

Preference weights for chemotherapy side effects from the perspective of women with breast cancer

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Received: 2 July 2013 / Accepted: 3 October 2013 / Published online: 16 October 2013
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Abstract Perceptions among women with breast cancer about the relative importance of different potential chemotherapy side effects is not well understood. A survey was performed by women receiving chemotherapy for breast cancer. Grade I/II (mild to moderate) and III/IV (moderate to severe) descriptions of nine common chemotherapy side effects were assigned preference weights using the standard gamble technique. For each hypothetical side effect, patients could choose to stay in the respective side effect state or take a gamble between full health (probability p) or being dead ($1 - p$). For each side effect, p was varied until the patient was indifferent between these options. The survey also included questions about the importance of survival, slowing

cancer growth, and quality of life. This analysis included 69 patients; mean age 54 years (range 35–84), representing all cancer stages. Standard gamble preferences were lowest (i.e., least preferred) for grade III/IV nausea/vomiting (0.621), indicating that patients would, on average, risk a 38 % chance of being dead to avoid having grade III/IV nausea/vomiting for the rest of their lives. The next least preferred side effects were grade III/IV diarrhea (0.677) and grade III/IV sensory neuropathy (0.694). Survival appeared more important than slowing cancer growth and maintaining quality of life across cancer stages. Nevertheless, patients with advanced disease placed less importance on survival ($p = 0.09$) and higher importance on quality of life ($p = 0.05$). These standard gamble utilities provide unique insights into chemotherapy toxicities from the patient perspective. Differences in the relative importance of overall survival and quality of life with treatment existed between patients with different stages of disease. These studies should be expanded as the data may also be used to calculate quality-adjusted life expectancy in cost-effectiveness evaluations of breast cancer chemotherapies.

Data has been previously presented as a poster presentation at ASCO meeting 2013, June 3, abstract #6595.

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Keywords Standard gamble · Utility · Breast cancer · Chemotherapy

Introduction

Women with early-stage and metastatic breast cancer are frequently treated with multiple lines of chemotherapy. Relatively little is known about how patient perceptions of the various possible side effects of chemotherapy affect decisions about ongoing and subsequent treatments [1]. There may be particular side effects that may make a patient decide not to receive a particular agent or to discontinue

treatment altogether. Knowing more about patient preferences associated with these side effects could help physicians, patients, and drug funding agencies make appropriate treatment and funding decisions [2].

Patient preferences (or utilities) are a key component in cost-effectiveness analyses that incorporate quality-adjusted life years (QALYs) by combining longevity with quality of life [3]. Specifically, a utility weight is assigned to each health state experienced by a patient on a scale where 0.0 reflects being dead and 1.0 reflects full health [4]. Evaluation of the incremental cost per QALY gained, or cost–utility analyses, is now a standard type of cost-effectiveness analysis [5, 6].

With respect to utility estimates that are relevant to patients with breast cancer, studies that have obtained such estimates have primarily focused on health states occurring in early-stage disease [7, 8], or have obtained such valuations from the general population [9] or nurses [10]. Moreover, we are not aware of any studies that have obtained utilities for individual mild/moderate and severe chemotherapy side effects directly from breast cancer patients receiving chemotherapy. The objective of this study was to obtain utility weights from patients with breast cancer for common side effects associated with adjuvant and as well as palliative chemotherapy.

Methods

This cross-sectional survey was performed at two Canadian Cancer Centres (Ottawa Hospital Cancer Center and Irving Greenberg Family Cancer Centre, Ottawa). Eligible patients were females with breast cancer, of all stage disease, who

were currently receiving adjuvant, neoadjuvant, or palliative chemotherapy. Participants had to have adequate written and oral fluency in English and be able to use a computer. After providing written informed consent, participants completed a secure Web survey. Depending upon the patient's preference, they could complete the survey on a laptop in the chemotherapy unit or at home. The participants completed surveys at their own pace and research team members were available via telephone and/or e-mail if the participant required additional assistance. The study was approved by the Ottawa Hospital Research Ethics Board.


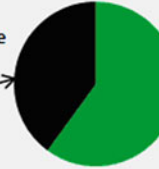
The survey was developed by the study team (NB, MC, KB, and JG) [11] and included questions on demographic/clinical characteristics; agree/disagree questions about the importance of survival, controlling the speed of cancer growth, and quality of life. It also included standard gamble questions, which are designed to obtain preference weights for selected health states. The standard gamble questions in the survey presented different hypothetical health states that each described a side effect of chemotherapy. For each health state, patients were given a choice between two options: the certainty of staying in the hypothetical health state the rest of their life or taking a gamble. The gamble had two possible outcomes: full health (with probability of occurrence p) or immediate death (with probability $1 - p$). The probability p was varied in 5 % increments until patients were unable to make a clear choice between staying in the certain state for the rest of their lives and taking the gamble [4]. The objective of the elicitation process is to derive the probability p associated with the indifference point (i.e., utility) between the certain and risky alternative. Figure 1 shows an example of a

Fig. 1 Example question in standard gamble exercise (grade I/II motor neuropathy state)

Please imagine that you are in Health State A:

- You are on chemotherapy.
- You feel weak, shaky, and unsteady in the arms and/or legs, which may make it difficult to hold objects or maintain balance while walking.

Now, imagine you had a choice. You can either remain in Health State A for the rest of your life (Choice A), or you can take a treatment with a 60% chance of full health and a 40% chance of being dead (Choice B). Which would you choose?

<p>Health State A</p> <p>You will remain in this health state for the rest of your life (100% certainty).</p>  <p>100% chance of health state</p>	<p>Choice B</p> <p>You have a 60% chance of full health and a 40% chance of being dead.</p>  <p>40% chance of being dead</p> <p>60% chance of full health</p>
<p>I would select Choice A (click below).</p> <input type="radio"/>	<p>I would select Choice B (click below).</p> <input type="radio"/>

standard gamble question focusing on the grade I/II motor neuropathy health state.

To identify the health states (side effects) to be included in the standard gamble exercise, the literature and medical labeling information for commonly used chemotherapies in breast cancer were reviewed (NB, MC, KB, and JG). As well, breast cancer web forums also were reviewed to confirm that the selected side effects substantially impacted daily life. A total of 17 health states were selected that included alopecia and both grade I/II and grade III/IV categories of eight side effects. The CTC grading criteria and patients' own descriptions of the side effects from patient web forums were used to develop the health state descriptions. The survey was pilot tested in five patients before finalization.

To minimize respondent burden due to the large number of side effect health states being assigned standard gamble utilities, two surveys were developed which differed only with respect to the standard gamble section. Specifically, the side effect health states were divided evenly between the two surveys; the two severity level health states, grade I/II and grade III/IV, for each health state, however, always appeared in the same survey. For example, grade I/II diarrhea appeared with grade III/IV diarrhea in the same survey. The target sample size for this study was 70 respondents, of which 35 would be randomized to one of the two surveys (group 1 and group 2). The target sample size was calculated to allow a 95 % confidence interval of ± 0.10 around the mean utility estimates [12].

Oversampling was permitted to allow for the target sample size to be reached, after elimination of illogical responses, assigning a more favorable utility to the severe versus the mild level of a side effect. For example, if a patient would take a higher risk of being dead to avoid grade I/II nausea than grade III/IV nausea this would be considered an illogical response. Prior experience with web-based standard gamble surveys has shown that illogical response rates, or assigning the same utility to the vast majority of the health states, may be as high as 20 % [13]. It was determined a priori to exclude such patients because these responses indicate that, for some reason, the standard gamble exercise is not working, either because the patient does not understand it or the exercise is not sensitive enough to detect differences between severity levels. Anticipating that such patients would be excluded from the analysis, the total target sample was 100 patients.

Analysis

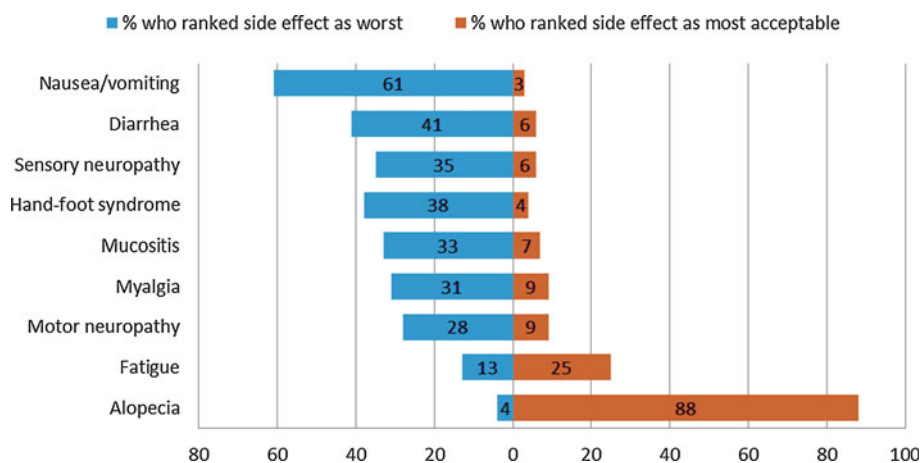
The analyses primarily were descriptive analyses, and means, standard deviations, ranges, and percentages were reported, as appropriate. With respect to the standard gamble scoring, for each health state, the probability p at

Table 1 Demographic/clinical characteristics

Characteristic	Overall ($N = 69$)
Age	
Mean \pm SD	54.0 \pm 10.7
Median (range)	53 (35–84)
Stage, n (%)	
1	12 (17.4 %)
2	16 (23.2 %)
3	29 (42.0 %)
4	12 (17.4 %)
Relationship status, n (%)	
Single	6 (8.7 %)
Married/partner	57 (82.6 %)
Other	6 (8.7 %)
Chronic health problems, n (%)	
Diabetes	3 (4.4 %)
High blood pressure	9 (13.0 %)
Arthritis	8 (11.6 %)
Depression	5 (7.3 %)
Other	18 (26.1 %)
No other health problems	30 (43.3 %)
Current health overall, n (%)	
Excellent	11 (15.9 %)
Very good	29 (42.0 %)
Good	21 (30.4 %)
Fair	8 (11.6 %)
Health in relation to a year ago, n (%)	
Much better	2 (2.9 %)
Somewhat better	5 (7.2 %)
About the same	30 (43.5 %)
Somewhat worse	20 (29.0 %)
Much worse	12 (17.4 %)
Time since diagnosis (months), mean \pm SD (median)	25 \pm 42 (12)
Number of chemotherapy cycles, mean \pm SD (median)	4.30 \pm 3.05 (4)
Number of different chemotherapy regimens received, mean \pm SD	2.3 \pm 1
Impact of any previous adverse events on chemotherapy administration, n (%)	
Skipped chemotherapy session	9 (13.0 %)
Discontinued chemotherapy	5 (7.3)
Switched chemotherapy medications	5 (7.3 %)

the indifference point between choosing to stay in the respective health state versus taking a gamble represents the utility score for the health state. Utility scores range from 0.0, reflecting being dead, to 1.0, reflecting full health. For purposes of interpretation, a mean utility of 0.75 indicates that patients would, on average, risk a 25 %

Fig. 2 Side effects ranked as worst and most acceptable



chance of being dead to avoid being in the selected health state. Exploratory subgroup analyses were conducted using an analysis of variance test. SAS 9.0 was used for all analyses.

Results

From June to December 2012 a total of 102 patients with breast cancer completed the survey. Of these, 33 (32 %) were excluded from the analysis due to having at least two illogical responses (8 %) or assigning at least 80 % of the health states the same utility (24 %), resulting in an effective sample size of 69 patients. Demographic/clinical characteristics did not differ significantly between the excluded patients versus those included in the analysis (Table 1). The mean age was 54 ± 10.7 (range 35–84 years), and each disease stage was represented. Mean time from diagnosis to participation in the study was $25 + 42$ (median-12) months (mean-10 months for adjuvant setting and 40 months for metastatic), and mean number of chemotherapy cycles was $4.30 + 3.05$ (4-median) cycles (mean 4 for adjuvant setting and 6 for metastatic). The patients had received an average of 2.3 different chemotherapy combinations and the majority were receiving anthracycline or taxane-based regimens at the time of the survey. As mentioned above two surveys were developed which differed only with respect to the standard gamble section, patient demographic/clinical characteristics were comparable between these two groups.

Figure 2 shows the frequencies with which each grade III/IV side effect was rated as the worst or the most acceptable side effect (multiple side effects could be rated as the worst or the most acceptable and thus the percentages add up to more than 100 %). Grade III/IV nausea and/or vomiting requiring a physician or emergency room visit was ranked as the worst side effect (60 %), followed by

grade III/IV diarrhea requiring hospitalization (40 %), grade III/IV hand-foot syndrome (37 %), and grade III/IV peripheral neuropathy (34 %). The side effects identified as most acceptable were alopecia (88.4 %) and grade III/IV fatigue (24 %).

Table 2 reports the standard gamble utilities for the side effect health states. The utility for the patients'

Table 2 Utility estimates for each side effect

Health state	Mean \pm SD	Range
Grade I/II diarrhea		
3–6 Episodes of diarrhea per day	0.760 ± 16.8	0.25–0.95
Grade I/II hand-foot syndrome		
Redness, swelling, itching, and peeling skin on hands and feet making it uncomfortable to use them	0.754 ± 16.7	0.20–0.95
Grade I/II mucositis/stomatitis		
Sores in mouth that make eating and drinking uncomfortable	0.747 ± 17.9	0.55–0.95
Grade III/IV mucositis/stomatitis		
Sores and blisters in mouth that make eating and drinking painful	0.739 ± 17.9	0.20–0.95
Grade I/II nausea		
Nausea (feeling sick to the stomach)	0.730 ± 13.0	0.50–0.95
Grade I/II sensory neuropathy		
Numbness, tingling (pins and needles), and burning sensation in hands and feet, making it uncomfortable to write or hold small objects	0.725 ± 18.9	0.50–0.95
Grade III/IV motor neuropathy		
Feeling very weak, shaky, and unsteady, making it difficult to hold objects and requiring a cane or walker or other assistance	0.725 ± 15.1	0.50–0.95
Grade I/II fatigue		
Tiredness requiring extra effort performing daily activities	0.719 ± 21.4	0.55–0.95

Table 2 continued

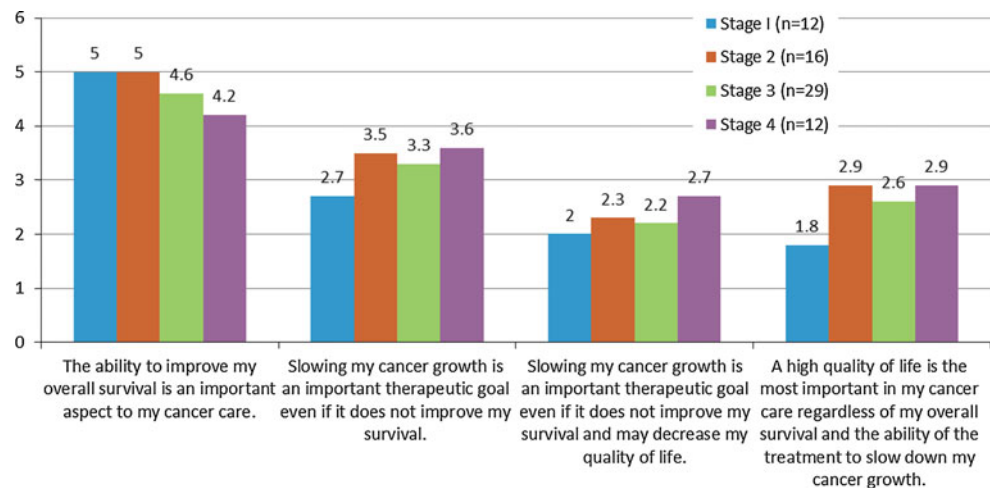
Health state	Mean \pm SD	Range
Grade III/IV fatigue		
Extreme tiredness, making it difficult to perform daily activities	0.717 \pm 18.1	0.10–0.95
Alopecia		
Hair loss, thinning of eyebrows/eye lashes	0.716 \pm 22.5	0.55–0.95
Grade I/II myalgia		
Mild to moderate joint/muscle aches, pains, and stiffness that making movement uncomfortable	0.715 \pm 14.5	0.50–0.95
Grade I/II motor neuropathy		
Feeling weak, shaky, and unsteady in the arms and/or legs, which may make it difficult to hold objects or maintain balance while walking	0.715 \pm 14.5	0.40–0.95
Grade III/IV myalgia		
Severe joint/muscle aches, pain, and stiffness making it difficult to move	0.704 \pm 13.8	0.50–0.95
Grade III/IV hand–foot syndrome		
Tightness of the skin, peeling, sores, and blisters on hands and feet making it very painful to use them	0.700 \pm 18.9	0.25–0.95
Grade III/IV sensory neuropathy		
Severe numbness, sharp tingling (pins and needles), and shooting pain in arms and legs, interfering with daily tasks like holding a pen, dressing, or cooking	0.694 \pm 19.1	0.40–0.95
Grade III/IV diarrhea		
More than 6 episodes of diarrhea per day, requiring intravenous (IV) fluids at the hospital	0.677 \pm 22.1	0.0–0.95
Grade III/IV nausea		
Severe nausea and/or vomiting requiring intravenous (IV) fluids at doctor's office or ER	0.621 \pm 22.2	0.0–0.90

Range = 0, reflecting being dead, to 1.0, reflecting full health

current health was 0.769 ± 15.9 . The utility was lowest (i.e., least preferred) for grade III/IV nausea/vomiting (0.621), indicating that patients would, on average, risk a 38 % chance of being dead to avoid having grade III/IV diarrhea for the remainder of their lives. The next least preferred states were grade III/IV diarrhea (0.677) and sensory neuropathy (0.694). The most preferred states were grade I/II diarrhea (0.760), hand–foot syndrome (0.754), and mucositis (0.747). No statistically significant differences were observed in the standard gamble utilities by cancer stage, age (under 50, 50–59, and 60 or older), and marital status (data not shown).

Responses to the agree/disagree statements regarding the importance of survival, control of tumor growth, and decreasing quality of life showed differences among those in earlier stages of cancer versus those in more advanced stages (Fig. 3). Although not statistically significant, the patients with earlier stage disease appeared to place higher importance on survival than more advanced stage patients. Those with stage 1 disease rated “improving survival is important” as 5.0, and those with stage 4 disease rated this as 4.2 on a 1–5 scale, where 1 reflects “least agree with” and 5 reflects “most agree with” ($p = 0.09$). In addition, patients with more advanced disease appeared to place higher importance on quality of life than those in earlier stages. For example, patients with stage 4 disease provided a mean rating of 2.9 for “a high quality of life is the most important in my cancer care regardless of my overall survival and the ability of the treatment to slow down my cancer growth” whereas patients with stage 1 disease rated this as 1.8 ($p = 0.05$). Nevertheless, across the four cancer stages, those statements that referred to the importance of improving survival generally had the highest agreement ratings compared to those referring to the importance of slowing cancer growth or maintaining quality of life.

Fig. 3 Mean responses to agree/disagree statements (0.0, “least agree with” to 5.0, “most agree with”)



Discussion

Chemotherapy remains an essential component of breast cancer therapy. However, given the increasing importance placed on patient quality of life it is critical that patients, physicians, and drug funding agencies fully understand the potential impact of treatment on patient quality of life. To this end, this study provides valuable information about commonly occurring side effects associated with chemotherapy from the perspective of patients with different stages of disease. It builds on the current literature by not just focusing on one severity level, but includes mild/moderate as well as severe effects. The utility weights derived from this study could also be used in future cost-effectiveness evaluations to quality-adjusted life expectancy based on the patient perspective.

When utilities are used to quality-adjusted survival in cost-effectiveness analyses, the utility weights for each health state experienced by a patient are multiplied by the duration in the respective health states. Given that the mean utility for the patients' current health state was 0.769, disutilities in relation to current or full health for each side effect in this sample of patients can be calculated based on the difference between 0.769 and the utility for the health states. These disutilities can be subtracted from the utilities for health states that may be obtained or estimated for current states of target patients in future cost-effectiveness analyses. When more than one side effect occurs at the same time Fu and Kattan [14] recommend using a minimum model, which predicts a joint-state utility as equal to the lower of the two given single state utilities.

In the current study, it is interesting that despite significant progress in development of anti-emetics, nausea and vomiting remain a major concern for breast cancer patients. Grade III/IV nausea/vomiting was rated as the worst side effect by the highest percentage of patients and also had the lowest utility. This finding was consistent with a previous study in ovarian cancer patients [15]. Previous studies have shown alopecia to be rated as a significant side effect by patients [16–18]. This was also observed in this study, in which alopecia was generally less preferred than other grade I/II side effects but more preferred than grade III/IV side effects.

The utility weights obtained through the standard gamble exercise were consistent with the ratings of the least preferred side effects. Grade III/IV nausea, diarrhea, and hand–foot syndrome were rated as the worst side effects, and they also had among the lowest utilities. This finding is consistent with those observed in previous studies evaluating preferences from the perspective of patients with cancer, in which nausea, vomiting, diarrhea, and sensory neuropathy were among the least preferred side effects [11, 16, 17]. It should be noted that grade III/IV nausea and

grade III/IV diarrhea were the only two side effects in this study that included a visit to the hospital or emergency room as part of the health state description.

The responses to the agree/disagree items show that maintaining quality of life appears to be increasingly important as disease stage progresses. Nevertheless, the agree/disagree data show that survival is as important for patients on palliative treatment (advanced stages) as for patients receiving adjuvant chemotherapy (earlier stages) regardless of quality of life.

This study has several limitations. Although we used a combination of CTC criteria, information from patient web forums, and patient feedback in the pilot test to inform the health state descriptions, the descriptions still may not represent the average experience for patients experiencing grade I/II or grade III/IV events. In addition, the standard gamble exercise was implemented in a web survey as opposed to face-to-face interviews, and this may have contributed to the high illogical or invariable responses obtained. There is clearly patient selection bias due to this methodology as patients had to be comfortable using a computer. The rate of illogical responses in this study of 32 %, however, largely is in the range of that observed in other internet utility surveys [13, 19]. Moreover, this survey took patients an average of 63 min to complete, which might have resulted in fatigue and thus being less careful about responses. Another potential limitation could be the idea of assigning a particular health state “for the rest of your life” as clearly in practice one could stop chemotherapy with resolution of many side effects. However, in standard gamble, the hypothetical state is assumed to last for the rest of life—this is done to obtain a utility value. However, when applied to clinical trial data, the utility is applied only during the duration of the actual health state. So the fact that these are acute health states are taken into account when the QALY is computed.

In conclusion, this study provides insight on chemotherapy side effects from the perspective of patients receiving chemotherapy for breast cancer. The findings help in better understanding patient preferences in oncology and may be used to enhance the medical decision-making process. Given the widespread use of chemotherapy in breast cancer patients, it is essential that we are fully aware of what the most significant side effects of treatment are from the patient's perspective so that we can better set patient expectations with respect to health-related quality of life.

Acknowledgments We would like to thank all the patients and their families for their help with this project. Funding for this study was received in the form of an unrestricted educational Grant from Eisai Pharmaceuticals.

Conflict of interest Susan Dent—speaking honoraria (Eisai). There is no conflict of interest for the other authors.

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