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PAMIDRONATE FOR THE PREVENTION OF SKELETAL-RELATED EVENTS IN MULTIPLE MYELOMA

What Does the Public Think It Is Worth?

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Abstract

Multiple myeloma is a disorder of the bone marrow that is associated with bone pain and osteolytic lesions. These complications can lead to the development of pathologic fractures and severe patient morbidity. However, the results of a recent randomized trial in patients with multiple myeloma demonstrated that single 90 mg monthly doses of pamidronate as an adjunct to chemotherapy reduced the incidence of skeletal-related events and improved patients' quality of life. A cost-benefit analysis using an *ex-ante insurance* willingness-to-pay (WTP) approach was conducted from a Canadian societal perspective to estimate the net cost or benefit of prophylactic pamidronate therapy for patients with multiple myeloma. This included direct costs for drug administration and hospital savings secondary to avoiding skeletal-related events. One hundred Canadian taxpayers were then interviewed to ascertain their maximum WTP for the benefits of pamidronate. The WTP survey instrument was simple to administer and easily understood by participants. Respondents stated that they would be willing to pay an average of Can $3,364 (95% CI: $2,096, $4,632) as an income tax increase to be paid over their lifetime for the value offered by the product. The benefit was then subtracted from the overall cost of nine monthly doses of pamidronate ($4,153) producing a net societal cost of $789 per patient (95% CI: (−$479, $2,057). The administration of monthly pamidronate therapy in multiple myeloma patients produces a situation of cost neutrality (societal benefits = costs). Additional clinical trials to identify high-risk patient subgroups that would most benefit from the drug are needed.

Keywords: Cost-benefit, Pamidronate, Multiple Myeloma, Willingness to Pay

An aging population in countries around the world has translated to an increased use of limited medical resources. One therapeutic area that is particulary prone to an increased consumption of high-cost pharmaceuticals is oncology. Furthermore, it has been projected that cancer patients will require the largest proportion of the health care budget because cancer will surpass cardiovascular disease as the leading cause of death beyond the year 2000 (11). Given these projections, the many therapeutic areas will be competing for limited health care funds. The emerging

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discipline of pharmacoeconomics may provide important information to facilitate health policy decision making by allowing an objective comparison of the costs and effects of treatment alternatives.

The most commonly used method for pharmacoeconomic assessment has been the cost-effectiveness analysis (CEA), where the outcome is expressed as an incremental cost per unit of effectiveness gained (e.g., quality-adjusted life-years [QALYs], pain-free days) (5). Although CEA is a valuable tool for identifying therapies that are economically dominant (e.g., more effective and less expensive), deficiencies develop when a given treatment is both more expensive and more effective. When such a situation occurs, health care decision makers are forced to make a value judgment on behalf of society. Further difficulties arise when the decision maker has to choose between two clinically attractive drug therapies from distinct treatment sites (cardiology vs. oncology) that present unique incremental cost-effectiveness ratios (e.g., incremental cost per life-year saved vs. incremental cost per vomiting episode avoided). Without a common yard-stick for comparison, inappropriate formulary decisions can be made.

Pharmacoeconomic league tables have been developed as sources of value judgment (12), but they are not comprehensive enough to include a wide variety of disease sites. In the Canadian health care setting, Lapaucis et al. (10) published guidelines for evaluating new medical technologies and recommended an incremental cost of Can $20,000 per QALY as a value cutoff, where any therapy below this level should be adopted into clinical practice. However, the data source and methodological process used in determining the $20,000 threshold has been extensively criticized (7;15). As a result, the recommendations of Lapaucis and colleagues have not been widely adopted by health economists and hospital formulary committees.

An alternative to CEA that has gained renewed interest in recent years is cost-benefit analysis (CBA). In this process, both the costs (inputs) and benefits (outcomes) of a given therapy are expressed in monetary units, thus permitting the net societal benefit (i.e., benefit minus cost) of the medical intervention to be calculated (5). What makes CBA attractive to health care decision makers is that each new medical technology can be presented as a net benefit or incremental cost to society, thus allowing a comparison of alternative drug therapies from a wide variety of disease sites (i.e., the common yardstick).

Another advantage of CBA is that, unlike CEA, it can be used to assess the value of a new medical intervention in subjects who do not directly benefit from the treatment, the so-called "spill-over effects" or externalities (16). For example, a man may derive external benefit (which he might be willing to pay for) when his spouse with breast cancer is offered an effective new therapy. Since CEA is unable to capture these nonuser benefits, it may underestimate the value of the treatment.

There has been considerable dialogue concerning the most appropriate method for measuring the dollar value of an improvement in health, but the general consensus has been toward a consumer estimate of willingness to pay (WTP) (6;16). This method has been used to assess the value of a broad range of medical specialties, including low osmolality contrast media, angina pectoris attacks, and chronic depression (1;9;17).

There are two methods for health care WTP studies, the *ex-post user*–based perspective and the *ex-ante insurance*–based approach (16). In the former strategy, the respondent has the disease in question and is at the point of requiring the medical intervention. Once information on the benefits and risks of the new therapy

is disseminated, the subject is then asked to estimate their WTP (in dollars) for the benefits offered by the new treatment.

In the latter technique, a healthy subject is presented with information on the risk of acquiring the disease and the potential benefits and risks offered by the new treatment program. The WTP question is then posed in the form of a hypothetical insurance scenario where respondents are asked what annual insurance premium they would be willing to pay for the rest of their lives in order to make the drug available to them for possible use in the future. In the Canadian health care setting and countries of the European Union, WTP questions for the *ex-ante insurance*–based approach should be presented as an income tax increase since health care is publicly funded.

There is ongoing discussion as to which method is most appropriate. It has been argued that the *ex-post user*–based approach is not consistent with the fundamental theory of CBA and may lead to an underestimation of WTP. The primary reason is related to the fact that nonuser values (for people at risk who do not get the disease) and spillover effects are not captured in the evaluation. Since the *ex-ante insurance*–based approach is able to capture values from all the relevant groups (nonusers, spillover effects), it is the recommended strategy (6;16).

In this study, an *ex-ante insurance*–based WTP strategy was used to estimate the value that the Canadian tax-paying public has for pamidronate, an agent in the bisphosphonate class of compounds that has been approved in Canada for the prevention of skeletal-related events (pathologic fractures and radiation therapy to bone) in patients with advanced multiple myeloma (3;18;21).

METHODS

Clinical Trial

The clinical efficacy data were obtained from a large randomized, double-blind, placebo controlled trial in patients with advanced multiple myeloma (2). Three-hundred and ninety-two patients were stratified based on chemotherapy treatment (first-line vs. second-line), then randomized in a 1:1 ratio either to receive a 4-hour intravenous (IV) infusion of pamidronate at a dose of 90 mg or to a placebo group. Treatment was repeated every 4 weeks for nine cycles. The objectives of the trial were to determine whether pamidronate reduced the incidence of pathologic fractures and radiation treatment to bone (2).

After nine cycles of treatment, the outcomes of the trial revealed that 54 of 181 evaluable patients (30%) in the placebo group developed at least one pathologic fracture compared to only 34 of 196 subjects (17%) in the pamidronate group ($p = .004$). In addition, the incidence of radiation treatment to the bone in the control and experimental arm was 14% and 22%, respectively ($p = .05$). The investigators also reported that patients receiving pamidronate had significant improvement in pain control relative to baseline, no increase in analgesic drug use, and no deterioration in performance status or quality of life compared to baseline. However, overall survival rates were similar between groups (2).

Estimation of Cost

The study was a cost-benefit analysis. The analytic time period for the investigation was 9 months and a societal perspective was taken. The cost portion of the CBA was calculated assuming a 90 mg 4-hour infusion of pamidronate administered every 4 weeks for a total of nine doses. The cost estimate also included expenditures for

patient admission to the ambulatory care unit, drug preparation, administration, supplies, and patient monitoring during the infusion. The final estimate was then adjusted for the potential hospital savings as a result of the absolute risk reduction (ARR) for pathologic fractures and radiation treatment to the bone.

Hospital resource consumption data secondary to pathologic fractures and radiation treatment were obtained from a retrospective chart audit of multiple myeloma patients who presented to the Princess Margaret Hospital (PMH) from 1990 to 1995. Eligible patients were selected via a random number table. To be eligible, patients had to have had an immunologic diagnosis of multiple myeloma, been receiving either first- or second-line chemotherapy, had at least one osteolytic bone lesion, and developed a pathologic fracture within 9 months of starting chemotherapy. Patients were ineligible if they had received bisphosphonates during the 9-month analytic period. After an initial screening process, a final sample of 25 multiple myeloma patients was selected. With a sample of 25 subjects, the hospital cost of a pathologic fracture was measured with a precision that extended to ±$3,000, 95 times out of 100.

Using cost statistics from the PMH, the average cost of a pathologic fracture and radiation treatment to the bone was determined. This included direct costs for daily hospitalization secondary to pain control or radiation treatment to bone, analgesic prescriptions (including the pharmacy dispensing fee), diagnostic imaging, fractionated radiation therapy, laboratory tests, and all related physician fees. These estimates and the ARRs for pathologic fractures and radiation therapy to bone were then used to adjust the total cost of pamidronate therapy over the 9-month treatment period. The final figure represented the "cost" portion of the economic evaluation.

The acquisition cost of pamidronate was obtained from Novartis Pharma Canada Inc. The cost of daily hospitalization for the PMH ($644/day) was estimated by Doyle et al. (4). The cost of physician fees for service was obtained from Schedule of Benefits: Physician Services Under the Health Insurance Act, Ontario Ministry of Health, October 1, 1992. The costs quoted in this study were in Canadian dollars (Can $1 = US $0.70 as of June 1998).

Estimation of Benefit

The "benefits" portion of the study was determined using the *ex-ante insurance*–based WTP approach (6;16). It has been recommended in the Canadian guidelines for economic evaluations that health care preferences for new drug therapy be estimated from members of the general public, who indirectly finance the Canadian Health Care System and are potential candidates for the new therapy (22). Hence, survey respondents consisted of 100 healthy volunteers who were Canadian taxpayers. With a sample of 100 subjects, maximum WTP was measured with a precision that extended to ±$65.00, 95 times out of 100.

Survey respondents were selected from a total of seven study sites (approximately 14 subjects per site). The objective of the WTP survey was to draw a random sample of respondents from five city districts in the metropolitan Toronto area, an alternative city in southern Ontario, and a northern Ontario township. Using a systematic multistage random sampling technique, respondents from the greater metropolitan Toronto area came from Mississauga, Etobicoke, Toronto, North York, and East York. Subjects from the alternative southern and northern Ontario sites were from Hamilton and Owen Sound, respectively.

To be eligible for the survey, subjects had to be 18 years of age or older, have permanent residence status in Ontario, indirectly support the Canadian health care system through tax contributions, and give informed consent to participate in the interview. Respondents were interviewed face-to-face by two trained field investigators via a door-to-door contact strategy. The participant's name was not asked at any point of the interview. The only personal information recorded was age, marital status, education, household income, religious affiliation, number of children, and family history of cancer.

Subjects were assured that participation was voluntary, and they were free to withdraw at any time. In order to maximize study generalizability, the interviews were conducted on weekends or in the evening, when most of the taxpaying public was not at work. At the completion of the session, each subject received a $10 honorarium. For nonresponders, demographic data and reason for refusal were obtained when possible.

In subjects who consented to be interviewed, the first part of the session attempted to standardize the knowledge base of all participants by presenting to them information on the Canadian incidence rate for multiple myeloma (14), the usual treatments including chemotherapy, expected length of survival, and the natural history of the malignancy. The development of osteolytic bone lesions was then described in detail. This included a description of bone pain, analgesic use, radiation therapy, and pathologic fractures. To avoid cognitive overload, information on each event was presented separately.

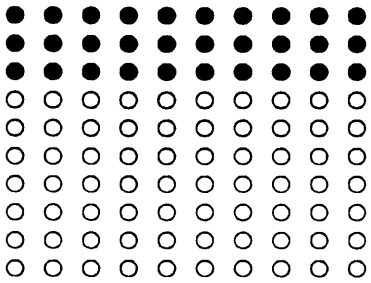
To introduce the WTP scenario to each respondent, the probability of each skeletal-related event (pathologic fractures, radiation to bone) associated with chemotherapy alone or in combination with pamidronate (referred to as the hypothetical new drug) was presented both numerically and graphically. This was similar to the approach used by O'Brien et al. (17) and Appel et al. (1). The graphical presentation consisted of a series of open and solid circles in order to illustrate the absolute risk reduction (for each event) in patients who received pamidronate with chemotherapy (Figure 1). The risk reductions presented to each subject were obtained from the clinical trial (2). Verbal information on the toxicity profile of the new drug (e.g., hypocalcemia) was also provided to each participant. Subjects were told to keep in mind that multiple myeloma was a rare disease, and that there are many other medical conditions (e.g., HIV, heart disease, etc.) that are competing for the same health care funds.

After all of the background data was introduced, respondents were asked to rank the significance of each risk reduction on an 11-point scale where zero represented, "not important at all" and 10 was "very important" (Figure 1). Subjects were then asked the maximum that they would be willing to pay to make the new drug available to them, to a family member, or to Canadians in general, given the current risk of multiple myeloma.

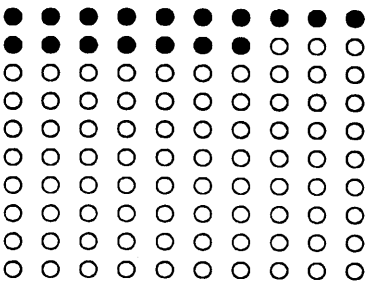
In order to make the scenario realistic relative to the Canadian health care system, the WTP questions were structured in the form of a hypothetical taxation question. Specifically, respondents were asked the following: "Now imagine that this new drug is not paid by the Canadian health care system. Thinking realistically about how much you can afford to pay, what is the maximum income tax increase per year, you would be willing to pay to make the new drug available to you, a family member or to Canadians in general for a possible use in the future. Please note that you cannot stop payments once they get started."

Out of 100 patients with multiple myeloma, 30 will have suffered from a broken bone within 9 months (Situation A). Suppose there is a new drug available to patients. When it is given intravenously every month for 9 months, it can protect patients against broken bones. With the new drug, the chance of broken bones is reduced to 17 of 100 patients (Situation B). Other benefits of the new drug are reduced bone pain, less need to take pain medication, delaying the advancement of broken bone and an improvement in a patient's overall strength.

SITUATION A
(Risk = 30%)



SITUATION B: WITH NEW DRUG
(Risk = 17%)



Pause for a moment and ask yourself whether it would be important for you to make this drug available to you, a family member or to Canadians in general for a possible use in the future.

Indicate on the scale below how important it would be for you to help patients reduce the chance of broken bones from 30 in 100 to 17 in 100.

not at all important					somewhat important					very important
0	1	2	3	4	5	6	7	8	9	10

Now imagine that this new drug is not paid for by the Canadian health care system. Thinking realistically about how much you can afford to pay, what is the maximum income tax increase per year, you would be willing to pay to make the new drug available to you, a family member or Canadians in general for a possible use in the future. Please note that you cannot stop payments once they get started.

Figure 1. Survey instrument used to measure maximum WTP for reducing the risk of bone fractures.

In order to minimize the effect of starting point bias, the payment card method was used as described by Mitchell and Carson (13). A respondent's initial value was recorded as their WTP estimate and a "bid up" was not attempted by the surveyor. To prevent cognitive overload, an identical scenario was presented for

each of the two risk reductions (pathologic fractures, radiation treatment) separately. To avoid an order effect, the two WTP scenarios were presented in a random fashion.

Comparison of Costs and Benefits

A classic cost–benefit framework was adopted for the analysis, where the total cost of nine cycles of pamidronate therapy was subtracted from the overall benefit, which was the maximum WTP estimate adjusted for the life expectancy of the respondent. It could not be assumed that the total sum of individual WTP estimates for each of the risk reductions would represent a respondent's overall WTP for pamidronate. As a result, a conservative approach was taken where the *greatest* of the two WTP responses was used as the maximum amount that a Canadian taxpayer would be willing to pay per year to make the new treatment available to them for a possible use in the future.

When the maximum WTP estimate was established for each subject, it was multiplied by his or her life expectancy, because WTP tax contributions would only cease at the end of a subject's life-time. Life expectancies for men and women living in Ontario were obtained from Statistics Canada (20). The maximum WTP for pamidronate was also discounted at a rate of 3%, as recommended by the Panel on Cost Effectiveness in Health and Medicine (19). The final age-adjusted WTP estimate represented the societal value for pamidronate therapy and was used in the CBA. To be consistent with welfare economic theory, the mean WTP was used to represent the average societal value. Lastly, a comprehensive sensitivity analysis was conducted to test the robustness of the baseline results.

Statistical Analysis

Demographic data and WTP estimates were presented as descriptive statistics as either means, medians, or proportions. Costs for bone fractures and radiation therapy were also presented as means with 95% confidence intervals (CI). In calculating the average WTP, the denominator was all surveyed persons, with zero imputed for those subjects who would not pay for the new drug. The Wilcoxan signed rank procedure was used to test the significance of the difference between the rating scores and the WTP estimates.

In order to measure the association between WTP and subject characteristics (e.g., sex, marital status, household income, age, etc.), a multiple regression approach was employed. The dependent variable in the model was the maximum (unadjusted) WTP estimate. Before the regression analysis was initiated, the relevant covariates for model inclusion were identified by a bivariate screening process with a preset alpha = 0.15. This is a recommended approach for removing unimportant covariates so that a more manageable set of variables can be submitted to multivariate techniques (8). The cut-off for significance for all of the statistical procedures was at the 5% level.

RESULTS

Estimation of Cost

In the comparative trial (2), multiple myeloma patients randomized to the pamidronate group received a 90-mg dose of study drug as a 4-hour infusion every 4 weeks. As a result, the cost of pamidronate would be $597 per 4-week cycle. This includes costs for drug preparation, administration, supplies, and ambulatory care admission.

Table 1. Clinical and Demographic Data of Multiple Myeloma Patients with Pathologic Fractures

Characteristic[a]	Patient data (n = 25)
Sex, %	
Male	13 (52)
Female	12 (48)
Age, yr	64 (40–82)
Weight, kg	65.5 (43.2–104)
Height, cm	159 (105–182)
Serum creatinine, μmol/L	90 (72–260)
Serum Ca, mmol/L	2.4 (2.0–3.6)
Myeloma subtype, %	
IgA	4 (16)
IgG	13 (52)
Light chain	4 (16)
Unknown	4 (16)
Chemotherapy, %[b]	
Melphalan/prednisone	25 (100)
Cyclophosphamide/prednisone	7 (28)
Vincristine/doxorubicin/dexamethasone	9 (36)
Bone marrow transplantation	1 (4)

[a] Median (range).
[b] All patients received melphalan/prednisone as primary chemotherapy.

Over nine treatment cycles, the total cost of pamidronate would be approximately $5,373.

The retrospective chart audit identified 25 PMH patients with multiple myeloma who developed pathologic fractures. Patient demographic and clinical data are presented for the entire sample in Table 1. A comparison with patients who participated in the randomized comparative trial revealed similar physical and disease characteristics (2).

In the PMH random sample, all patients developed at least one pathologic fracture during the 9-month evaluation period. The total number of hospital days secondary to fractures was 258 with a 10-day mean length of stay (Table 2). When health care resource costs for hospitalization, drug therapy (including take-home

Table 2. Cost of Treating a Pathologic Fracture in Patients with Multiple Myeloma

Resource item	Mean cost (n = 25)
Total hospital days	258
Length of hospitalization, days (range)	10 (0–47)
Cost of hospitalization[a]	6,646
Drug therapy[b]	1,453
Medical consultations[c]	36
Diagnostic imaging[d]	302
Laboratory tests[e]	142
Total cost per patient (95% CI)	$8,579 ($4,392–$12,766)

[a] Daily cost abstracted from Doyle et al. (16).
[b] Analgesics, stool softeners, antidepresssants etc.
[c] Pain, orthopedic, anesthesia.
[d] Skeletal surveys, CT scans, MRI, X-rays.
[e] Serum creatinine, calcium, etc.

Table 3. Cost of Radiation Treatment to Bone in Patients with Multiple Myeloma

Resource item	Mean cost (n = 23)[a]
Total radiation consultations	63
Median, range	2 (1–8)
Consultation costs	$368
Total number of fractions	182
Median, range	6 (2–27)
Total median dose, cGy, range	2,400 (400–7,600)
Fractionated radiation costs	$903
Total cost per patient (95% CI)	$1,311 ($878–$1,744)[b]

[a] Two patients from the original sample of 25 were not referred for radiation therapy.
[b] Individual mean costs do not necessarily add up to the final sum.

prescriptions), medical consultations, diagnostic imaging, and laboratory tests were included, the total cost per patient was approximately $8,579 (Table 2).

From the original sample, 23 of 25 patients required radiation therapy to the bone. The total number of radiation oncology consultations was 63, with a median of two per patient (Table 3). Over the 9-month evaluation period, a total of 182 radiation fractions were delivered to the 23 patients. This translated to a median of six fractions per patient for a total dose of 2,600 centigray (cGy). Combining expenditures for consultations and radiation therapy, the mean cost per myeloma patient receiving fractionated radiation to the bone was approximately $1,311 (Table 3).

The cost estimates for bone fractures ($8,579) and radiation therapy ($1,311) were then multiplied with the corresponding pamidronate ARRs (fractures: 13%; radiation to bone: 8%) to determine the expected hospital savings. By using adjuvant pamidronate in patients with multiple myeloma, the Canadian health care system would save approximately $1,115 in fracture and $105 in radiation therapy costs for an overall savings of $1,220 per patient. The figure was then subtracted from the total cost of pamidronate administration ($5,373). Hence, the net incremental hospital cost of adjuvant pamidronate therapy in multiple myeloma would be $4,153 per patient, which represented the "cost" portion of the CBA.

Estimation of Benefit

The sampling objective of the WTP survey was to interview 100 subjects who were permanent residents of Ontario. A total of 179 people were approached and 79 refused to be interviewed, for an overall response rate of 56%. In this nonresponse group, 38 of 79 nonresponders were male (48%). The interviewers also asked nonresponders for their age and reason for refusal. The approximate median age of this group was 48 years (range, 25–80) and the primary reasons for refusal were that they were "too busy" or "not interested." These results imply that there may be systematic differences between responders and nonresponders.

In subjects who consented to be interviewed (n = 100), the WTP scenarios (Figure 1) were presented for the two risk reductions. The majority of people (76%) came from the greater metropolitan Toronto area. Hamilton and the northern Ontario town of Owen Sound contributed 14 and 10 subjects, respectively. The median age of respondents was 39.5 years, with a balanced distribution for marital

Table 4. Demographic Characteristics of Survey Respondents

Subject characteristics	n = 100
Median age, range	39.5 (18–84)
Sex, %	
Male	33
Female	67
Marital status, %	
Married/common law	51
Single	48
Missing	1
Number of children, %	
None	56
One to two	29
Three to five	13
More than 5	2
Education, %	
Less than high school	11
High school	22
Post-secondary	67
Employment status, %	
Full-time	58
Part-time	19
Unemployed/retired	23
Household income, %	
$Can 0–29,000	38
$Can 30,000–69,000	46
$Can 70,000+	15
Missing	1
Religious affiliation, %	
Christian	79
Jewish	2
Other	15
Missing	4
Family history of cancer, %	
Yes	55
No	44
Missing	1

status and presence of children (Table 4). Approximately two-thirds of subjects were female and had received a post-secondary school education. Seventy-seven percent of the sample were either employed full- or part-time but only 15% had household incomes that exceeded $70,000 (Table 4). The majority of participants (79%) were Christian and just over one-half of the group reported a positive family history for cancer.

After the background information for bone fractures and radiation treatment was presented, subjects were asked to rate the importance of individual risk reductions on an 11-point scale (Figure 1). The outcomes of the survey revealed a median score of 9 ("very important") for each of the two risk reductions (Table 5). The results of the Wilcoxon signed rank test were not statistically significant ($p = .41$), suggesting that respondents valued all the benefits of pamidronate to an equal degree. These observations are not surprising given the similar magnitudes of the two risk reductions (Table 5).

Following the importance rating scale, subjects were then asked to select their maximum WTP for the benefits offered by the hypothetical new drug. The risk

Table 5. Results of Risk Reduction Ratings for Fractures and Radiation Therapy to Bone

Adverse effect	Absolute risk[a] reduction (%)	Mean rank[b] score (95% CI)	Median rank[b] score (range)	*p*-value[c]
Multiple Myeloma				
Pathologic fractures	13	8.2 (7.7–8.6)	9 (2–10)	.41
Radiation therapy to bone	8	8.2 (7.8–8.6)	9 (2–10)	

[a] Difference in the incidence of skeletal-related events between pamidronate and placebo.
[b] Measured on an ordinal scale from zero to 10.
[c] Within-subject ratings evaluated by the Wilcoxon signed rank test. Null hypothesis was that no difference existed in respondent's rating for each risk reduction. This result demonstrated that respondents considered each risk reduction equally important.

reductions were presented as mutually exclusive events using the payment card method (13). Respondents reported that they were willing to pay an average of $135 and $126 per year for a new drug that reduces the risk of pathologic fractures and radiation treatment to bone by 13% and 8%, respectively (Table 6). As indicated by the Wilcoxon signed rank test, the intrasubject WTP estimates were not significantly different ($p = .46$).

From a qualitative point of view, some respondents stated that reducing the risk of fractures and the need for radiation to bone was important to them, but they were not impressed with the modest clinical benefits. They desired more value for each health care dollar spent. Other participants felt that a greater proportion of societal resources should be redirected toward the prevention of cancer as opposed to the treatment of an advanced and usually fatal disease.

Once the final WTP estimates were determined, each value was age-adjusted for the life expectancy of the respondent using Life Table Statistics for Ontario and then discounted at a rate of 3%. Based on these adjustments, participants were willing to pay an average of $3,265 (95% CI: 1,999–4,526) and $3,043 (95% CI: 1,917–4,169) for reducing the risk of fractures and radiation to bone in patients with multiple myeloma. As expected, the two WTP estimates were not significantly different ($p = .47$), suggesting that even after adjusting for age, respondents still considered the benefits of pamidronate to be equivalent. This observation is consistent with the rating scale scores in that people gave identical rankings for each of the benefits (Table 5).

For the "benefits" portion of the economic analysis, the highest of the two WTP estimates represented the maximum amount that a Canadian taxpayer would

Table 6. Maximum WTP Estimate for Risk Reductions in Fractures and Radiation Therapy to Bone

Adverse effect	Absolute risk reduction (%)[a]	Maximum WTP (95% CI)	($) per year Median (95% CI)	*p*-value[b]
Pathologic fractures	13	135 (83–188)	32 (20–55)	.46
Radiation therapy to bone	8	126 (80–173)	28 (20–55)	

[a] Difference in the incidence of skeletal-related events between pamidronate and placebo.
[b] Within subject WTP estimates were evaluated by the Wilcoxon signed rank test. Null hypothesis was that no difference existed in respondent's WTP for each risk reduction. This result demonstrated that respondents were willing to pay equivalent amounts for each risk reduction.

pay over a lifetime to make the drug available to them for possible use in the future. Hence, the maximum WTP for multiple myeloma would be an age-adjusted average of $3,364 (95% CI = $2,096–$4,632).

Multivariate Analysis

The greatest of the two unadjusted WTP estimates was used as the dependent variable in the multivariate analysis. An initial assessment of maximum WTP (dependent variable) revealed that it was highly skewed by a small number of high-value cases and also contained several zero WTP responses. This is a common occurrence in contingent valuation studies, and the standard practice of normalizing the distribution by adding one to each value and then taking its natural logarithm [Ln(WTP + $1)] was employed. The adequacy of the procedure was verified by inspection of the normal plots and calculation of the Shapiro-Wilks W test statistic.

The final multiple regression model generated a disappointing adjusted R^2 value of 0.12, suggesting that only 12% of the variability observed in the dependent variable was accounted for by the independent variables. The results of the regression procedure determined that only children in the family and religious affiliation were significantly associated with the maximum WTP. A closer examination of the parameter for children revealed that while controlling for the other covariates, respondents with children were willing to pay approximately threefold more than those without. The model also implied that non-Christians were willing to pay three times as much as Christians.

Comparison of Costs and Benefit

The age-adjusted average value of respondent's maximum WTP ($3,364; 95% CI: $2,096–$4,632) was then subtracted from the overall cost of 9 months of pamidronate therapy ($4,153). This resulted in an incremental cost of approximately $789 per patient (95% CI: −$479–$2,057). Since these limits encompass the zero value, they imply that pamidronate use in patients with multiple myeloma may result in a situation of cost neutrality (health care costs = societal benefits).

Sensitivity Analysis

A comprehensive sensitivity analysis was then conducted to test the robustness of the primary results. For the baseline CBA, a conservative approach with the WTP estimate was taken in that only a respondent's highest value was used ($3,364) in the analysis. However, if a simple cumulative model was assumed, the upper limit of a subject's maximum WTP would be $6,308. Reanalyzing the baseline results with this upper limit altered the original finding of the analysis. The outcome produced a net societal benefit of $2,155 per patient. However, a cumulative sum of respondent WTP estimates is an unlikely scenario. What is more probable is that the true WTP would be between the single maximum estimate ($3,364) and the cumulative sum ($6,308).

The sensitivity investigation was then continued on the cost of bone fractures $8,579 (95% CI: $4,392–$12,766), and radiation to bone $1,311 (95% CI: $878–$1,744) estimated from the chart audit (Tables 2 and 3). Using the combined upper confidence limits, the results of the procedure reduced the incremental societal cost from $789 to $210 per patient. Contrary to this, reanalyzing the data with the lower confidence limits increased the net cost to $1,368. These results suggest that the baseline outcomes were relatively insensitive to variations in the cost estimates for fractures and radiation to bone.

Since respondents were informed that annual WTP payments would continue for the balance of their lives, the final sensitivity maneuver focused on the 3% discount rate. The data were reanalyzed with the discount rate set at 5%. The age-adjusted maximum WTP was reduced from $3,364 at the 3% rate to $2,533 (95% CI: $1,579–$3,488). Subtracting this estimate from the total drug cost ($4,153), the impact was to increase the overall societal cost ($1,620; 95% CI: $665–$2,574), suggesting that the baseline results were highly sensitive to the discount rate used.

DISCUSSION

Within the framework of the scenarios presented in the current study, the results of the CBA suggest that the use of adjuvant pamidronate in patients with multiple myeloma produces a situation of cost neutrality (e.g., health care costs = societal benefits). These outcomes were stable despite extremes in the cost of treating fractures and radiation to bone. However, the baseline results were sensitive to variations in respondents' maximum WTP and discount rates.

The net societal cost of pamidronate ($789 per patient) was highly dependent on the average WTP estimates. An analysis with the 95% CI of the maximum WTP ($2,096–$4,632) revealed an overall societal cost between −$479 and $2,057. This outcome is consistent with a situation of cost neutrality. However, a major objective of health care policy decision making is to introduce new medical therapies that produce an overall societal benefit. In order for prophylactic pamidronate therapy to become economically attractive (benefits > costs), additional clinical studies are required to identify high-risk patient subgroups who would receive the most benefit from the drug.

The WTP survey provided some insight into cancer care as perceived by members of the Canadian public. All subjects ranked the risk reductions as being equivalent and were willing to pay similar amounts for each (Tables 5 and 6). This outcome could be related to the fact that the two risk reductions were within 5% of each other. Furthermore, the study may not have had the statistical power to detect WTP differences at this threshold.

The multivariate model of association revealed some interesting relationships between subject demographic characteristics and maximum WTP. The results suggested that respondents with children were willing to pay approximately three times as much as those without children. The positive effect of children on WTP may be related to the general desire of Canadian society to protect the dependents of patients with potentially terminal diseases. However, the multivariate analysis was disappointing because the adjusted R^2 for the model was only 12%, indicating that other more important factors were involved when respondents were contemplating value for money. Without additional research into an individual's decision-making process for health care, one can only speculate what these factors could be.

The utilization of the WTP approach within the framework of a CBA is new to the oncology setting. The most commonly used methods for economic evaluations have been cost-effectiveness/utility analyses, with outcomes reported as incremental cost per life-year saved or QALY gained. These methods have been useful but are limited by their inability to include nonuser values (externalities) and common economic outcomes for comparison between disease sites (e.g., cost per QALY vs. cost per infection cured) are not available. The advantage of WTP is that it is able to measure externalities. In addition, the outcomes are in monetary terms that

allow for comparisons between a wide variety of medical specialties and other societal programs (e.g., resource allocation for health care vs. education).

The limitations of the current CBA must be addressed. A major drawback was due to the cost of treating skeletal-related events. These estimates were obtained from patients treated at the PMH only and may not necessarily represent resource use of other institutions across the country. Furthermore, only direct hospital and drug-related expenditures were collected; additional costs for physiotherapy, chronic care, and time off work were not included in the analysis. The inclusion of these additional costs would improve the economic profile of pamidronate in patients with multiple myeloma.

Another point that has to be discussed is related to the survey sample interviewed in this investigation. Response rate was low (56%), the number of subjects was small (n = 100), and subjects were from Ontario only. In addition, systematic differences in sex and age were observed between responders and nonresponders. Therefore, selection bias may have been introduced, and the sample of Canadian taxpayers interviewed may not be representative of the entire population. It is possible that subjects who consented to be interviewed were those people who were most interested in issues related to cancer. Therefore, it is reasonable to speculate that this "interested" subgroup of the population would have been willing to pay a higher amount than the nonresponders. A random digit dialing telephone survey may have provided a more representative sample and a higher response rate. This strategy should be considered for future WTP studies.

In conclusion, the results of the CBA suggest that adjuvant pamidronate (90 mg/cycle) administration in patients with multiple myeloma produces a situation of cost neutrality. In order to use the drug in situations where societal benefits exceed cost, additional clinical studies are required to identify patient-specific subgroups who would most benefit from the drug. This will ensure that optimum patient care is achieved at a reasonable cost to the health care system.

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