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ORIGINAL RESEARCH ARTICLE

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Abstract

Background There have been recent important changes to adjuvant regimens and costs of taxanes for the treatment of early breast cancer, requiring a re-evaluation of comparative cost effectiveness. In particular, weekly paclitaxel is now commonly used but has not been subjected to cost-effectiveness analysis.

Aim Our aim was to estimate the cost effectiveness of adjuvant docetaxel and weekly paclitaxel versus each other, and compared with standard 3-weekly paclitaxel, in women aged ≥25 years diagnosed with regional breast cancer in New Zealand.

Methods A macrosimulation Markov model was used, with a lifetime horizon and health system perspective. The model compared 3-weekly docetaxel and weekly paclitaxel versus standard 3-weekly paclitaxel (E1199 regimen) in the hospital setting. Data on overall survival and toxicities (febrile neutropenia and peripheral neuropathy) were derived from relevant published clinical trials. Epidemiological and cost data were derived from New Zealand datasets. Health outcomes were measured with health-adjusted life-years (HALYs), similar to quality-adjusted life-years (QALYs). Costs included intervention and health system costs in year 2011 values, with 3 % per annum discounting on costs and HALYs.

Results The mean HALY gain per patient compared with standard 3-weekly paclitaxel was 0.51 with weekly paclitaxel and 0.21 with docetaxel, while incremental costs were $NZ12,284 and $NZ4,021, respectively. The incremental cost-effectiveness ratio (ICER) of docetaxel versus 3-weekly paclitaxel was $NZ19,400 (purchasing power parity [PPP]-adjusted $US13,100) per HALY gained, and the ICER of weekly paclitaxel versus docetaxel was $NZ27,100 ($US18,300) per HALY gained. In terms of net monetary benefit, weekly paclitaxel was the optimal strategy for willingness-to-pay (WTP) thresholds >$NZ27,000 per HALY gained. However, the model was highly sensitive to uncertainty around survival differences, while toxicity-related morbidity had little impact. Thus, if it was assumed that weekly paclitaxel and docetaxel had the same efficacy, docetaxel would be favoured over weekly paclitaxel.

Conclusion Both weekly paclitaxel and docetaxel are likely to be cost effective compared with standard 3-weekly paclitaxel. Weekly paclitaxel was the optimal choice for WTP thresholds greater than $NZ27,000 per HALY gained (PPP-adjusted $US18,000). However, uncertainty remains around relative survival benefits, and weekly paclitaxel becomes cost ineffective versus docetaxel if it is assumed that the two regimens have equal effectiveness. Reduced uncertainty about the relative survival benefits may improve decision making for funding.

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Key Points for Decision Makers

The cost effectiveness of both weekly paclitaxel and docetaxel compared with standard 3-weekly paclitaxel is below common willingness-to-pay (WTP) thresholds.

While docetaxel is more cost effective than weekly paclitaxel when compared with standard 3-weekly paclitaxel in our model, weekly paclitaxel provides more than twice as much health gain in terms of health-adjusted life-years (HALYs).

The additional cost associated with weekly paclitaxel would be acceptable in order to gain additional health at a potentially acceptable WTP threshold of >$NZ27,000 (purchasing power parity [PPP]-adjusted $US18,000) per HALY gained.

However, uncertainty remains around relative survival benefits, and docetaxel would be favoured over weekly paclitaxel if it is assumed that the two regimens have equal effectiveness.

1 Introduction

Breast cancer is the most commonly registered cancer, and the second most common cause of death from cancer, among women in high-income countries such as New Zealand [1]. Postoperative adjuvant chemotherapy for regionally invasive breast cancer reduces the risk of recurrence and death [2–4].

Until the early 1990s, adjuvant chemotherapy was most commonly based on cyclophosphamide, methotrexate and fluorouracil, but such regimens have largely been superseded by anthracycline-based regimens (doxorubicin or epirubicin) because of their greater effectiveness. The taxanes, paclitaxel and docetaxel, were introduced in the late 1990s and were found to improve survival in the adjuvant setting when used sequentially with anthracycline-based regimens compared with the anthracycline-based regimens alone [5]. Guidelines recommend that a taxane should be considered in all cases where adjuvant chemotherapy is contemplated for women with early breast cancer [4]. Endocrine therapy and trastuzumab may also be included depending on the individual woman's hormone receptor and human epidermal growth factor receptor (HER)-2 status.

Paclitaxel and docetaxel differ in terms of their pharmacokinetic and toxicity profiles. However, most guidelines do not specify which taxane is preferred for adjuvant treatment of early breast cancer because they have conventionally been considered to be similarly effective [4, 6, 7].[1] Indeed, Australian guidelines from 2008 state that "decisions on scheduling and dosing of taxane-containing regimens should be based on factors other than survival outcomes," with emphasis instead being placed on the patient's risk profile and comorbidities and consideration of the different toxicities of the taxanes [7].

Under a scenario of assumed equal effectiveness, acquisition cost rather than cost effectiveness has tended to dominate the choice of taxane. For instance, until recently in New Zealand, only paclitaxel was publicly funded for adjuvant treatment of early breast cancer, other than where a combination of docetaxel and trastuzumab was indicated. This was due to the substantially higher acquisition cost of docetaxel compared with paclitaxel at the time of the funding decision [9]. However, a number of cost-effectiveness analyses have shown that the adjuvant treatment of early breast cancer with docetaxel is cost effective compared with non-taxane-containing regimens [10–15], whereas cost-effectiveness data have been less convincing for adjuvant standard 3-weekly paclitaxel [16, 17].

However, taxane regimens for adjuvant treatment of breast cancer have been refined in recent years, resulting in different costs and better outcomes and challenging the traditional wisdom that the taxanes cannot be differentiated by effectiveness. Of particular importance is the move towards weekly rather than 3-weekly administration of paclitaxel. In the pivotal E1199 clinical trial, which compared four different taxane regimens in combination with cyclophosphamide and doxorubicin chemotherapy, the hazard ratio (HR) for overall survival with weekly paclitaxel was reported as 1.32 (95 % confidence interval [CI] 1.02–1.72; equivalent to a mortality HR of 1/1.32 = 0.76) compared with standard 3-weekly paclitaxel treatment [18]. However, the weekly paclitaxel regimen requires greater resources to deliver, with implications for costs, cost effectiveness and patient convenience.

While weekly paclitaxel and 3-weekly docetaxel are now the two most commonly used taxane regimens in adjuvant treatment of breast cancer, we are not aware of any economic analyses that directly compare the cost effectiveness of these two regimens. Furthermore, re-evaluation of the cost effectiveness of the taxanes is needed given recent dramatic changes in acquisition costs as generic agents have become available. In mid-2011, the acquisition cost of docetaxel in New Zealand was reduced

[1] The UK National Institute for Health and Care Excellence (NICE) recommends adjuvant treatment with docetaxel rather than paclitaxel in node-positive breast cancer. However, this is because there is a lack of evidence for the use of paclitaxel in combination with the standard chemotherapy regimens used in the UK, rather than because of a clinical advantage per se [8].

by 80 % in tandem with public funding of docetaxel being extended to include all early breast cancer [19–21]. Lesser changes in prices than this have previously been reported to significantly change the outcome of cost-effectiveness analyses of docetaxel [12].

The aim of this paper is to evaluate the cost effectiveness of adjuvant docetaxel and weekly paclitaxel compared with standard 3-weekly paclitaxel in the New Zealand hospital setting for women with early (regional) breast cancer in order to help guide funding decisions for taxanes.

2 Methods

A macrosimulation Markov model was developed to compare taxane regimens in the adjuvant treatment of early (regional) breast cancer in a cohort of women diagnosed with this type of cancer in New Zealand in 2011, as shown in Fig. 1. A macrosimulation model simulates a cohort of individuals with an average experience of events, which is captured by transition probabilities, avoiding the additional complexity of modelling individuals (microsimulation). The key parameters are given in Table 1, and the model inputs and assumptions are discussed in the following sections and summarised in the Electronic Supplementary Material (ESM) 1, Table 1.

The interventions of interest were weekly paclitaxel and 3-weekly docetaxel. The comparator was 3-weekly paclitaxel, as this represents the previous standard adjuvant taxane regimen for New Zealand that has now been largely superseded by docetaxel and weekly paclitaxel regimens. In line with current clinical strategies, the model was limited to sequential taxane regimens incorporating anthracyclines and cyclophosphamide in which the taxane component of the chemotherapy was started after the anthracycline component had been completed. These regimens are described in greater detail below. While taxanes can be given concurrently with anthracyclines, such regimens are not included in the model because they are less commonly used in clinical practice due to the higher risk of febrile neutropenia than with sequential regimens [5].

A literature search was conducted to determine overall survival and toxicity rates (refer to the ESM 1 for search strategy and inclusion and exclusion criteria). While a number of meta-analyses were identified [5, 16, 22–25], none provided pooled estimates for overall survival that differentiated between weekly and 3-weekly paclitaxel and sequential taxane regimens separately from concurrent regimens according to the type of taxane as required for our model. Thus, overall survival and toxicity rates were obtained from the individual major clinical trials of the taxane regimens of most interest, as described in the remainder of the section.

2.1 Interventions

The model starts at the initiation of adjuvant chemotherapy, after completion of surgery for regional breast cancer. The taxane regimen to be included in the model was selected based on the regimen most commonly used in New Zealand.

For efficacy, the model compared weekly paclitaxel 80 mg/m^2 (12 cycles) and 3-weekly docetaxel 100 mg/m^2 (four cycles) versus standard 3-weekly paclitaxel 175 mg/m^2

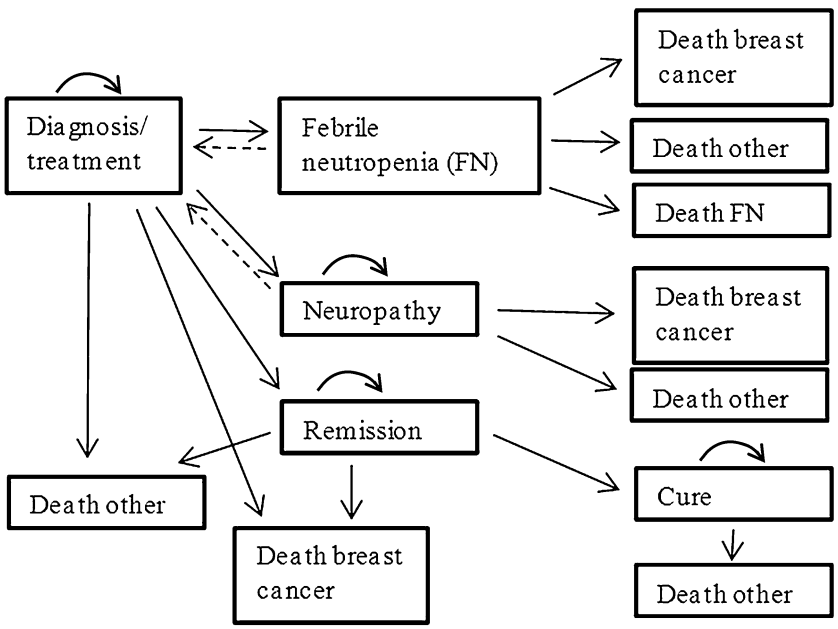

Fig. 1 Stylised depiction of Markov model of adjuvant treatment of regional breast cancer with taxanes. Death from cancer is preceded by preterminal and terminal states

Table 1 Key parameters for model of adjuvant treatment of regional breast cancer with taxanes

Variable	Best estimate	Variation	Source
Probability death from breast cancer			Excess mortality rates for regional breast cancer from NZ Cancer Registry data, varying by sociodemographic strata [30]
Probability death from other causes			Mortality rates from NZ lifetables incorporating heterogeneity by sociodemographic strata [31]
Relative survival			
HR for breast cancer death (vs. standard 3-weekly paclitaxel[a])			
Docetaxel[b]	0.87	LogNormal distribution SE(lnHR) = 0.105	E1199 study [18] adjusted from death from all causes to death from breast cancer
Weekly paclitaxel[c]	0.73	LogNormal distribution SE(lnHR) = 0.108	
Toxicity			
Probability of severe (grade 3 or 4) febrile neutropenia		Beta distribution	Weighted average from clinical trials of adjuvant treatment of regional breast cancer with taxanes [18, 35–37, 40], with beta distribution for SE set at 20 % of mean (refer to ESM 1, Table 6)
– Standard paclitaxel 3-weekly[a]	0.07	Alpha 1 = 23.2 Alpha 2 = 308	
– Docetaxel[b]	0.15	Alpha 1 = 21.1 Alpha 2 = 120	
– Weekly paclitaxel[c]	0.06	Alpha 1 = 23.4 Alpha 2 = 367	
Probability of death from febrile neutropenia	0.036	Alpha 1 = 98 Alpha 2 = 2,622	US data for >50,000 episodes of febrile neutropenia [28] Applies only to proportion of patients who experience grade 3 or 4 febrile neutropenia
Probability of severe (grade 3 or 4) peripheral neuropathy		Beta distribution	Weighted average from clinical trials of adjuvant treatment of regional breast cancer with taxanes [18, 35–39], with beta distribution for SE set at 20 % of mean (refer to ESM 1, Table 7)
– Standard paclitaxel 3-weekly[a]	0.045	Alpha 1 = 23.8 Alpha 2 = 506	
– Docetaxel[b]	0.03	Alpha 1 = 24.2 Alpha 2 = 783	
– Weekly paclitaxel[c]	0.095	Alpha 1 = 22.5 Alpha 2 = 215	
Disease model states			
DT duration	6 months	NA	Period of chemotherapy in clinical study [18]

Table 1 continued

Variable	Best estimate	Variation	Source
Preterminal duration	11 months prior to entering terminal state	NA	Derived from Australian burden of disease models [26, 54]
Terminal duration	1 month prior to death	NA	
Statistical cure timepoint	20 years	NA	
Disability weights			
DT disability weight	0.194	Beta distribution	Derived from GBD 2010 adapted for NZ [26, 34]
		Alpha 1 = 17.57	
		Alpha 2 = 72.99	
Preterminal disability weight	0.513	Alpha 1 = 19.59	
		Alpha 2 = 18.6	
Terminal disability weight	0.521	Alpha 1 = 18.75	
		Alpha 2 = 17.24	
Remission disability weight	0.174	Alpha 1 = 17.14	
	Discounted at 20 % p.a. from end of year 1	Alpha 2 = 81.34	
Disability weight of severe febrile neutropenia	DW = 0.028	Alpha 1 = 26.07	Based on disability weight from GBD 2010 for acute severe infectious episode of 0.21 (95 % CI 0.139–0.298), applied for the 4-day febrile period within the 1-month cycle (i.e. disability weight per day = 0.007) [26, 34]
		Alpha 2 = 904.89	
Disability weight of severe sensory neuropathy	0.15	Alpha 1 = 22.67	Based on average between disability weight for diabetic neuropathy (DW = 0.099; 95 % CI 0.066–0.145) and disability weight for mild MS (DW = 0.198; 95 % CI 0.137–0.278) from GBD 2010 [26, 34]
		Alpha 2 = 128.46	
Duration of severe febrile neutropenia	4 days	NA	US data for >50,000 episodes of febrile neutropenia [28]
Duration of severe sensory neuropathy	3 months	NA	Estimate from literature [42–45]
Costs			
Population health system costs		Gamma distribution with SE of ±5 %	Ministry of Health databases [26]
Intervention costs		Gamma distribution with SE of ±5 %	Refer to Table 2

AC (60/600) doxorubicin 60 mg/m^2, cyclophosphamide 600 mg/m^2, *CI* confidence interval, *DT* diagnosis and treatment, *DW* disability weight, *ESM* Electronic Supplementary Material, *GBD* Global Burden of Disease, *HR* hazard ratio, *MS* multiple sclerosis, *NA* not applicable, *NZ* New Zealand, *SE* standard error

[a] AC (60/600) 3-weekly × 4 cycles then paclitaxel 175 mg/m^2 3-weekly × 4 cycles

[b] AC (60/600) 3-weekly × 4 cycles then docetaxel 100 mg/m^2 3-weekly × 4 cycles

[c] AC (60/600) 3-weekly × 4 cycles then weekly paclitaxel 80 mg/m^2 × 12 cycles

(four cycles) as per the 24-week regimen of the E1199 study, which is the only major clinical trial to directly compare these three regimens [18]. Taxane treatment was preceded by four cycles of doxorubicin 60 mg/m^2 plus cyclophosphamide 600 mg/m^2 in 3-weekly cycles. All chemotherapy was modelled as being administered intravenously in an outpatient hospital setting, as per current New Zealand clinical practice. Characteristics of the E1199 study are provided in the ESM 1, Table 3 [18].

2.2 Model Structure

Study methods followed the BODE^3 (Burden of Disease Epidemiology, Equity and Cost-Effectiveness programme) protocol and applied a health system perspective [26].

The target population was women aged ≥25 years with a recorded diagnosis of SEER (Surveillance, Epidemiology, and End Results Program)-stage regional breast cancer in the New Zealand Cancer Registry in 2011. To allow analysis of heterogeneity, this sub-population was stratified by age, ethnicity (Māori, non-Māori) and deprivation tertile (NZDep [27]), creating 84 independent cohorts. Those aged <25 years were excluded because of the low incidence of breast cancer in this age group.

Cycle length was 1 month in order to capture the effects of chemotherapy given over 6 months and related toxicities with effects lasting weeks to months. A lifetime horizon was applied to fully capture all consequences and costs, with each cohort followed up until death or age 110 years. Briefly, survivors and those dying of another cause had their first 6 months (or less if dying of other causes) assigned to a diagnosis and treatment state, then up to 19.5 years assigned to the remission state. A statistical cure was assumed to occur at 20 years post-diagnosis. For those dying of the cancer, their last month was assigned to a terminal state, and the 11 months preceding this to a pre-terminal state. Additional states for the two major dose-limiting toxicities, febrile neutropenia and peripheral neuropathy, were also included in the model. It was modelled that febrile neutropenia, but not peripheral neuropathy, is associated with an increased risk of death [28]. Thus, death from breast cancer, death from febrile neutropenia and death from other causes act as competing risks.

All key parameters are summarized in Table 1, with further details provided in the ESM 1.

2.3 Modelling of Health Consequences

2.3.1 Incidence Rates

Incidence rates for regional breast cancer in 2011 were derived from the New Zealand Cancer Registry, further disaggregated by ethnicity and deprivation using rate ratios from linked census cancer data (ESM, Table 2) [29].

2.3.2 Survival

2.3.2.1 Mortality Rates Excess mortality rates due to breast cancer, differentiated according to age, ethnicity and deprivation, were derived from the New Zealand Cancer Registry, as described elsewhere [30]. Background mortality rates (i.e. for diseases other than breast cancer) by sociodemographic strata using a lifetable approach were derived from death rates from standard New Zealand life tables, adjusted for the proportions of the New Zealand population in deprivation groups and corresponding rate ratios to obtain death rates for deprivation groups, and projected to the future [31].

2.3.2.2 Effect of Interventions on Survival The effect sizes for interventions with regards to survival were input as HRs for breast cancer death (Table 1). These HRs were derived from the overall survival rates reported for the E1199 study (ESM 1, Table 4) [18]. To convert the HR for any death into an HR for breast cancer death, we estimated that breast cancer accounted for 90 % of deaths in the study, as has been reported in other studies [32, 33], and that the study HR would apply to only that proportion of the deaths, with an HR of 1 applied to the remaining 10 % of deaths from other causes.

The HR for cancer death was assumed to be constant over time, but a survival advantage lasting only the 5 years of study follow-up was tested in scenario analysis.

2.3.3 Health-Adjusted Life-Years

The outcome of the model was health-adjusted life-years (HALYs). The HALYs used are essentially the same as quality-adjusted life-years (QALYs), except we use the complement of disability weights (rather than utilities), and we allow for expected background morbidity. Disability weights were sourced from the 2010 Global Burden of Disease [34], with modification to the New Zealand distribution of cancers [26]; the disability weights for each non-fatal model state are shown in Table 1. Expected population morbidity was allowed for by using the average ethnic- and age-specific prevalent years of life lived in disability from the New Zealand Burden of Disease Study [26], thus limiting the maximum HALYs that can be gained with increasing age. (Refer to the BODE^3 protocol [26] for a full explanation of the rationale and methods of the HALY measurement.)

Survivors who do not die from breast cancer or other causes remain in the remission stage for a maximum of 19.5 years, during which time they accumulate the HALYs associated with the remission disability weight

(see Table 1). After that time, they return to a state of normal health where their morbidity is the same as that of others of the same age and ethnicity who have not experienced breast cancer. Those dying of breast cancer assume the higher disability weights of the preterminal phase for the final 11 months and terminal phase for the last month of life. No additional disability weight is assigned prior to death for those dying of other causes.

2.3.4 Morbidity Related to Toxicity

Febrile neutropenia and peripheral neuropathy of grade 3 or 4 severity (World Health Organization [WHO] or National Cancer Institute Common Toxicity Criteria) were included in the model. Because of the variability in toxicity rates reported for individual trials, we averaged data for rates of febrile neutropenia and peripheral neuropathy from randomized controlled clinical trials of adjuvant treatment of breast cancer in which data could be derived from at least one arm using sequential taxanes at the same doses as modelled for efficacy and with similar anthracycline-based regimens (i.e. an anthracycline plus cyclophosphamide with or without fluorouracil at standard doses for three or four 3-weekly cycles) [18, 35–40]. To reflect current practice, studies were included only if use of granulocyte-colony stimulating factor (G-CSF) was discretionary and/or secondary to occurrence of febrile neutropenia. The characteristics of these studies are given in the ESM 1, Table 5.

The inverse-variance weighted average incidences for grade 3 or 4 febrile neutropenia and peripheral neuropathy input into the model are shown in Table 1. To allow for uncertainty around applying rates from clinical trials in various countries to New Zealand, the standard error for input into the model's uncertainty analysis was increased from that originally reported (4–13 % of the mean value) up to 20 % of the mean value.

The data from which these weighted averages were derived are provided in ESM 1, Tables 6 and 7.

Using toxicity rates directly from the E1199 study was tested in scenario analyses.

2.3.4.1 Febrile Neutropenia Febrile neutropenia was modelled as occurring in the first cycle of the taxane component of the chemotherapy and occurring only once for each patient, as described in ESM 1, Table 1. Febrile neutropenia is represented by an 'average' experience of those experiencing severe febrile neutropenia with hospitalization for 5 days [28]. A disability weight for severe acute infection is applied to the average 4 days for which it was estimated that patients remain febrile and require treatment with intravenous antibiotics (Table 1). Febrile neutropenia is assumed to be either fatal (3.6 % of patients hospitalized with grade 3 or 4 febrile neutropenia [28]) or to resolve with no significant residual disability.

In line with New Zealand practice, the model included only secondary prophylaxis with G-CSF and assumed that 25 % of patients with febrile neutropenia would receive pegfilgrastim for subsequent cycles of their chemotherapy [35, 41]. Costs but no morbidity or mortality impacts of G-CSF were included.

2.3.4.2 Peripheral Neuropathy Grade 3 or 4 peripheral neuropathy was modelled as first occurring in the final cycle of the Markov diagnosis and treatment phase, and to be of sufficient severity to incur significant morbidity for 3 months on average, after which symptoms would improve or resolve without significant disabling sequelae (ESM 1, Table 1) [42–45].

Disability weights and costs (Table 1) were based on sensory neuropathy, which is the predominant taxane-induced neuropathy [44, 45].

2.4 Costs

Costs are from a health system perspective and are in year 2011 values. Source costs were adjusted by the New Zealand Consumer Price Index to 2011 values when required. Costs are in New Zealand dollars ($NZ), with purchasing power parity (PPP) conversion rates provided (Organisation for Economic Co-operation and Development [OECD] values 2011; $NZ1 = $US0.675 = €0.54).

The methodology of the BODE^3 programme was followed [46]. A discount rate of 3 % per annum was applied to both costs and benefits. All costs exclude goods and services tax (GST).

2.4.1 Intervention Costs

Unit costs of the components of each intervention and the number of resource units consumed are shown in Table 2.

Costs were derived from various New Zealand Ministry of Health, District Health Board and PHARMAC sources, as described elsewhere [46]. Inpatient and outpatient costs were derived from purchase unit costs, including overheads and all other services provided by the hospital (e.g. physician time, nursing time, pharmacist time, hotel costs, etc.) [46]. The latter costs also included all pharmaceuticals other than cancer drugs. The costs of chemotherapy drugs were derived from the New Zealand Pharmaceutical Schedule [21].

The chemotherapy costs included the costs of the pharmaceuticals, outpatient admission for each administration (weekly or 3-weekly depending on the regimen), blood tests, patient travel, and patient accommodation

Table 2 Unit costs for Interventions. Costs are in New Zealand dollars, adjusted to year 2011 values[a]

Cost item	2011 unit cost	No. of units	Cost		Source and notes
			Per cycle	Total	
1. Laboratory					MoH Price of Cancer Report [55]
Urea	3.13	1	3.13		Simplifying assumption that all patients receive all blood tests each course
Complete blood count	10.94	1	10.94		
Creatinine	3.26	1	3.26		
Electrolytes (Na/K)	6.57	1	6.57		
Total laboratory tests			*23.90*		
2. Outpatient admission for chemotherapy administration	493.83	1	493.83		MoH/DHBNZ Outpatient Purchase Unit national price for outpatient attendance for IV chemotherapy for cancer (MS02009) [56] Includes all pharmaceuticals administered other than cancer drugs. Includes day-case treatment (including physician and nursing care, overheads, hotel costs, etc.)
3. Patient travel and accommodation					Average distance based on incidence multiplied by each patient's distance to hospital using Census Area Units, described elsewhere [46]
Travel (per km)	0.245	45.4	11.11		National Travel Assistance reimbursement rate per km for private vehicle use [57] multiplied by the average distance travelled by patients with regional cancer to nearest chemotherapy centre [46]
Accommodation	174.00	0.038	6.78		National Travel Assistance reimbursement rate for accommodation for a 2-night stay [57] applied to proportion of patients with regional breast cancer travelling >100 km [46]
3. Chemotherapy[b]					NZ Pharmaceutical Schedule (Section H) July 2011 [21]
Docetaxel 100 mg/m^2 (170 mg IV)	438.75	1	438.75		Unit cost for 2 × 80 mg vial plus 1 × 20 mg vial
Weekly paclitaxel 80 mg/m^2 (136 mg IV)	137.50	1	137.50		Unit cost per 150 mg vial
3-weekly paclitaxel 175 mg/m^2 (298 mg IV)	275.00	1	275.00		Unit cost per 300 mg vial
Doxorubicin 60 mg/m^2 (102 mg IV)	80.00	1	80.00		Unit cost per 100 mg vial
Cyclophosphamide 600 mg/m^2 (1,020 mg IV)	23.65	1	23.65		Unit cost per 1,000 mg vial
4. Peripheral neuropathy					
GP visit	62.22	2		124.44	Calculation from MoH capitation rates and DHBNZ data [46]
GP-referred neurological tests	369.00	1		369.00	MoH/DHBNZ Outpatient Purchase Unit national price for neurological tests referred by a GP, e.g. electroencephalogram, evoked potential test, and electromyogram (CS04002) [56]. Includes interpretation and reporting of the test
Amitriptyline 50 mg/day × 3 months	3.60	1		3.60	NZ Pharmaceutical Schedule (Section H) July 2011 [21]. Unit cost per 100 tablets
Peripheral neuropathy total				*497.04*	
5. Febrile neutropenia treatment					
Inpatient admission	4,567.49	1.13		5,146.62	MoH WIESNZ11 case-mix cost weights [58, 59]
					Inpatient admission for septicaemia without catastrophic complications or comorbidities (T60B): cost weight 1.1268
Tazobactam/piperacillin 4.5 g q8 h × 4 days IV	12.00	12		144.00	NZ Pharmaceutical Schedule (Section H) July 2011 [21]

Table 2 continued

Cost item	2011 unit cost	No. of units	Cost		Source and notes
			Per cycle	Total	
Oral amoxicillin-clavulanate 500 mg/125 mg tid × 7 days	0.26	21		5.46	NZ Pharmaceutical Schedule (Section H) July 2011 [21]
Febrile neutropenia total				*5,296.08*	
6. G-CSF					NZ Pharmaceutical Schedule (Section H) July 2011 [21]
Pegfilgrastim 6 mg					Assumes 25 % of patients who experience febrile neutropenia in the first cycle of taxane treatment are subsequently treated with G-CSF for remaining chemotherapy cycles
G-CSF for 3-weekly taxane regimens × 4	1,395.00	0.75		1,046.25	0.25 units for remaining three 3-weekly taxane cycles
G-CSF for weekly taxane regimens × 12	1,395.00	1.5		2,092.50	0.25 units for every alternate remaining weekly taxane cycle ($n = 6$)

DHBNZ District Health Boards of NZ, *DOX* doxorubicin, *G-CSF* granulocyte colony-stimulating factor, *GP* general practitioner, *IV* intravenous, *MoH* NZ Ministry of Health, *NZ* New Zealand, *PPP* purchasing power parity, *q8h* every 8 h, *tid* three-times daily, *WIESNZ11* New Zealand weighted inlier equivalent separation 2011

[a] $NZ1 = PPP-adjusted $US0.675 in 2011. Where costs were not already in 2011 values, costs were inflated using the NZ Consumer Price Index [46]

[b] Costs based on single-use vials where any remainder would be discarded. Doses based on an average body surface area for female patients with cancer of 1.7 m^2 and bodyweight 67 kg [60, 61]

when required. Costs for febrile neutropenia included inpatient hospitalization, administration of antibiotics and use of G-CSF. Costs for peripheral neuropathy included two additional general practitioner (GP) visits in association with GP-referred neurology tests and treatment with amitriptyline. Details are provided in ESM 1, Table 1.

As described in Sect. 2.4.2, baseline health system costs derived from the real costs for patients with regional breast cancer in New Zealand are also included in the model. Because these costs already include the real costs for chemotherapy averaged across all patients with regional breast cancer, only the incremental cost of the chemotherapy compared with the comparator were included in the intervention costs.

Costs for diagnosis and staging of breast cancer and initial surgery were not included because these costs occur before entry into the model and would be the same for all arms.

2.4.2 Health System Costs

Health systems costs are those costs incurred or averted as a downstream result of the intervention. Both disease-related and unrelated health system costs are included [26]. For instance, a patient who survives because of an intervention may incur other healthcare costs later in life, and we do not attempt to delineate what is a breast cancer cost versus that arising due to another condition.

These costs are derived from routine linked administrative health data for the entire New Zealand population with costs attached, as described elsewhere [26]. We are able to assign health system costs by age to the healthy state (i.e. the simple average of all health system use and attendant cost for each age group, as estimated in 2011; we assumed real costs to be the same in the future). The additional cost for regional breast cancer patients at different stages of their care (diagnosis/treatment, remission, and preterminal and terminal for those dying from cancer) were then estimated using gamma regression. Following van Baal et al. [47], we separately determined expected costs for those in the last 6 months of life for those dying from causes other than cancer.

2.5 Simulations and Uncertainty

By calculating a weighted average using the heterogeneity distribution, incremental HALYs and costs were obtained for all expected breast cancer patients diagnosed in 2011 as well as separately for Māori and non-Māori; neighbourhood deprivation tertiles I, II and III; and those aged <65 years or ≥65 years. Analyses were undertaken in TreeAge Pro 2012.

Table 3 Summary of results for the total population from Monte Carlo simulation: costs ($NZ[a], year 2011 values) and health-adjusted life-years per patient

Parameter	Standard 3-weekly paclitaxel	Docetaxel	Weekly paclitaxel
Intervention costs[b]	457	1,538	5,018
Health system costs	212,241	215,181	219,964
Total costs	212,698	216,719	224,982
HALYs	9.62	9.82	10.13

HALY health-adjusted life-year, *NZ* New Zealand, *PPP* purchasing power parity

[a] $NZ1 = PPP-adjusted $US0.675 in 2011

[b] Only chemotherapy and administration costs incremental to those of 3-weekly paclitaxel are included. Other costs included are those of prevention and treatment of febrile neutropenia and peripheral neuropathy

Table 4 Summary of incremental results for the total population from Monte Carlo simulation: costs ($NZ[a], year 2011 values) and health-adjusted life-years per patient

Output	Docetaxel vs. standard 3-weekly paclitaxel	Weekly paclitaxel vs. docetaxel
Incremental total costs		
Mean	4,021	8,263
2.5th percentile	−1,400	1,648
Median	4,077	8,222
97.5th percentile	9,112	15,361
Incremental HALYs		
Mean	0.21	0.31
2.5th percentile	−0.16	−0.14
Median	0.21	0.30
97.5th percentile	0.55	0.78
ICERs ($ per HALY gained)		
Expected value[b]	19,400	27,100
2.5th percentile	Dominant	Dominant
Median	18,262	25,054
97.5th percentile	59,623	138,672

HALY health-adjusted life-year, *ICER* incremental cost-effectiveness ratio, *NZ* New Zealand, *PPP* purchasing power parity

[a] $NZ1 = PPP-adjusted $US0.675 in 2011

[b] Mean ICERs across the 2,000 simulations were difficult to interpret because HALYs were often close to zero, driving ICERs in some Monte Carlo simulations towards positive or negative infinity. Thus, we report expected value (i.e. central estimate of each distribution), not mean, ICERs

Monte Carlo simulation was used to address parameter uncertainty, with 2,000 draws from input parameters based on the following distributions: log-Normal distribution for the HR for death; beta distributions for the proportions experiencing a toxicity and disability weights; gamma distributions for costs (see Table 1).

We reran models (expected values only; no uncertainty about input parameters) for a range of scenarios to assess the impact of structural assumptions:

- discount rate 0 or 6 % per annum
- exclusion of prevalent life-years with disability (pYLDs) related to population morbidity such that HALYs more closely represent QALYs
- limiting survival benefit of the intervention to the 5 years of study follow-up by 'turning off' the HR at year 5
- use of toxicity rates directly from the E1199 study rather than averaged across trials
- exclusion of unrelated health system costs.

Given uncertainty around the relative effectiveness of docetaxel and weekly paclitaxel, a scenario of these regimens having equal effectiveness was tested by setting the HR for breast cancer death versus standard 3-weekly paclitaxel to 0.87 in both arms. The latter represents a cost minimization approach.

Additionally, we rely on these expected value-only analyses for incremental cost-effectiveness ratios (ICERs), as with parameter uncertainty many simulations resulted in negative HALYs and sometimes also negative costs, making mean and median ICERs difficult to interpret.

We also undertook a range of one-way sensitivity analyses, using the 2.5th and 97.5th percentile values of input parameters, to assess which input parameters contributed the most to uncertainty in the model HALY and incremental cost outputs, but not the ICERs for the reason give above.

Finally, we also performed a net monetary benefit (NMB) analysis and produced cost-effectiveness acceptability curves using these NMB values rather than ICERs because of the greater validity of NMBs in this instance given the occurrence of negative ICERs. A cost-effectiveness threshold of $NZ45,000 (≈PPP-adjusted $US30,000) per HALY was set for NMB analysis. This threshold equates to the New Zealand gross domestic product (GDP) per capita in 2011 [48].

3 Results

Both docetaxel and weekly paclitaxel produced mean HALY gains compared with standard 3-weekly paclitaxel, but at a greater cost (Table 3). The HALY gain was greater with weekly paclitaxel than with docetaxel, with an estimated incremental HALY gain of 0.31 (95 % Uncertainty Interval −0.14 to 0.78) for weekly paclitaxel versus docetaxel. However, the extreme of the uncertainty

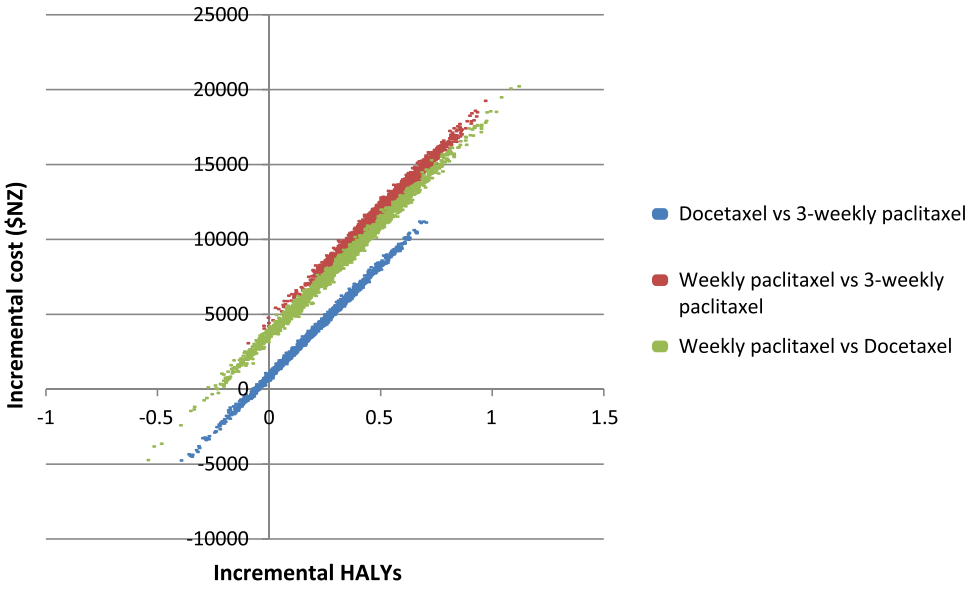

Fig. 2 Cost-effectiveness plane for docetaxel and weekly paclitaxel versus standard 3 weekly paclitaxel from Monte Carlo simulation of 2,000 iterations. *HALY* health-adjusted life-year

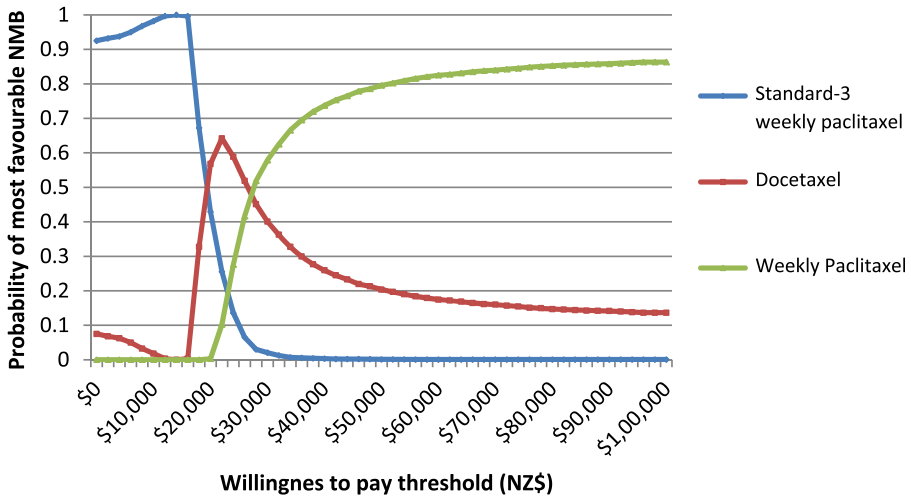

Fig. 3 Cost-effectiveness acceptability curve using net monetary benefit (NMB)

intervals (UIs; i.e. the negative 2.5th percentiles) included HALY losses (Table 4). Costs were also higher with weekly paclitaxel than with docetaxel ($NZ8263 [$US5577]; 95 % UI $NZ1,648–15,361).

Due to negative incremental HALYs in approximately 12 % of simulations for docetaxel, along with some negative incremental costs (see Fig. 2), univariate statistics about the ICER values across simulations are difficult to interpret. Therefore, we used expected value analysis, where the incremental costs and HALYs are the same or close to the averages from the Monte Carlo simulations. The expected value ICERs versus standard 3-weekly paclitaxel were $NZ19,400 ($US13,100) and $NZ23,900 ($US16,200) per HALY gained for docetaxel and weekly paclitaxel, respectively. Applying incremental analysis principles, the ICER for weekly paclitaxel versus docetaxel was $NZ27,100 ($US18,300) per HALY gained (Table 4).

For all population subgroups other than those aged ≥65 years, ICERs (using expected values) were consistently less than $NZ21,000 ($US14,000) and $NZ28,000 ($US19,000) per HALY gained for docetaxel versus standard 3-weekly paclitaxel and for weekly paclitaxel versus docetaxel, respectively (see ESM 2, Table 1). The HALY gain was halved for those in the older age group but costs were also reduced, resulting in an ICER of $NZ34,500 ($US23,300) per HALY gained for weekly paclitaxel versus docetaxel.

Returning to the Monte Carlo simulations including parameter uncertainty, a NMB approach allows the generation of the cost-effectiveness acceptability curve shown in Fig. 3. For willingness-to-pay (WTP) thresholds ≤$NZ20,000 ($US13,500) per HALY gained, standard 3-weekly paclitaxel is the preferred option, i.e. it is the most likely to produce the most favourable NMB across simulations. At WTP thresholds between $NZ20,000

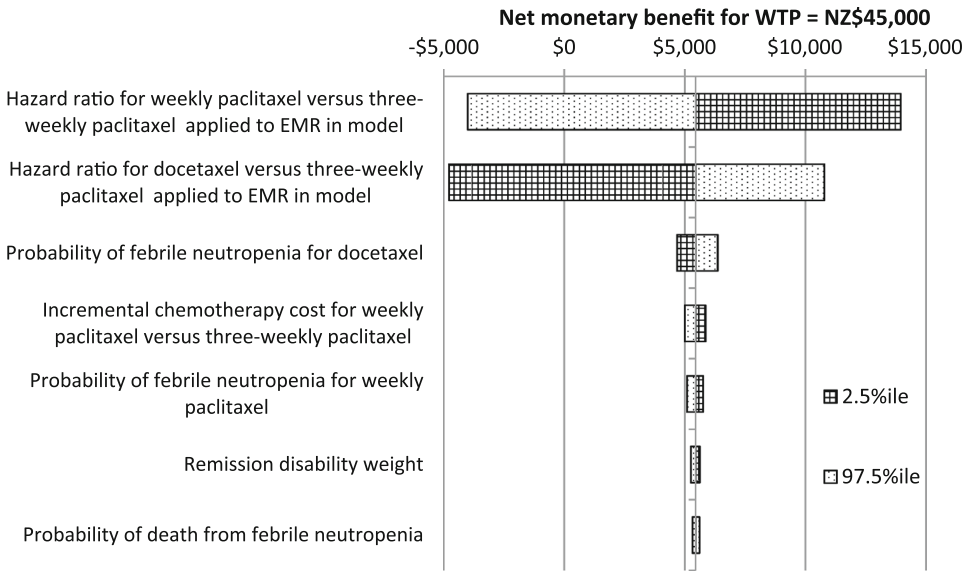

Fig. 4 Tornado plot of difference in net monetary benefit between weekly paclitaxel and docetaxel for univariate sensitivity analyses about 2.5th and 97.5th percentile values of selected input parameters for a willingness to pay threshold of $NZ45,000 ($US30,000). All other input parameters (e.g. disability weights in diagnosis and pre-terminal states, cost of febrile neutropenia) had a negligible impact and are not shown. *EMR* excess mortality rate for breast cancer

($US13,500) and up to $NZ27,000 ($US18,200), docetaxel becomes the preferred option. When the WTP threshold is higher than $NZ27,000 ($US18,200), weekly paclitaxel is the most likely to have the best NMB and is (based on this model and cost-effectiveness criteria alone) the optimal decision. However, and notably, it is not a clear-cut preference for weekly paclitaxel in that, at our defined WTP threshold of $NZ45,000 ($US30,000) per HALY gained, there is still a more than 20 % probability that docetaxel is preferred.

At the $NZ45,000 WTP threshold, the NMB for weekly paclitaxel is $NZ5448 ($US3677) greater than for docetaxel (based on expected values). A tornado plot was constructed by setting all input parameters to their expected value, then undertaking univariate sensitivity analyses for the 2.5th and 97.5th percentile values of the input parameters for NMB (Fig. 4). At the 97.5th percentile value of the paclitaxel HR and the 2.5th percentile value of the docetaxel HR for breast cancer death, a big shift in the NMB occurs such that docetaxel is favoured (i.e. NMBs are negative). However, uncertainty about all other input parameters has a negligible impact on NMB.

In scenario analyses based on expected values, excluding pYLDs, such that the HALYs gained more closely resembled QALYs gained, reduced ICERs by about 25 % to $NZ14,600 ($US9900) and $NZ20,500 ($US13,800) per HALY gained for docetaxel versus standard 3-weekly paclitaxel and for weekly paclitaxel versus docetaxel, respectively. Limiting the differential survival effect to the 5-year follow-up period of the clinical study (i.e. HR for breast cancer death = 1 in all arms after year 5) reduced both HALY gains and costs and subsequently increased ICERs by about 20 %, but all remained below $NZ35,000 ($US23,600) per HALY gained (Table 5).

The model was sensitive to the relative survival effects of docetaxel and weekly paclitaxel. If the two agents were set to have equal effectiveness (i.e. the HR for breast cancer death for weekly paclitaxel was set to that of docetaxel = 0.87), HALY gains were halved for weekly paclitaxel and became much the same as those for docetaxel, with only a small incremental HALY advantage to weekly paclitaxel due to less toxicity-related morbidity. Consequently, the ICER for weekly paclitaxel compared with docetaxel increased to more than $NZ130,000 per HALY gained, emphasizing both the sensitivity of model outputs to uncertainty about the mortality HR and the (much) lesser impact of differences in morbidity effects between the two treatments. Further confirming this, changing toxicity rates to the higher rates seen in the E1199 study [18], rather than a weighted average across clinical trials (most notably febrile neutropenia for docetaxel 22 % vs. weighted average of 15 %), caused only a 10 % increase in the ICER for docetaxel versus standard 3-weekly paclitaxel and decreased the ICER for weekly paclitaxel versus docetaxel by only 5 %.

4 Discussion

Re-evaluation of the cost effectiveness of the taxanes in adjuvant treatment of breast cancer is timely given the emergence of weekly paclitaxel as a more effective option than the previous standard (3-weekly paclitaxel) and significant changes in the relative cost of the taxanes that have occurred with the availability of generic docetaxel. For the first time, to our knowledge, the current economic analysis directly compares the cost effectiveness of weekly paclitaxel and docetaxel with each other and with 3-weekly

Table 5 Results of scenario analyses using expected values for incremental analysis: costs ($NZ, year 2011 values)[a] and health-adjusted life-years per patient

Scenario	Output	Docetaxel vs. standard 3-weekly paclitaxel	Weekly paclitaxel vs. docetaxel
Expected value	Incremental cost	$4,033	$8,214
	HALYs gained	0.21	0.30
	ICER	**$19,400**	**$27,100**
Undiscounted HALYs and costs	Incremental cost	$5,828	$10,818
	HALYs gained	0.35	0.50
	ICER	**$16,800**	**$21,700**
Discount rate 6 % for HALYs and costs	Incremental cost	$3,036	$6,740
	HALYs gained	0.14	0.20
	ICER	**$22,000**	**$33,100**
Toxicity rates set to those of E1199 study [18]	Incremental cost	$3,962	$8,241
	HALYs gained	0.18	0.32
	ICER	**$21,500**	**$25,700**
Turn off HR at end of year 5	Incremental cost	$3,017	$6,998
	HALYs gained	0.13	0.21
	ICER	**$23,500**	**$33,600**
Assume weekly paclitaxel has equivalent efficacy to docetaxel	Incremental cost	$4,033	$4,132
	HALYs gained	0.21	0.03
	ICER	**$19,400**	**$138,800**
Set population morbidity (i.e. pYLDs) to zero (≈QALYs)	Incremental cost	$4,033	$8,214
	HALYs gained	0.28	0.40
	ICER	**$14,600**	**$20,500**
Set all disability weights (incl. pYLDs) to zero (=life-years gained)	Incremental cost	$4,033	$8,214
	HALYs gained	0.27	0.40
	ICER	**$14,900**	**$20,300**
Exclude unrelated health system costs	Incremental cost	$2,880	$6,532
	HALYs gained	0.21	0.30
	ICER	**$13,800**	**$21,500**

HALY health-adjusted life-year, *HR* hazard ratio for breast cancer death, *ICER* incremental cost-effectiveness ratio, *NZ* New Zealand, *PPP* purchasing power parity, *pYLD* prevalent life-years with disability, *QALY* quality-adjusted life-year

[a] $NZ1 = PPP-adjusted $US0.675 in 2011. ICERs are rounded to $100 units

paclitaxel in adjuvant treatment of early (regional) breast cancer.

The results show that both weekly paclitaxel and docetaxel are likely to be cost-effective options compared with standard 3-weekly paclitaxel, with both having ICERs less than $NZ25,000 ($US17,000) per HALY gained. Using an incremental approach to compare the options, weekly paclitaxel had an ICER of $27,100 ($US18,300) per HALY gained compared with docetaxel. When approximated to QALYs, the ICERs were less than $NZ20,500 ($US14,000) per QALY gained. While there is no set cost-effectiveness threshold in New Zealand, the ICERs are below the threshold based on GDP per capita (approximately $NZ45,000 [≈$US30,000] in 2011 [48]), which is defined as highly cost effective by the WHO CHOICE (CHOosing Interventions that are Cost Effective) programme [49].

However, the question of which is the most cost-effective taxane regimen when choosing between docetaxel and weekly paclitaxel is not clear-cut and this is best explored by considering the NMB. When compared with 3-weekly paclitaxel in our analysis, docetaxel had better cost effectiveness than weekly paclitaxel because of the higher costs of weekly administration of paclitaxel. However, the health gain was more than twice as much with weekly paclitaxel than with docetaxel. Thus, based on this model, weekly paclitaxel would be the preferred option if the health system was willing to pay the additional cost to benefit from the additional health gain. Indeed, our analysis showed that, at WTP thresholds above $NZ27,000 ($US18,000) per HALY gained, weekly paclitaxel would have a greater probability of producing a more favourable NMB than docetaxel. However, if the WTP threshold was less than this, docetaxel would be preferred. If the WTP threshold was <$20,000 ($US13,500) per HALY gained, 3-weekly paclitaxel would be preferred, although there would be a loss of health gain compared with the other more effective taxane options. At an NMB threshold of $NZ45,000 (≈US30,000) (i.e. equivalent to New Zealand's GDP per capita, and representing a possible cost-effectiveness

threshold for New Zealand), weekly paclitaxel had a 77 % probability of being the preferred strategy under the conditions of our model.

However, the model was highly sensitive to differences in health gain, especially around HRs for survival. There remains uncertainty around whether weekly paclitaxel has a survival advantage over docetaxel. The E1199 study from which the mortality HRs were derived for this model was the first, and, to date, the only, study to directly compare weekly and 3-weekly paclitaxel and docetaxel in regional breast cancer. The E1199 results were substantially in favour of weekly paclitaxel, showing a significant survival benefit over 3-weekly paclitaxel, with an HR for overall survival of 1.32 (95 % CI 1.02–1.72) [18]. While 3-weekly docetaxel was also more effective than 3-weekly paclitaxel in E1199, its CI included the null (HR 1.13; 95 % CI 0.88–1.46). Using the log-Normal assumption about the reported 95 % CI, we calculated that the probability of weekly paclitaxel being superior to docetaxel in terms of survival was 88 % in E1199. Nevertheless, because of the overlapping CIs, it can be argued that the efficacy of docetaxel and weekly paclitaxel are not significantly different and therefore should be modelled as equal using a cost-minimization approach. When this was tested in the scenario analysis that set the efficacy of weekly paclitaxel to be the same as that of docetaxel, weekly paclitaxel became highly cost ineffective compared with docetaxel (ICER $NZ138,800 [$US93,700]).

While the E1199 study is the only study to directly compare weekly paclitaxel and docetaxel, an indirect comparison can be made from other studies of taxane regimens similar to those included in this model. PACS01 [32] compared docetaxel with the anthracycline-based regimen FEC (fluorouracil, epirubicin, cyclophosphamide), while GEICAM 9906 [33] also compared weekly paclitaxel with FEC in a similar patient group to that in our model. The HR for all death versus FEC was 0.73 (95 % CI 0.56–0.94) for docetaxel and 0.78 (95 % CI 0.57–1.06) for weekly paclitaxel. Running this indirect comparison through our model structure showed that the HALY gain favoured docetaxel (0.55 HALYs gained) over weekly paclitaxel (0.46 HALYs) under these conditions, while weekly paclitaxel was more expensive. Thus, weekly paclitaxel was dominated by docetaxel, although with considerable uncertainty. At a WTP threshold of $NZ45,000 ($\approx$$US30,000) per HALY gained for NMB analysis, there was a 77 % probability of docetaxel being the preferred option and 23 % probability of weekly paclitaxel being the preferred option (results available from authors on request). We fully acknowledge the limitations of this indirect comparison and present it only for illustrative purposes of the significant impact of changing the relative survival rates for docetaxel and weekly paclitaxel.

Thus, we conclude that even relatively small changes in survival are sufficient to swing the relative cost effectiveness in favour of either docetaxel or weekly paclitaxel. Nevertheless, the finding that both docetaxel and weekly paclitaxel are cost effective compared with 3-weekly paclitaxel appears to be relatively robust.

In contrast to the major impact of survival on the results of the model, morbidity had little effect on the HALYs gained despite differences in the toxicities of the taxanes. Until the E1199 study demonstrated the superiority of weekly paclitaxel, the taxanes were generally regarded as having comparable effectiveness, and differences in their toxicity profiles were considered more important [7]. In sensitivity analyses, we set the survival advantage to be the same for weekly paclitaxel and docetaxel, making the toxicities the driver of differences in HALY gains. A modest 0.03 difference in HALYs favouring weekly paclitaxel was found. This suggests that paclitaxel-induced neuropathy has a lesser detrimental effect on health gain than docetaxel-induced febrile neutropenia, because, while neuropathy has a greater disability weight and longer duration, it is not usually fatal, whereas febrile neutropenia has high costs and can be fatal. However, the morbidity impacts were minor compared with the mortality impacts. Thus, while toxicities may be an important clinical factor in choosing between the taxanes for individual patients, toxicities have little impact on the cost effectiveness of the different options.

While, to our knowledge, no other cost-effectiveness analyses have directly compared different taxane regimens, the finding that docetaxel is cost effective compared with standard 3-weekly paclitaxel is not surprising given the higher ICERs previously reported for 3-weekly paclitaxel when both were evaluated against non-taxane regimens (e.g. ICERs vs. non-taxane-containing regimens of £12,000 per QALY gained for docetaxel and around £40,000 per QALY gained for standard 3-weekly paclitaxel in a series of models reported from the UK in 2005/6 values) [16]. Other cost-effectiveness analyses of docetaxel compared with non-taxane-containing regimens for adjuvant treatment of early breast cancer have also reported ICERs below accepted cost-effectiveness thresholds (e.g. ICERs $\leq$ $Can20,000, £20,000 or €10,000 per QALY gained reported in year 2002–2008 values) [10–15]. Our model captures the improved cost effectiveness of docetaxel resulting from a lower acquisition cost following the introduction of generic docetaxel.

4.1 Study Strengths and Limitations

Strengths of the model include the wealth of epidemiological data in New Zealand upon which the model was able to draw, including analyses by heterogeneity and

national health system costs, allowing inclusion of both related and unrelated costs throughout the patients' lifetimes. In New Zealand, heterogeneity in health outcomes has potentially significant effects on cost effectiveness of interventions because Māori have a 7-year lower life expectancy and higher cancer-related mortality rates (age-standardized breast cancer death rate per 100,000 women in 2010 = 19.8 for non-Māori vs. 32.9 for Māori [1]). These inequities also have socioeconomic patterning. Nevertheless, the cost effectiveness of docetaxel and weekly paclitaxel did not vary significantly by ethnicity or deprivation in our model. We were not able to incorporate any heterogeneity in the response to taxanes; however, we believe this would have minimal effect on the differential health gain between the taxanes compared with heterogeneity in demographics and we are not aware of any evidence to suggest that the effectiveness of taxanes differs between Māori and non-Māori.

We used HALYs as the measure of health consequences in this analysis. They are very similar to QALYs, involving epidemiological estimation of life-years gained adjusted for health state. However, the health status valuation is through disability weights derived from the 2010 Global Burden of Disease [34], with slight modifications for the New Zealand setting [26]. We also allow for expected background comorbidity using pYLD from a New Zealand Burden of Disease study. These HALYs might be considered 'disability-adjusted life-years (DALYs) averted', but it is critical to note that the own population's lifetable is used for HALY calculation, rather than an 'ideal' lifetable, as is done for calculation of DALYs in burden of disease studies, and no age weighting is used. Our analyses could be repeated with QALYs using one set of the many possible disutilities that have been obtained from breast cancer patients, but it is likely to have a negligible influence given the trivial impact of the uncertainty in disability weights shown in the tornado plot.

The model was limited by the paucity of direct comparative data for docetaxel, weekly paclitaxel and 3-weekly paclitaxel. Given the importance of relatively small differences in survival effects in this analysis, further direct comparisons are needed if decision makers want to recommend one or other of docetaxel or weekly paclitaxel.

Dose reductions and dose delays were not modelled in the analysis due to the complexity of incorporating these. However, this is not likely to have significantly affected the results. When chemotherapy is potentially curative, a reduction in relative dose intensity below 85 % is considered to be clinically important [50–52]. In the E1199 study used in our model, the proportion of patients receiving all doses was 87–95 % [18].

The model does not explicitly model relapse as a state because such data were not directly available from the epidemiological data upon which the model was based. However, the preterminal and terminal phases of the model capture the costs and disability weights associated with progression to metastatic disease and subsequent death. Our model does not capture the (uncertain, and probably small) differences in morbidity between treatments whilst in relapse states that are not preterminal.

Treatment of HER2-positive women with trastuzumab was not specifically included in the model because trastuzumab was not routinely administered within the taxane efficacy trials, although some women did receive it. Thus, the overall survival achieved with taxanes from these trials partially but incompletely captures the additional benefit of trastuzumab, and can be considered as modestly overestimating the HALY gains compared with the scenario that all HER2-positive patients (approximately 20 % of all patients) were receiving trastuzumab.

This analysis was modelled to occur within the current structure of the New Zealand health system. The regimens used are from international studies and are likely to be largely similar in other countries. Disability weights are from the Global Burden of Disease, with only minor adaptation for New Zealand and are thus internationally valid. However, there may be different practice patterns in managing adverse events in different countries, which could affect costs, particularly those costs associated with management of febrile neutropenia. Primary G-CSF prophylaxis to prevent febrile neutropenia is not usual clinical practice in New Zealand but is in certain other countries. Because of the higher rates of febrile neutropenia associated with docetaxel, recipients of the latter are more likely to be given primary G-CSF than those receiving paclitaxel. How important this would be in terms of reducing the difference in costs between docetaxel and weekly paclitaxel depends on the proportion of docetaxel recipients that would be expected to receive primary prophylaxis; as well as the risk associated with docetaxel, the decision to give primary prophylaxis will also depend on the individual's risk factors for febrile neutropenia [53]. Finally, pharmaceutical costs in New Zealand are often substantially lower than in other similar countries such as Australia because of the widespread use of generics and the strong price negotiation abilities of the central funding agency, PHARMAC. Nevertheless, as this is an incremental analysis, lower pharmaceutical costs may not greatly affect the ICER.

5 Conclusions

Both weekly paclitaxel and docetaxel are likely to be cost effective compared with standard 3-weekly paclitaxel if we assume even a relatively modest survival advantage for docetaxel and weekly paclitaxel over standard 3-weekly

paclitaxel. While the ICER was lower for docetaxel, the health gains were greater for weekly paclitaxel in our model and weekly paclitaxel was the optimal choice for WTP thresholds that may be acceptable in New Zealand (>$NZ27,000 [$US18,200] per HALY gained). However, the model was highly sensitive to uncertainty around survival differences, while toxicity-related morbidity had little impact. Thus, if it was assumed that weekly paclitaxel and docetaxel had the same efficacy, weekly paclitaxel became highly cost ineffective versus docetaxel, and the latter was favoured. Reduced uncertainty about the relative survival benefits may improve decision making for funding.

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Competing interests The authors have no competing interests.

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