxel consistently has higher health utility scores and higher total costs than paclitaxel under a variety of scenarios. Using the most likely parameter values (base case), docetaxel costs $15 683 from the start of chemotherapy until death for a patient having an average of seven chemotherapy cycles. The equivalent figure for a patient having six cycles of paclitaxel is $13 904. The cumulative QALYs are 0.867 for docetaxel and 0.6605 for paclitaxel for an equivalent time frame. The incremental cost for the increase in quality adjusted life with docetaxel compared to paclitaxel is $8615 (Table 5).

Table 5. Costs and utilities for metastatic breast cancer patients treated with docetaxel or paclitaxel

Treatment	Costs per patient ($)	Utility per patient	Incremental cost ($)/QALY
Docetaxel	15683	0.8670	8615[a]
Paclitaxel	13904	0.6605	

[a]Calculated by: (cost of docetaxel − cost of paclitael)/(utility of docetaxel − utility of paclitaxel).

Table 4. Oncology nurse utility scores for metastatic breast cancer model

Health state (base case)	US average utility	Six-country average utility (sensitivity analysis)
At start of second-line chemotherapy	0.69	0.64
Partial/full response (PR)	0.84	0.81
Stable disease (SD)	0.70	0.65
Progressive disease (PD)	0.49	0.39
Terminal disease	0.23	0.16
Peripheral neuropathy+PR	0.58	0.56
Peripheral neuropathy+SD	0.41	0.44
Severe edema+PR	0.82	0.76
Severe edema+SD	0.68	0.62
Severe skin condition	0.65	0.56
Cardiac toxicity	0.54	0.59
Febrile neutropenia with hospitalization	0.42	0.30
Infection no hospitalization	0.56	0.60
Death	0	0

Sensitivity analyses changing important variables were conducted and the results in terms of cost/QALY gained are shown in Table 6. The range in cost for increased benefit is not wide. The most costly scenario for the gain in QALYs is lowering the docetaxel TTP from 26 to 21 weeks. The lowest ratio results from using the costs of only six cycles of docetaxel (the same average number as paclitaxel) without changing the response rate or the rate of toxicities ($3942 for the increase in QALYs). A best-case analysis for paclitaxel using the lowest estimated rates of infection resulted in little difference from the base case.

To analyze the impact of generically available paclitaxel, we estimated 40–80% lower chemotherapeutic agent costs for the paclitaxel treatment group compared to no change in docetaxel costs. The resulting incremental rates range between $11 618 and $21 514 for the increased QALYs due to docetaxel.

We examined the breakdown of the costs for the management of docetaxel and paclitaxel patients under the base case scenario. The majority of the costs were related to the chemotherapy itself (65% docetaxel and 58% paclitaxel). Drug administration accounted for 10 and 16%, respectively, progressive disease 10 and 17%, and terminal disease less than 5% for each therapy. Chemotherapy-related toxicities were higher with docetaxel (9 versus 2%) and febrile neutropenia/infection costs (3% each) were small. (Data not shown.)

Discussion

This study suffers for the limitations inherent in comparing two agents in the absence of head to head trials. The major difference is in the proportion of patients having had previous chemotherapy (100% in docetaxel versus 30% in paclitaxel). Additionally, the definitions of toxicities may not be consistant. The sensitivity analyses were conducted to overcome these limitations.

This study is one of the few published cost-utility analyses in breast cancer patients. A study also comparing docetaxel and paclitaxel therapies in France[45] used preliminary trial data and physician opinion. Based primarily on hospital costs, the authors found that docetaxel was cost saving by FF700 (US$140) per patient compared to paclitaxel and the quality-adjusted progression and discomfort-free survival was also greater. The response rates used in the Launois study were 57% for docetaxel and 29% for paclitaxel, compared to 48 and 25% in this study. The French study incorporated considerable hospital costs, whereas in the US most of the breast cancer patients are managed in an out-patient basis with little hospitalization until terminal disease. The differences between the models are mainly in the treatment patterns (there is probably a reduction in hospital days for docetaxel patients because there is a longer TTP), response rates and variation in the outcome measure. The quality adjusted progression-free survival is not strictly comparable to the more commonly used QALY measure. The more favorable cost comparison in the Launois study is a result of the greater assumed difference in response rates, the limitation of docetaxel therapy to six cycles, and the differences in treatment patterns and costs between France and the US.

The model described here differs from Hutton *et al.*[46] by using phase 3 response rates, TTP, intercurrent and cumulative toxicity rates, and 1 year survival. The earlier analysis was completed with more preliminary trial data supplemented with physician expert opinion as necessary to fill in missing model

Table 6. Incremental cost/QALY gained for docetaxel over paclitaxel

Analysis	Cost ($)/QALY gained
Base case (see text)	8615
Docetaxel response rate increased to 52%	8051
Docetaxel TTP decreased to 21 weeks	9545
Paclitaxel lowered rates for infection (5%) and infection with hospitalization (2.5%) (best case)	8976
Changing resource use for infection/FN patients to 80% managed in out-patient setting instead of 20% in out-patient setting	8739
Adding cost for G-CSF to patients managed in the hospital	8427
Docetaxel therapy cycles reduce to six	3942
Average utilities from all European and US nurses instead of US-specific utilities (see Table 3)	9418
Using manufacturer list prices instead of Readbook prices for docetaxel and paclitaxel	8654
Paclitaxel drug cost decreased by 40%	24169
Paclitaxel drug costs decreased by 80%	39719

TTP, time to progression.

values. The purpose of the early model was to provide guidance for health authorities needing to make decisions before final trial data were available. Compared with the former model the parameters used here are based more upon clinical results and less upon expert opinion, and, therefore, should provide answers closer to real-world experience. It is particularly interesting that the former model base case results using US treatment patterns, US costs and US-specific utilities were $8091/QALY for docetaxel, less than a $600 difference from the current analysis ($8615). This compatibility speaks strongly for the usefulness of modeling during the early phases of a drug development program. Early models, carefully constructed to employ clinical data supplemented with physician opinion, can provide fairly realistic estimates of what might be expected once better data are available.

The $8615 cost per QALY for docetaxel therapy versus paclitaxel therapy for advanced metastatic breast cancer patients falls within the acceptable limit (Canadian $100 000) proposed by Laupacis *et al.*[50] Even against paclitaxel priced as a generic (40–80% lower), the cost per QALY remains within this proposed limit. Epstein[51] has suggested a cost per QALY cut-off point of $30 000 for medical treatment in general and all but one docetaxel analysis falls within this range. Other QALY ratios in breast cancer patients range widely depending upon the disease stage, the patient population and the therapy considered. Adjuvant endocrine therapy ranges between $4300 and $6000/QALY (1991 US$) for node-positive and estrogen-receptor (ER)-positive breast cancer patients who are pre- and postmenopausal, respectively.[47] Adjuvant tamoxifen therapy for premenopausal ER-negative women ranged between $50 000 and $200 000/QALY, illustrating a highly inefficient therapy.[52] The only other cost-utility study in a comparable patient group is by Hillner *et al.*[47] who estimated $100 000/QALY for high-dose chemotherapy with bone marrow transplantation support for metastatic breast cancer patients. Thus, for decision makers faced with selecting a taxoid therapy, docetaxel would appear to be a cost-effective option.

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