

Health-related quality of life and enrollment in Phase 1 trials in children with incurable cancer

MARU BARRERA, PH.D.,¹ NORMA D'AGOSTINO, PH.D.,² JANET GAMMON, R.N.,³
LYNLEE SPENCER, B.SC.,⁴ AND SYLVAIN BARUCHEL, M.D.³

¹Department of Psychology, Haematology/Oncology Program, Population Health Sciences, Research Institute, The Hospital for Sick Children, and University of Toronto, Toronto, Ontario, Canada

²Department of Psychosocial Oncology, Palliative Care, After Care and Survivorship Program, Princess Margaret Hospital, Toronto, Canada

³Haematology/Oncology Division, The Hospital for Sick Children, Toronto, Ontario, Canada

⁴Department of Psychology, Haematology/Oncology Program, The Hospital for Sick Children, Toronto, Ontario, Canada

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ABSTRACT

Objectives: To investigate health-related quality of life (HRQOL) in children eligible for Phase 1 trials and the reasons why families consider participating in these trials.

Methods: Individual, semistructured interviews were conducted with parents (seven mothers, two fathers) and three children, after a child was invited to participate in a clinical trial. Information regarding disease and treatment progression, daily life, and decision making about experimental treatments was elicited. Interviews were recorded, transcribed, and coded for themes.

Results: HRQOL themes were grouped into four main domains: physical, psychological, social, and spiritual. Minimal physical restrictions, maintaining normalcy and control, information sharing, and having hope for life seemed to be critical HRQOL components. Hope for a cure and prolonging the child's life were the main reasons for enrolling in Phase 1 trials.

Conclusions: Normalcy and control are key end-of-life HRQOL components, and hope for life is a main reason for participating in Phase 1 trials.

KEYWORDS: Quality of life, Childhood cancer, End of life, Palliative care

INTRODUCTION

Families of children with cancer unresponsive to conventional treatments face difficult decisions (Hinds et al., 1996). The effect of a particular treatment on their child's health-related quality of life (HRQOL) is a major consideration (Masera et al., 1999). Yet, what constitutes good HRQOL in children at the end-stage of life remains unclear. When conventional treatments no longer work, experimental protocols become attractive alternatives. Phase 1 clinical trials are experimental treatments whose

main goal is to determine optimal dose and major side effects of new anticancer drugs, already tested with animal and adult populations, in children with recurrent malignancies. Why a child is enrolled in these trials, however, is not well understood. The focus of this study is to examine key components of HRQOL that emerge during the child's end of life, and why families of these children consider enrollment in Phase 1 trials.

The World Health Organization defines health as "a state of complete physical, mental, and social well-being and not merely the absence of disease" (World Health Organization, 1947). Individuals with recurrent cancer can enhance their health by physical and nonphysical means. Research on HRQOL has investigated the impact of illness and treatments on daily life, spawning the development

Corresponding author: Dr. M.E. Barrera, Department of Psychology, The Hospital for Sick Children, 555 University Ave., Toronto, ON, M5G 1X8, Canada. E-mail: maru.barrera@sickkids.ca

of several multiattribute instruments for adults (Osaba, 1992) and children (Goodwin et al., 1994; Landgraff et al., 1997; Ravens-Sieberer & Bullinger, 1998; Varni et al., 1998, 1999, 2002). To date, no measures exist for ascertaining the unique HRQOL concerns of children with end-stage disease.

Patients' perspectives in evaluating HRQOL are increasingly valued by the medical field, yet clinical research and medical practice have not routinely ascertained them (Varni et al., 2002). Since eliciting this information directly from very sick or very young children is particularly challenging, parents can act as proxy informants. In this study we investigated HRQOL in children at the end of life considering enrollment in Phase 1 trials, using qualitative interviews with parents and older children. In qualitative research, all opinions of participants are valid, and first-hand experience is a reliable source of knowledge. The critical components in qualitative research are collecting rich data and sampling until saturation is reached (Varni et al., 1998), which typically involves a variable, rather than large, sample.

METHOD

Participants

Families of children with recurrent disease treated in the Hematology/Oncology unit of a large children's hospital, eligible for Phase 1 trials, were asked to participate. Families of children identified by staff as being too ill or too overwhelmed were not approached, and children under age 7 were considered too young to be interviewed. Twelve families were invited: Nine families of four girls and five boys varying in age from 7 to 15 years participated. Only one of the participating families decided to opt for palliative care instead of the Phase 1 trial. Seven mothers, two fathers, and three male children were interviewed. Five children were diagnosed with a brain tumor, three with Neuroblastoma, and one with Acute Lymphoblastic Leukemia. Time since initial diagnosis varied from 2 to 93 months ($M = 38.89$, $SD = 30.85$). Children presented with physical symptoms ranging from mild to severe, and all had progressive disease and fatigue. For two children, pain management, eating, and mobility were major problems.

Data Collection

Upon approval by the hospital's Research Ethics Board, the responsible oncologist advised families of the study only after they had decided whether or not to enroll in the Phase 1 trial. The study coordinator then met with parents and children to further

explain the study, and to obtain signed consent and assent. Interviews were conducted individually at the hospital or at home, depending on the family's preference. The interviews were taped and transcribed verbatim for subsequent content analysis.

Interviews

Following the Semi-structured Long Interview Method (McCracken, 1988), two interview guides were prepared: one for parents and a shorter and simpler one for children. Open-ended questions prompted parents and children about the impact of illness and treatment on daily life, family communication about disease progression and treatment issues, and about enrollment in Phase 1 trials. The list of open-ended questions can be supplied upon request.

Each parent interview lasted approximately 2 h ($M = 117$ min, $SD = 34$), whereas children's interviews were much shorter ($M = 36$ min, $SD = 19$). The interview ended with a "cool down" period where interviewees had an opportunity to reflect on being interviewed. The interviews were conducted by an experienced clinical psychologist familiar with end-of-life care and bereavement, who referred participants to counseling in their community or within the hospital, when necessary.

Qualitative Data Analyses

NVivo™ software, a computer program designed for nonnumerical data analysis, was used to analyze transcripts. Salient "like text" units, and repeated themes on HRQOL and reasons for enrolling in Phase 1 trials were extracted and organized for children and parents separately. Though ideal, participants were not asked to review extracted themes because it might add burden to their lives. Instead, credibility of results was ensured by comparing derived themes to field notes collected by the interviewer.

RESULTS

Themes Related to HRQOL

The following four domains of HRQOL were derived from interviews with mothers, fathers, and children: physical, psychological, social, and spiritual. Themes within each domain are described below and exemplified by direct quotes.

Physical

Most children were relatively well, with minimal symptoms or treatment side effects. Nonetheless,

level of physical functioning emerged as a significant issue for parents and children with the key distinction being whether or not children were able to perform their “normal” activities.

Performing “normal” physical activities at the same level as before the illness was a main theme and included walking, eating, and playing. One mother said: “He is still doing everything he was before.” One father stated: “He is running around [and] everything, nobody can tell he is sick.” In describing the impact of illness on his activities, one child stated that “It hasn’t really changed at all.”

Limited physical functioning, on the other hand, emerged as a theme that reflected serious concern over the child’s deterioration, which had major implications for HRQOL. One father said: “We’ve described how bad he gets, which is paralyzed so he can’t even lift [his] head to move his ear.” Children also recognized how the illness had affected previous physical capabilities, as one child explained, “I can’t run that fast [anymore].”

Psychological

Greater richness was found in this domain, with five areas identified across parents and children: maintaining normalcy, maintaining control, illness awareness, awareness of body changes, and perspective taking.

Maintaining normalcy. Efforts to maintain life as normal as possible appeared consistently throughout child and parent transcripts. This theme reflected the importance of children being perceived as similar to their peers. One child said: “I am a normal boy.” A mother stated: “We’re able to live a pretty normal life.” A father put it best: “He just wants to be a 7-year-old boy and do armpits and all that stuff.”

Maintaining control. This theme captured families’ efforts at retaining some sense of control within the health care system. One mother said: “[We] call all the shots. The doctors are a part of our team but they don’t call the shots.” One child said: “It’s the doctors who always make the choices . . . but they ask my mom to ask me if I wanted to live or not.”

Illness awareness. This theme was identified only in children’s interviews. One child expressed his understanding as follows: “It was just another cell that went wild.” Their personal journeys with illness can make children more in tune with their bodies. One child sincerely expressed “I knew I was dying,” and another explained that he “had a feeling . . . it would one day come back for some reason.”

Awareness of body changes. This theme was evident in parent and child transcripts, and captured how noticeable physical changes can impact the

child’s sense of self. Aware of her daughter’s negative body image, one mother commented: “She hates how she looks. She just hates how she looks.” Children verbalized what appeared as a gradual change in self-concept over the course of the disease: “If people see me, who cares? I’m bald, that’s the way I am.” In referring to his hearing aids, another child asserted that he felt “pretty happy about them.”

Expressing the perspective of others. This theme, identified only in children, captures their ability to offer insights into the emotional state of caregivers. One child told how his mom “worries a lot about me.” Another reflected on how his parents might be dealing with his illness: “[They are] kind of sad a little bit.” Referring to his parents and doctors during a frightening episode of his illness, one 7-year-old child recounted: “When I was dying they were scared.” (Note: This child had been close to death but then improved).

Social

Within this domain, maintaining family relationships was a major theme for parents and children expressed in three areas: open information sharing, limited sharing of information, and a focus on enjoyable family activities.

Open information sharing was noted in some families around issues of disease prognosis and feelings. One father described his approach to communication: “We talk about everything with our kids, to the degree which they want to talk about it.” Similarly, a mother explained: “We always tried to include [him] in any decision making.” From the perspective of the sick child, open lines of communication instilled a sense of confidence and trust: “My mom was honest with me,” and “My mom usually explains everything.”

Limited sharing of information. Difficult issues such as poor response to treatment and death and dying were less likely to be shared within some families. One father said: “If I let him know too much, he might get this fear and in turn it will affect his immune system.” A child also withheld information from his mom: “I don’t want her to worry.” Nonetheless, parents and children often had a sense of each other’s thoughts and feelings. Reflecting on how his parents were coping, one child said: “They never, like, get upset around me.” Parents also struggled with knowing how much to share. One mother said: “I don’t talk about it with her, but I don’t know if I’m right to not discuss it with her, but I don’t know what to really say to her.” Similarly, a father expressed: “I didn’t tell him very much detail . . . I don’t know if this is right or wrong.”

Focus on fun and enjoyable family activities was probably the “safest” way families expressed their knowledge that their time together was limited. A mother explained: “We want to have as much fun as we can in the time we have together.” A father said: “We are making sure we’ve got some real fun stuff planned. . . .” Focusing on enjoyable activities was often how children coped with their illness—simply put: “I just have fun.”

Spiritual

Both parents and children thought about the meaning of life and the existence of a power beyond themselves. Within this domain, three subthemes emerged: maintaining hope, spiritual connection with God, and finding meaning in life.

Maintaining hope was consistently seen across time and between family members, who conceptualized hope as giving them strength in the face of uncertainty. One child explained: “You can always believe in hope.” One father viewed hope as “what makes us all survive,” and another as something “you can’t live without.” Hope acquired a variety of forms, particularly in parents. One mother described this best: “I think you have different hopes . . . now, I hope she’ll die in peace.”

A spiritual connection with God was usually associated with belief in a supportive presence. One mother said: “I think God is a God of compassion and love . . . sometimes life sucks, but you don’t have to be alone.” Similarly, a father shared: “I see the love of God big time.” Spiritual beliefs often helped parents accept death as an outcome as one father expressed: “If you are truly a Christian, you don’t think death is such a bad thing.” Children often associated spirituality with magic healing properties: “People have, like, energies inside of us . . . to, like, cure ourselves.” A spiritual connection that reflected direct anger or apathy at God, or toward religion and spirituality, was noted in two mothers. One mother viewed God as “the devil himself,” and elaborated: “I don’t really find comfort in [religion].” Another mother explained: “My religious beliefs have become less personal.”

Finding meaning in life was another common theme. Many reflected on the illness experience, and concluded that their family learned from it. One father said: “Maybe we got something right in trying to have happiness through the difficult times.” A mother described a meaningful life as one “that’s worth living with the people you love.” From a child’s perspective: “You make life what it’s supposed to be.”

Themes Regarding Participation in Phase 1 Trials

Four subthemes emerged from transcripts regarding participation in Phase 1 trials: hope for a cure, continuity of care, focus on quality of life, and ambivalence.

Hope for a Cure

No amount of realism can take away the hope that remains even in families of children at the end stage of life, and the decision to enroll in Phase 1 trials illustrates well the dichotomous interplay between hope and reality. Even though families are aware that Phase 1 trials do not test anticancer drug effectiveness, they still identified “hope for a cure” as the main reason for participating. One mother viewed it as “another chance for a cure,” and another felt her daughter’s participation would “keep her stable for a little longer . . . she might be old enough that she can have radiation.” Fathers echoed these views: “It works in animals as a cure, not just as a delay,” and “Right now I see a cure for this disease so close that I’d do it just to buy some more time.” In children, this was the only theme that factored into their decision to enroll in these trials. One child viewed Phase 1 trials as “giving someone another chance,” and another recounted: “I had been hearing things about people with brain tumors that actually got cured by it.”

Continuing Care

Some families believed enrolling in these trials would lead to continuity of care, and opting for no more treatment would not. Thus, one father felt his son would “get better attention.” One mother explained: “I was worried that . . . her health care might be compromised [if she did not participate].”

Focus on Quality of Life

In weighing the decision to enroll in Phase 1 trials, maintaining quality of life was of the utmost importance. One mother said: “I couldn’t do something that was going to hurt the person she is,” and another offered that her family would try anything “as long as it does not hurt him.”

Ambivalence / Uncertainty

This theme reflected the difficult decision parents had to make and the doubts they experienced as to whether Phase 1 trials were in the child’s best interest. As one mother put it: “I just decided . . . you’re damned if you do . . . damned if you don’t.”

Similarly, another mother expressed: "Sounds too good to be true, but what the hell."

DISCUSSION

This study describes HRQOL themes in children with a terminal disease who were eligible for Phase 1 trials, and decision making about enrolling in them. Interviews with parents and children revealed four main HRQOL themes: feeling normal, maintaining control, maximizing family fun, and preserving hope. Since all but one child were relatively well with good pain management, physical symptoms were minimally addressed. In addition, lack of severe physical symptoms reported during the interview is consistent with the varied time interval across children from date of interview to date of death: from 1 to 19 months ($M = 7.11$, $SD = 5.67$).

Maintaining a "normal" life remained a key focus for parents and children facing the end of life, which is consistent with retrospective reports from parents of children who have died (Reilly et al., 1983; Faulkner, 2001). Engaging in "normal" activities may allow families to focus on life instead of death, and may also increase sense of control and competence in children whose disease progression might render them physically and psychologically powerless.

Maintaining a sense of control emerged as an important theme that seemed to have a different driving force in parents than in children. Parents often struggle to advocate for their children within the health care system, whereas children try to control their health despite its gradual deterioration. Awareness of illness and body changes were evident in all children, whose self-concepts often adapted to incorporate them. The ability of children to use these changes as indicators of disease progression is not surprising given reports that dying children understand the irreversibility and finality of death as early as age 6 (Sourkes, 1995; Faulkner, 2001), particularly when they have death-related experiences (Reilly et al., 1983). Children are often more aware of their illness progression than their caregivers might realize, and if children are perceptive of bodily changes, they are likely processing recurrence and death as possible outcomes.

Families appeared to use two modes of communication during the end-stage of a child's life: Some valued open and honest communication; others believed that maintaining a positive approach was best even if it meant lying. These communication styles likely reflect family cultural values regarding issues of health and death (Paasche-Orlow, 2004). Families who believe that truth will take hope away from the child may not be able to deal with the

imminent death of the child openly or may be unsure of the best approach. Limited communication appears to serve a protective function: parents not answering their child's question about dying for fear he or she will lose hope; a child not sharing fears of dying to prevent upsetting a parent. Research suggests that sharing developmentally appropriate information during the terminal stage of illness will improve quality of the life (Sourkes, 1995), and that parents who talked with their child about death had no regrets (Kreicbergs et al., 2004). When families are struggling with sharing information, support or intervention may be warranted.

While struggling to find meaning in the child's life, families reflected on their spiritual and religious beliefs, a finding consistent with previous research in adult (Potts, 1996; James & Johnson, 1997) and child (Sourkes, 1995) populations. Parents expressed comfort in believing the child will be in a better place after dying. Children talked about using energies inside of them to cure themselves. Further examination is needed to understand developmental changes in children's concept of spirituality as they face their own mortality.

Families' main reasons for enrolling in Phase 1 trials were hope for a cure or prolongation of the child's life and their belief that participating would ensure continuity of care. One might speculate that families who participate in these trials may not be prepared to accept the inevitability of death. Mothers' greater tendency to express ambivalence about Phase 1 trials than fathers was intriguing. Parental fears of discontinuation of care when conventional treatment is no longer an option needs further investigation in the context of palliative care.

The main limitation of this study was small numbers of participating fathers and children, relative to mothers. Saturation was likely only reached in mother interviews. Many children in our sample were deemed not mature enough to be interviewed. Fathers were less available for participation as they remained working during the child's illness due to financial necessity. Another possible limitation of this study is that the sample consisted primarily of families who opted for experimental treatment, which might not represent the perspectives of those who elected palliative care. The consistency of our findings with previous reports regarding pediatric palliative care, however, provides credibility to our data.

Its prospective, rather than retrospective, approach is a major strength of this study. Moreover, it elicited important HRQOL themes and reasons for enrolling in Phase 1 trials directly from dying children and their parents. Maintaining a sense of normalcy and control in daily life, maximizing fam-

ily fun, and having hope for life emerged as key elements of HRQOL. Current standardized HRQOL questionnaires do not typically measure these areas, which warrants their inclusion as items. The reasons for enrolling in Phase 1 trials—hope for a cure and prolonging the child's life by remaining in the care of the primary team—reflect parents' desire for their dying children to receive continuity of care, which has direct implications for delivering pediatric palliative care.

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