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ORIGINAL ARTICLE

Perspectives toward oral mucositis prevention from parents and health care professionals in pediatric cancer

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Abstract
Purpose The objectives of this study were: (1) to describe parents and health care professionals (HCPs) perceived importance of oral mucositis prevention in children with cancer; (2) To describe utilities and willingness-to-pay (WTP) to prevent mucositis.
Methods Respondents included parents of children receiving intensive chemotherapy for leukemia/lymphoma or undergoing stem cell transplantation and HCPs caring for children with cancer. Importance of mild and severe oral mucositis was estimated using a visual analogue scale (VAS). Mucositis-associated utilities were elicited using the time trade-off technique (TTO). WTP to avoid mucositis was obtained using contingent valuation. These techniques quantify how much time or money the participant is willing to relinquish in order to prevent mucositis.
Results Eighty-two parents and 60 HCPs were included. Parents and HCPs believed mild mucositis to be of similar importance (median VAS 2.5 versus 3.6; P=0.357) while parents considered severe mucositis less important than HCPs (median VAS 8.3 versus 9.0; P<0.0001). No differences in parent versus HCP responses were seen with TTO (mild or severe mucositis) and most parents were not willing to trade any survival time to prevent severe mucositis. Parents were willing to pay significantly more than HCPs to prevent mild mucositis (average median WTP $1,371 CAN vs. $684 CAN, P=0.031). No differences were seen in WTP to prevent severe mucositis.
Conclusions Parents and HCP believe severe mucositis to be important, although it is more important to HCPs. Parents would not be willing to reduce life expectancy to eliminate mucositis.

Keywords Mucositis · Pediatric · Time trade-off · Visual analogue scale · Willingness-to-pay · Preferences

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Introduction

Oral mucositis is a common consequence of chemotherapy, occurring in about 40% of chemotherapy regimens [15]. Children with hematological malignancies receiving more intensive therapies such as those with acute myeloid leukemia (AML), relapsed acute lymphoblastic leukemia (ALL) and advanced lymphoma, and those receiving stem cell transplantation (SCT) are at higher risk for mucositis [5, 9, 12, 19].

Some therapies to prevent mucositis are costly, such as keratinocyte growth factor [29]. Other interventions designed

to prevent mucositis require significant infrastructure and training, such as low-level laser therapy [27]. Mucositis is a side effect of therapy that will resolve with time, and thus, it may be difficult to know how to prioritize resources that are used to prevent or treat mucositis within a given institution, region, or country against other health care needs. Consequently, it is important to know how patients, families, and health care professionals (HCPs) prioritize the importance of mucositis, and how much individuals value the prevention or treatment of mucositis.

In addition to asking respondents to rank the importance of different side effects of chemotherapy, the value of prevention or treatment of mucositis may be measured using utilities for mucositis health states. Utility can be defined as the strength of an individual's preference for a health state measured under conditions of uncertainty that reflect the axioms of von Neumann–Morgenstern expected utility theory [30]. Utilities are an important measure, in part, because of their use in health economic analyses. An accepted method for measurement of utility is the standard gamble (SG) [13]. An SG utility can be represented on a scale that ranges from 0, which represents death or the worst possible health, to 1, which represents perfect or best possible health. However, SG is difficult to elicit [2]; an alternative approach to estimating a SG utility is the time trade-off technique (TTO). TTO is a method that asks respondents to compare different combinations of quantity and quality of life. Finally, to determine the monetary value of a health state, researchers have directly elicited respondents' willingness-to-pay (WTP) to prevent a poor health outcome, an approach termed contingent valuation (CV) [14]. CV can provide a holistic monetary value of the health benefit associated with the prevention of mucositis, where health benefit is defined by a number of quality of life or non-health characteristics [7]. CV has been used to estimate the value of health care interventions such as in vitro fertilization and autologous blood donation [16, 22]. Both TTO and CV are techniques that are widely used within health care [10].

The overall objective of this research was to describe perspectives toward prevention of oral mucositis from parents of children with cancer and HCPs who care for these children. The primary objective was to describe parents and HCPs perceived importance of oral mucositis prevention in children with cancer. The secondary objectives were to value the utility of health states associated with mucositis and to elicit WTP to prevent mild and severe oral mucositis.

Patients and methods

Participants

Two groups of subjects were included in this study: the parent group consisted of parents of children with cancer ≥1 and <18 years receiving induction or consolidation chemotherapy for AML (any type or relapse status), relapsed ALL, advanced lymphoma (any relapse status), or undergoing myeloablative SCT for any indication. Each respondent had to be able to read English. There were no other eligibility criteria. The second group consisted of HCPs caring for children with cancer and included physicians, nurses, or pharmacists. Respondents were drawn from The Hospital for Sick Children (SickKids) in Toronto.

Study design

The study was approved by the Research Ethics Board at SickKids. Written informed consent was obtained from all participants. The study consisted of a single interview to determine the perceived importance and utilities associated with mild and severe mucositis and WTP to avoid these outcomes. Both parents and HCPs were interviewed by trained research assistants using standardized scripts. Hypothetical scenarios of mild (National Cancer Institute Common Toxicity Criteria for Adverse Events (CTCAE v.3) grades 1 or 2) and severe (CTCAE grades 3 or 4) oral mucositis were created and described (see Table 1).

A listing of ten common side effects of chemotherapy was presented and participants were asked to rank them. Next, using a visual analogue scale (VAS), respondents were asked to rate the importance of mild and severe oral mucositis on 100-mm lines anchored at one end by "least important" and the other end by "most important." Then, TTO utilities were elicited; TTO asks what is the smallest

Table 1 Descriptions of mild and severe mucositis states

Mild mucositis
Pretend that your child:
may have none or a few small ulcers and sores inside the mouth (if your child has sores, then, they will not bleed)
will have redness inside his/her mouth (although there is not a lot of redness, but there will be some)
will be able to eat and drink normally or need soft foods (because your child may have some problems swallowing
will have minor discomfort or pain (at this moment and your child may need pain medicine such as mouthwashes and Tylenol
Severe mucositis
Pretend that your child:
will have many large ulcers and sores inside the mouth (your child will have sores that may either bleed on their own or bleed when he/she does things such as brushing his/her teeth
will have redness inside his/her mouth (but it is more red than mild mucositis)
will not be able to eat and drink normally (so that your child would need other ways to eat such as feeding with a tube through a vein)
will have severe discomfort or pain (so that your child may need pain medication given through a vein

number of years in perfect health that the respondent would give up in order to prevent mild or severe mucositis after 1 cycle of chemotherapy/SCT. To facilitate understanding of this concept, a TTO visual aid board was used and respondents were asked to pretend that there was an imaginary treatment that could prevent mucositis but that a side effect of the treatment would shorten the child's life span. Two options were presented using the visual aid board: (1) to accept mucositis and to live for an additional 50 years, or (2) to accept the imaginary treatment that would prevent mucositis but also reduce length of life. The reduction in life associated with elimination of mucositis was systematically altered using a ping-pong approach until the respondent was indifferent to the choice. This exercise was repeated for both mild and severe mucositis. The TTO value was estimated as the point of indifference and was presented as both the number of weeks that the respondent would give up to avoid mild and severe mucositis and as a TTO utility which was determined by the following: TTO= $(50-x)/50$ where x is the number of years given up at the point of indifference. TTO could range from 0 to 1.0.

The final task asked respondents whether they would pay a specified bid amount for an imaginary treatment that would prevent the child from experiencing mild or severe oral mucositis with the next cycle of chemotherapy/SCT. Respondents were instructed to imagine that the cost of the imaginary treatment was not covered by private insurance or the Ontario Health Insurance Plan (OHIP) and that the family would be responsible for paying for these costs out-of-pocket. The starting bid amount each respondent faced was $0; if raters responded with "yes," the bid was set to $100,000. Intermediate bid amounts below $100,000 were determined using a ping-pong approach, where respondents' WTP was accurate up to an interval of $100. For example, if a respondent's final WTP was $400, their "true" WTP would be between $400 and $499. If respondents replied with "no" to the initial bid of $0, the answer was treated as a protest response and subsequently excluded from the analysis [25]. For amounts >$100,000, respondents were asked to state their maximum WTP. Respondents' understanding of the ping-pong task was facilitated using a WTP visual aid board, which was anchored at one end with a $0 amount at one end and $100,000 bid amount at the other. All costs presented are in Canadian dollars. For both TTO and WTP, qualitative comments were also recorded verbatim if possible.

Statistical methods

We compared the ranking of mucositis as a side effect between parents and HCP by examining whether mucositis was the most important side effect and compared these responses using the Chi-square test or Fisher's exact test as appropriate. The importance of VAS and TTO utilities for mild and severe mucositis were compared between parents and HCPs using the Wilcoxon rank-sum test. Respondents' median WTP to avoid mild and severe mucositis was estimated using interval regression, where a log transformation of respondents' WTP was regressed on a categorical variable that indicated if the respondent was a HCP. The standard error of transformed median WTP was obtained through a first-order Taylor series expansion.

The analyses were conducted with SAS software (version 9.2; SAS Institute Inc., Cary, NC, USA) or Stata (version 9.2; StataCorp LP, College Station, TX, USA). Statistical significance was considered as $P<0.05$ and all statistical tests were two-sided.

Results

Between July 19, 2007 and August 5, 2009, 104 potentially eligible parents were approached. Twenty-two were excluded for the following reasons: respondent did not read English ($n=7$), no parent available ($n=1$), declined study participation ($n=13$), and withdrawal of consent prior to the start of the study ($n=1$). A total of 82 parents were therefore included in the study. During the study timeframe, 61 potentially eligible HCPs were approached. One physician refused, leaving 60 HCPs that were included.

Parent and HCP demographics are shown in Table 2. For the parent cohort, the median years since diagnosis of cancer in their child was 0.3 years (interquartile range (IQR) 0.2 to 0.5 years) and the median days since last chemotherapy was 2.5 days (IQR 0 to 15.0 days). Forty-seven out of 82 (57.3%) parents had previous experience with mucositis in their child. All HCPs in this study indicated that they had previously cared for children with mucositis. The most common HCP respondents were 25/60 (41.7%) physicians and 24/60 (40.0%) ward or clinic nurses.

Table 3 illustrates that 7% to 10% of respondents thought that mucositis was the most important side effect of chemotherapy and this proportion was similar among parents and HCPs. Table 4 illustrates that while parents and HCPs believe mild mucositis to be of similar importance, HCPs consider severe mucositis more important than parents. No differences were seen in TTO values with either the mild or severe mucositis health states. Importantly, most parents were not willing to give up any length of life to prevent severe mucositis. Table 5 shows that parents were willing to pay significantly more than HCPs to prevent one episode of mild mucositis (average median WTP $1,371 vs. $684, $P=0.031$). No statistically significant differences were seen in WTP to prevent severe mucositis from parents compared with HCPs (average median WTP $5,499 vs. $5,180, $P=0.814$), although both groups were willing to pay large amounts of money to prevent one episode of severe mucositis. We examined

Table 2 Demographics of parents and healthcare professionals

Characteristic	Parents N=82	Healthcare professionals N=60
Respondent characteristics		
Male (%)	23/82 (28.1%)	14/60 (23.3%)
Age group (%)		
<30 years	7/82 (8.5%)	13/59 (22.0%)
30 to <50 years	71/82 (86.6%)	41/59 (69.5%)
≥50 years	4/82 (4.9%)	5/59 (8.5%)
At least college education (%)	55/82 (67.1%)	–
Married (%)	72/82 (87.8%)	–
Median gross annual income in Canadian dollars (IQR)[a]	75,000 (55,000, 100,000)	–
Supplemental insurance (%)	60/82 (73.2%)	–
Occupation (%)		
Physician	–	25/60 (41.7%)
Advanced practice nurse	–	6/60 (10.0%)
Ward or clinic nurse	–	24/60 (40.0%)
Pharmacist	–	5/60 (8.3%)
Median years working with children with cancer (IQR)	–	7.0 (3.8,12.5)
Working full time (%)	–	47/60 (78.3%)
How often care for children with mucositis (%)		
Always	–	12/58 (20.7%)
Almost always	–	26/58 (44.8%)
Sometimes	–	20/58 (34.5%)
Almost never	–	0/58 (0.0%)
Never	–	0/58 (0.0%)
Child characteristics		
Child male (%)	51/82 (62.2)	–
Median child age in years (IQR)	7.6 (3.7, 11.7)	–
Diagnosis (%)		
Leukemia/lymphoma	41/82 (50.0)	–
Solid tumor	14/82 (17.)	–
Brain tumor	9/82(11.0)	–
Other[b]	18/82 (22.0)	
Metastatic disease (%)	23/66 (34.9)	–

[a] Approximate gross family annual income. Income was recorded in $10,000 ranges (i.e., $70,000–$79,999) with the lowest recorded amount being <$20,000 and the highest amount being ≥$100,000

[b] Other diagnoses include aplastic anemia (n=8), adrenoleukodystrophy (n=2), hemophagocytic lymphohistiocytosis (n=2), post-transplant lymphoproliferative disorder (n=2), chronic granulomatous disease (n=1), Langerhans cell histiocytosis (n=1), Hurler's syndrome (n=1), and Fanconi's anemia (n=1)

whether HCP type (physician versus non-physician) was associated with TTO or WTP to prevent mild and severe mucositis. Physicians were willing to pay less money to prevent mild mucositis (β=−3,063.5, SE=1,341.3; P=0.03) compared with non-physicians, whereas no association between provider type and WTP for severe mucositis (P=0.33) or for TTO for mild (P=0.43) or severe (P=0.13) mucositis were seen. History of mucositis was not a significant predictor of TTO or WTP for severe mucositis (P=0.223 and P=0.690).

A reason why parents were not willing to give up length of life to prevent mucositis is that mucositis is a condition that resolves on its own and it is not life-threatening. One parent stated: "I would prefer to have a child with mucositis rather than [have] less time with my child." HCPs willing to trade time felt that a child free of pain was an important factor in their decision. The question of WTP generated many comments from parents. Those willing to pay more to prevent one episode of mild or severe mucositis stated that they would do anything for their child to be free of the mucositis pain. Three parents stated they would pay $100,000 out-of-pocket to prevent one episode of severe mucositis. Some parents reflected on their financial situation

Table 3 Comparison of side effect ranking

	Parents N=82	Healthcare providers N=60	P value
Mucositis most important	8/82 (9.8%)	4/60 (6.7%)	0.728
Nausea most important	14/82 (17.1%)	10/60 (16.7%)	1.000
Diarrhea most important	4/82 (4.9%)	2/60 (3.3%)	1.000
Infection most important	49/82 (59.8%)	41/60 (68.3%)	0.383
Fatigue most important	1/82 (1.2%)	3/60 (5.0%)	0.311
Bruising/bleeding most important	7/82 (8.5%)	3/60 (5.0%)	0.519
Fever most important	14/82 (17.1%)	16/60 (26.7%)	0.240
Constipation most important	2/82 (2.4%)	3/60 (5.0%)	0.650
Pain most important	17/82 (20.7%)	9/60 (15.0%)	0.514
Hair most important	2/82 (2.4%)	3/60 (5.0%)	0.650

and said that they could not afford to pay for medical treatment but would have been willing to pay more, had they been in a better financial position. Two parents were uncomfortable with the notion of receiving a treatment only if they could afford to pay and stated that everyone has a right to equal access to care. HCPs considered the number of courses of chemotherapy when providing their answer to the WTP question. One HCP said they would be willing to pay more for those with only one expected episode of mucositis, such as in SCT, but less for those receiving multiple course of chemotherapy. HCPs willing to pay more for the prevention of severe mucositis indicated that avoidance of prolonged intensive care unit admissions and decreasing the length of hospitalization were the main reasons.

Discussion

The results of this study demonstrate that mucositis is considered the most important side effect of treatment for about 7% to 10% of parents and HCPs. While most parents would not be willing to give up any survival time to prevent severe mucositis, typically, both parents and HCPs would be willing to pay a little over $5,000 to prevent one episode of severe mucositis and many would be willing to pay considerably more.

HCPs thought that severe mucositis was more important than parents while they both viewed mild mucositis equally important. Conversely, HCPs were willing to pay a similar amount as parents to prevent severe mucositis but parents are willing to pay significantly more for the prevention of mild mucositis. The qualitative comments may suggest different motivations behind WTP and may explain these differences in stated preferences. While parents were "willing to do anything" for their child to be free of pain, HCPs considered other health care costs associated with mucositis, which may balance the cost of the treatment, in their decision making.

Our study also shows that physicians are willing to pay less money to prevent mild mucositis, compared to non-physicians, whereas there was no association between provider type and WTP to prevent severe mucositis or TTO. This variability in findings is in keeping with other studies. While one study demonstrated that there is significant variation in attitudes depending on different health care professional type [17], another study reported that there is no difference in health states scores between physician and nurses [26]. Differences in thresholds of decision making between various health care providers have also been qualitatively reported [1].

While we demonstrated that parents are not willing to give up survival time in order to avoid mucositis, there are numerous studies in which parents of children with chronic health conditions were willing to decrease survival time to achieve perfect health. For example, parents of children with type 2 diabetes mellitus, hemophilia, and severe mental retardation were all willing to give up 3% to 49% of their child's survival time in order to achieve perfect health [4, 21, 24].

Table 4 Comparison of mucositis importance and time trade-off utilities for mild and severe mucositis

	Parents N=82	Healthcare providers N=60	P value
Importance visual analogue scale[a]			
Mild mucositis	2.5 (1.5, 5.4)	3.6 (2.5,5.5)	0.357
Severe mucositis	8.3 (7.1, 9.3)	9.0 (8.1, 9.8)	<0.0001
Reduction in survival time with time trade-off (weeks)[a]			
Mild mucositis	0.0 (0.0,0.0)	0.0 (0.0, 1.0)	0.296
Severe mucositis	0.0 (0.0, 4.5)	3.0 (0.2, 27.0)	0.060

[a]Median and interquartile range

Table 5 Willingness-to-pay for prevention of mild and severe mucositis

	Values	95% Confidence interval	Standard error	*P* value
Mild mucositis				
β Coefficient				
Parents	7.22		0.32	<0.0001
HCPs	−0.69		0.21	0.031
Average median WTP				
Parents	$1,371	($797–$1,945)	293	
HCPs	$684	($363–$1,005)	164	
Severe mucositis				
β Coefficient				
Parents	8.61		0.25	<0.0001
HCPs	−0.06		0.17	0.814
Average median WTP				
Parents	$5,499	($5,201–$5,797)	152	
HCP	$5,180	($3,230–$7,130)	995	

HCPs health care professionals, *WTP* willingness-to-pay

The results of this study may be used in several ways. First, the results may be used for decision and economic analyses although the TTO results suggest that respondents are not willing to give up any time to prevent mucositis. Second, this study sheds insight into how parents and HCPs perceive mucositis. They both perceive mucositis as a transient health state such that they would not be willing to trade any survival time to prevent even severe mucositis. This suggests that neither parents nor HCPs would be willing to tolerate an experimental therapy to prevent mucositis if the therapy could affect survival; this may be translated into drugs which could interact with chemotherapy and reduce their effectiveness. Our results also suggest that parents and HCPs would be willing to pay large amounts of money to prevent one episode of severe mucositis, which could have implications for health care systems.

While our study sheds insight into how much respondents would be willing to pay to prevent mucositis, it is important to emphasize that one should also consider costs associated with mucositis occurrence, as these costs might be averted if mucositis was prevented. Several studies have demonstrated that here are substantial costs associated with increasingly worse mucositis [11, 23, 28]. Thus, these issues should be considered when administrators prioritize resources to prevent mucositis. It is also important to stress that we examined attitudes toward prophylaxis of mucositis; attitudes toward treatment of mucositis are likely to differ substantially.

Few studies focused on transient conditions in children, such as mucositis, have reported parental TTO or WTP [6, 20, 31]. One study used WTP to assess whether parents would pay the market price of a drug to decrease pain in their child during blood sampling [31]. The median WTP was €27–40 ($38–57CAN) which is lower than the WTP results from our study to prevent one episode of mucositis. This difference could be related to the time frame of mucositis, which lasts for several days, compared to an acute painful procedure such as blood sampling which lasts for only moments.

Our study has several limitations. In our study, hypothetical scenarios were used to elicit respondents' stated preferences. Actual behavior in real-life decision making (i.e., revealed preference) may differ from decision making during hypothetical scenarios [8]. However, although the amount respondents stated that they were willing to pay may not be representative of the real purchase decision to prevent mucositis, their WTP indicates the value or importance of mucositis to them. Second, the median income of our sample ($75,000) is above the estimated median income in Canada ($68,860), as well as for the province of Ontario ($70,910). While previous research suggests that WTP is higher in those with greater income [3, 18], we could not examine such a relationship given our limited sample size. Thus, the relatively high income of our sample may have biased our findings. Third, it is important to stress that all of our respondents lived in Canada, a country with universal health care. It is very possible that WTP from respondents living in countries with alternate types of health care would have very different values. Finally, we only included English-speaking respondents from one Canadian hospital and thus, it is unclear how generalizable our results are although our hospital has substantial representation from many ethnic and cultural groups.

In summary, parents and HCPs believe mucositis to be important but they would not be willing to reduce life expectancy to eliminate mucositis. This suggests that neither parents nor HCPs would be willing to tolerate an experimental therapy to prevent mucositis if the therapy could affect survival; this may be translated into drugs

which could interact with chemotherapy and reduce their effectiveness. This type of analysis suggests what parents and HCPs are willing to risk in order to improve short-term quality of life. These results may be used in future decision and economic analyses to evaluate different prophylactic strategies.

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Conflict of interest No conflicts of interest to declare.

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