The purpose of this manuscript is to summarize issues relevant to health-related quality of life (HRQL), physical function, and neurocognitive function for survivors of pediatric hematopoietic stem cell transplantation (HCT). The physiologic and psychological demands of HCT and its sequelae have the potential to substantially alter HRQL. When compared with research on adult HCT recipients, research in pediatric HRQL following HCT has lagged considerably. Initially, this lag was because of limited validated questionnaires, small numbers of affected patients, and a general lack of salience for the topic relative to traditional endpoints, such as transplant-related toxicity and potential mortality. The percentage of childhood HCT survivors with physical disability ranges from 7% to 17% in studies where the outcome was based on clinician or self-report measures, to over 40% in studies where the outcome was based on a directly measured physical performance task. Direct and comprehensive measures of physical performance may help further clarify the proportion of individuals who have subclinical problems amenable to intervention before apparent functional loss becomes a problem. There is a need to include longer term survivors in such an assessment. In terms of neurocognitive function, the majority of reports demonstrate relatively good function in survivors. However, it is clear that little or no data on outcomes beyond 5 years posttransplant have been obtained, and clinicians working with this population remain concerned regarding the cognitive functions of these survivors. Research focused on these domains should attempt to better understand the prevalence of the problem using child self-report and direct measurements of function, standardize measurement methods, and tools across trials, obtain longer term evaluations and begin to consider interventional trials.

**INTRODUCTION**

Hematopoietic stem cell transplantation (HCT) is an important therapy that has improved outcomes for some children with cancer when prognosis is poor. However, until recently, little attention has been paid to the late effects of HCT. In April 2011 the National Cancer Institute/National Heart, Lung and Blood Institute, along with the Pediatric Blood and Marrow Transplant Consortium, sponsored a consensus conference of international experts in clinical and biologic research into late effects after HCT in order to review the state of the science of pediatric studies and identify key areas for future research. This article represents the fifth in a series of summary articles covering the major topics discussed at the conference and is focused on health-related quality of life (HRQL), functional and neurocognitive outcomes.

Among survivors of childhood HCT, these outcomes have several common themes. First, the
literature on longitudinal trajectory of these outcomes is sparse. The existing literature is limited by the wide variety of instruments and approaches that have been used across trials. Second, much of the literature includes only indirect assessments of function including proxy reports. Third, many studies have had limited follow-up; few have described these outcomes in very long-term survivors. Finally, concurrent medical events that are likely to complicate these outcomes have not been included as covariates in many of these studies. The following sections summarize each domain and conclude with recommendations for future research.

HRQL

HRQL is a multidimensional construct, grounded in the World Health Organization’s 1948 definition of health. Health is defined as not merely the absence of disease, but rather, a state of complete physical, mental, and social well-being [1]. Over time, although definitions of quality of life (QOL) and HRQL have varied [2], there is general consensus about the multi-dimensionality of the construct and its incorporation of the subjective appraisal of one’s functioning/well-being. In addition, the terms of QOL and HRQL are often used interchangeably. Although QOL refers to a broader construct, including a variety of domains within and outside of the purview of the healthcare system, HRQL refers to the impact of the health states on overall QOL, principally one’s own health issues [3,4].

Multiple stakeholders can use information on HRQL outcomes. For clinicians, it can improve our understanding of the impact of health issues on everyday life. It can assist in early identification of complications of treatment, serve as the basis of anticipatory guidance, and allow for timely introduction of additional services. For researchers, HRQL can be used to help evaluate the benefits of treatments or interventions. For policy makers, HRQL can be used, particularly when reported as health state preferences, in the review of resource allocation. In the field of HCT, HRQL studies have been largely descriptive.

Cross-sectional Studies Mark Beginning of HRQL Investigation

Researchers first began to explore HRQL in adult HCT survivors in the mid-1980s, producing a rich literature on the trajectories of HRQL over time, and reporting the factors associated with altered functioning [5]. Research in pediatric HCT lagged behind that in the adult population until the mid-1990s with the development of new child self-report instruments, several with companion parent reporting. Few of these measures were developed solely for use in pediatric HCT. More commonly, they were designed for use in the general pediatric population or in subpopulations of children with chronic illness, and applied successfully in populations of children with HCT. Examples are the Pediatric Quality of Life 4.0 General Core Scales [6], the Child Health Questionnaire [7], the Child Health Ratings Inventories-General Health Module [8-10], and the Health Utilities Index 2/3 [11]. Only 1 instrument was designed specifically for use with survivors of childhood HCT, the Child Health Ratings Inventories-HCT instrument, a 10-item module to complement the overall generic HRQL instrument(s) [9,10].

Most of the early studies in children were cross-sectional in design. Despite the variety of instruments used in these studies, consistent results indicated that HRQL was found to vary by time posttransplant (earlier, worse), by transplant type (unrelated worse than autologous or allogeneic related), and by presence or absence of HCT-related sequelae (eg, worse with chronic graft-versus-host disease [GVHD]) [9]. In short, the early picture of children’s HRQL post-HCT made sense and was clinically recognizable.

These early studies were important for several reasons. First, despite the complexity of care and the severity of the children’s state of health, researchers were able to successfully enroll participants and efficiently collect HRQL information. Second, building on increasing interest in collecting HRQL directly from the child rather than solely from their parent or other proxy rater, these early studies demonstrated that it was possible to collect valid and reliable self-reported HRQL from the children themselves. Third, important and not overlapping information could also be obtained from parents whose perspective adds additional information to the overall picture of the child’s HRQL.

Longitudinal Studies Explore 12-Month HRQL Trajectories

By the early 2000s, research in HRQL among children with HCT shifted to longitudinal studies. The approach to HRQL measurement in longitudinal studies, like that in HRQL measurement in cross-sectional studies, has not been standardized across studies. Going forward, the field of pediatric HRQL research may benefit from consensus about measurement to allow for comparisons across studies and in clinical trials, as reported by the National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease [12].

Baseline (pre-HCT) factors, such as family cohesion and the child’s adaptive functioning, have been shown to affect HRQL scores and behavioral adjustment post-HCT [13]. Several groups have also identified the importance of pre-HCT parenting stress on
parental ratings of children’s HRQL post-HCT [5,13-16]. The trajectories of HRQL over the 12 months following HCT, first reported in 2006 by 2 different groups [5,17] were similar. One study by Parsons et al. [5] demonstrated that baseline HRQL varied by child age and program (treatment) site. The poorest HRQL was seen at 3 months post-HCT with steady improvement thereafter. Recipients of unrelated donor transplants had the steepest declines in HRQL from baseline to 3 months. By 12 months, HRQL was similar across transplant types and surpassed baseline scores. A second study by Felder-Puig et al. [17] reported a similar HRQL trajectory. They also reported that compromised emotional functioning, high levels of worry, and reduced communication during the acute recovery period had a negative impact on HRQL at 1 year post-HCT. In the “Journeys to Recovery” Study of 165 parent-child dyads, day 45 assessments, timed to coincide with end of the initial HCT hospitalization for the majority of recipients, a nadir in HRQL scores was observed at day 45 for all transplant types, although the depth of the nadir varied by domain of HRQL [18]. This finding has been confirmed in a subsequent sample of 200 parent-child dyads [19].

Recent longitudinal studies have identified an association of additional baseline risk factors with the trajectory of HRQL following HCT, including child age (older, worse HRQL) [14,19,20], child gender (female, worse HRQL) [20], rater (mothers report lower HRQL than fathers; children report better HRQL than parents) [18,21], concordance by primary language or by gender of the raters (concordant pairs, higher HRQL) [22], parental emotional distress (greater distress, worse HRQL) [18,23], and child race, (African American, better HRQL) [20]. Larger studies are needed to confirm these findings in medically and demographically diverse samples. A systematic review of the literature, prepared by Clarke and coworkers [24], provides an excellent summary through 2008.

**Relationship between HRQL and Clinical Factors**

Few studies have documented an association between post-HCT clinical events and HRQL trajectories among pediatric survivors. This is likely to be the result of several important factors. First, it is not routine for researchers to collect in depth clinical outcomes data alongside HRQL information. The process is time consuming, requires trained study personnel, and careful oversight to ensure completeness and accuracy. Second, clinical events in pediatric HCT, although potentially devastating, are relatively rare, especially in contrast to their frequency in adult recipients. Third, studies to date have not been large enough to have sufficient power to detect meaningful changes in HRQL because of discrete clinical events.

In earlier cross-sectional studies of a total sample of 122 pediatric HCT recipients at a median of 1.4 years post-HCT [9,10], we demonstrated that HRQL varied significantly by physician-rated clinical severity (more severe, worse HRQL). Forinder et al. [25] reported in a cross-sectional evaluation of HRQL among 52 pediatric HCT survivors at a median of 8 years from HCT [25], that children with moderate to severe chronic GVHD reported worse HRQL. In 2006, a report on the impact of specific HCT complications on children’s HRQL indicated that HRQL was worse among children with severe end-organ toxicity, systemic infection, or GVHD [5]. In subsequent studies, we have found that the presence and severity of clinical events explains parent-child differences in ratings of the child’s HRQL at both early and later time points in the first year post-HCT [18].

**Paucity of HRQL Studies for Longer Term Survivors**

One of the striking gaps in the literature describing HRQL among pediatric HCT recipients is the paucity of studies beyond 12 months posttransplantation, despite the fact that the majority of pediatric HCT recipients are long-term survivors. Two cross-sectional studies by Lof et al. [26] and Sanders et al. [27] report on the HRQL among pediatric HCT survivors of 5 years or more with similar findings. In general, HRQL is reasonably good, although psychological, cognitive, or physical problems appear to negatively influence HRQL. Female sex, causal diagnosis for HCT (acute myelogenous leukemia, worse HRQL), and intensity of pre-HCT therapy were all identified as affecting HRQL post-HCT. Vrijmoet-Wiersma and coworkers [16] in their 2009 cross-sectional study of children 5 to 10 years post-HCT describe parental concerns about the child’s vulnerability, which the authors caution may induce overprotective parenting. The 2010 review article by Baker et al. [28] provides an excellent review of the literature on HRQL assessment for pediatric HCT survivors.

**Summary and Recommendations for Future Research**

We face numerous challenges going forward in the evaluation of the HRQL for pediatric HCT recipients. To accommodate proposed larger samples with improved representativeness, we will need to enhance the ease of data collection. Historically, we have relied largely on in-person assessments and collected HRQL with paper-and-pencil measures, with assessments timed to the medical encounter. Although this approach has been successful, it is cumbersome and resource intense. Younger children within the 5- to
7-year age range have required interviewer assistance because of emerging literacy. We have explored the use of computerized animation to facilitate data collection and minimize potential for interviewer bias [29,30], a technique that has also been shown to be successful in other pediatric populations. For adults and older children, electronic data collection has greatly facilitated the collection of HRQL. With electronic data collection, HRQL could be collected more frequently, such as monthly, during the periods of most rapidly changing clinical course and then, for studies beyond the first year, annually. If future studies are designed to collect HRQL information outside of the regular healthcare encounter, alternative access to clinical information is needed, either through integrated medical records across sites of care or elicitation of clinical data from parents or older survivors.

To ensure representativeness of the sample and generalizability of the findings, it is imperative that we strive to collect HRQL information from families across racial and ethnic groups, levels of formal education and literacy, and languages. The complexity of language and acculturation on HRQL reporting were highlighted in the 2009 report by Feichtl and co-workers [22], who demonstrated that parent-child dyads speaking the same language had higher agreement in HRQL than language discordant pairs. To understand the broad picture of HCT survivorship, we will not want to restrict our samples to the subset of patients that might continue to receive care at the HCT center.

Building on our 2 decades of progress in HRQL assessment following HCT, the purpose of HRQL measurement must be explicit. What are we trying to understand about the complex HCT recovery process and of that, what information can we only obtain directly from our pediatric HCT recipients? We must collectively address the issues of standardization of measurement, expanded representativeness, and rigorous approaches to analysis. We must address the HRQL issues of longer term survivors, a obvious challenge of which is dealing with the transition from child-based to adult-based scales and from proxy-rated to self-reported outcomes. Future studies will need to address how best to capture the full experience of HCT survivorship within the context of ongoing clinical sequelae, as well as the broader focus.

**FUNCTIONAL OUTCOMES**

**Chronic Disease and Physical Function**

Chronic conditions that impair the structure and or physiology of the musculoskeletal, neurological, cardiac, pulmonary, endocrine, and integumentary systems are prevalent in over 90% of children who survive following HCT [31]. These impairments have the potential to interfere with physical function as these systems provide the foundation upon which movement occurs. Problems with physical function have been reported among adult survivors of childhood HCT; however, prevalence rates depend largely on the measurement mechanism and on the person who reports or documents the outcome. The literature describing observed functional loss, perceived functional loss, and measured functional loss do not provide consistent estimates of either the magnitude or the severity of the problem. Clinician reports on physical function suggest that problems are present in less than 10% of survivors [32], and survivor self-reports indicate only slightly higher rates of functional loss (17%) [33]. However, in the few studies where physical performance (capacity) is directly measured, prevalence rates are markedly higher, with estimates of the proportion of HCT survivors who demonstrate significantly impaired physical capacity ranging from 40% to 62% [34,35]. Studies that rely on clinician opinion or survivor report to estimate the degree of physical performance limitation report mild and moderate limitations respectively [26,36], whereas studies that measure physical performance report more severe functional loss [34,35,37,38].

Limitations in physical function are problematic, not only because the ability to move is necessary for participation in daily life, but also because poor physical health is associated with poor adherence to preventive healthcare practice. Khera et al. [39] reported that HCT survivors with disability are 1.43 (95% confidence interval 1.11-1.85) times less likely to adhere to preventive healthcare practices than are those without a disability. Additionally, reduced performances on measures of physical capacity are associated with increased mortality rates. Among persons in the general population 34 to 75 years old, all-cause mortality across a 5-year period increases by 20% for every 5 kg decrease in hand grip strength [40], and for men and women, respectively, mortality increases by 13% and 20% for every 1 metabolic equivalent decrease in exercise capacity [41,42].

**Clinician-Reported Physical Performance**

Clinician reports of long-term disability among childhood HCT survivors suggest that the prevalence and severity of functional loss is low. Duell et al. [32], using data from the European Group for Blood and Marrow Transplantation, used the Karnofsky performance scale to report outcomes among 647 5+ year HCT survivors. In this cohort, 40% of survivors were younger than 18 years of age when transplanted; only
19% had Karnofsky scores of <100. Only 7% had scores <80, defined as the inability to work. Similar low rates of clinician-graded poor functional outcome were reported by 2 other groups [26,36]. Among 50 survivors of childhood allogeneic HCT treated at the City of Hope National Medical Center and Stanford University Hospital, all had Karnofsky scores of 90 or 100 [36]. Among 73 young adults (mean age 26 years) treated at the Karolinska University Hospital, the median Karnofsky score 10 years post-HCT was 90 [26].

**Self-Reported Physical Performance**

Some self-report and proxy data among survivors of childhood HCT indicate similar low rates of functional loss. Helder et al. [43] evaluated 22 survivors of childhood allogeneic HCT (mean age at HCT 11 years, mean age at questionnaire 25 years) and reported no differences between survivors’ scores and population expected values on the physical components of the Sickness Impact Profile, the Medical Outcomes Survey Short Form 36 (SF-36) or the Functional Assessment of Cancer Therapy—Bone Marrow Transplant Scale. In this cohort, 3 survivors were unemployed, but only 1 had a documented physical disability. Michel et al. [44] compared a group of survivors transplanted for childhood leukemia (N = 142) to a group of childhood leukemia survivors treated with chemotherapy alone (N = 288). There were no differences between the groups on the physical function and leisure scales of the Vecu et Sante Percue de l'Adolescent et de l'enfant (8-17 year olds) or the physical function and role physical scales of the SF-36 (18+ year olds).

Conversely, in the Bone Marrow Transplant Survivors Study, among 235 survivors of childhood HCT, 17% reported long-term physical performance limitations compared with 8.7% of a sibling comparison group [33]. Additionally, Sanders et al. [27] evaluated physical function in 214 young adults (median age at questionnaire 28.7 years, 118 males) who were transplanted at a median age of 11.9 years. When compared with age- and sex-matched controls, the HCT survivors in this cohort scored a half a standard deviation lower on the physical function, role physical and physical component summary subscales of the SF-36. Lof et al. [26] also identified lower self-reported physical health among 73 young adult (median age 26 years) HCT survivors who were a median of 10 years from transplant. HCT survivors completed the Swedish Health-Related Quality of Life Profile and scored significantly below population normative values on physical functioning (90.2 HCT survivors versus 95.3 population), satisfaction with physical health (66.0 HCT survivors versus 78.7 population) and role limitation because of physical health (72.7 HCT survivors versus 84.9 population).

**Measured Physical Performance**

Objective measurements of function in the pediatric HCT patient and survivor population hints that loss of physical capacity may be a much bigger problem than revealed in studies that rely on either clinician or self-report data. Most of these data are from objective measures of cardiopulmonary fitness. Larsen et al. [35] examined exercise capacity with cycle ergometry in a group of 20 patients before HCT, 31 patients 1 year post-HCT, and in 70 healthy controls. Pre-HCT patients were 6.9-25.8 years old when tested, and post-HCT patients were 6.1-32.7 years old when tested. Average peak oxygen consumption was 21 mL/kg/min in the pre-HCT group, 24 mL/kg/min in the post-HCT group, and 34 mL/kg/min in the healthy controls. Among the HCT survivors, 62% of those with cancer diagnoses scored in the lowest fifth percentile for peak oxygen consumption when compared with healthy controls. Eames et al. [34] examined exercise capacity with a Bruce treadmill protocol in 31 survivors of pediatric HCT, a mean age of 11.7 years, and a mean time since HCT of 4.7 years. In this cohort, 25.8% of HCT survivors had exercise capacities in the 70% to 79% of predicted category and 41.9% had exercise capacities in the <70% of predicted category. Hogarty et al. [37] report similar results. In their study of exercise capacity among 33 HCT survivors transplanted at a mean age of 11.3 years, they indicate that, at the 5-year post-HCT time point, only 4 of 33 survivors scored above the 75th percentile on a serial cycle ergometry test.

Limitations on cardiopulmonary fitness testing among survivors of pediatric HCT may be accompanied by poor muscle strength and endurance. Hovi et al. [38] examined 94 HCT survivors 1 to 2 and 6 years posttransplant and 522 age- and sex-matched controls. Participants performed a series of strength exercises. The number of correct repetitions on each exercise was the outcome measure. On average, HCT survivors scored between 1.1 and 2.0 standard deviation scores 1 to 2 years post-HCT and between 0.6 and 1.8 SDS lower than their peers on tests of muscle strength and endurance.

**Predictors of Poor Physical Performance**

Only a few studies have evaluated the predictors of poor physical performance. In the Bone Marrow Transplant Survivors Study [45], associations were found between chronic GVHD, cardiac conditions, immune suppression, or treatment for a second malignant neoplasm and poor physical performance outcomes. In the Study done at Fred Hutchison Cancer
Research Center by Sanders et al. [27], poor performance was associated with myeloid disease.

Summary and Recommendations for Future Research

The percentage of childhood HCT survivors with physical disability ranges from 7% to 17% in studies where the outcome is based on clinician or self-report measures, to over 40% in studies where the outcome is based on a directly measured physical performance task (Figure 1). In general, scores in the few studies where physical performance was directly measured are from 1 to 2 SD below expected in the pediatric HCT survivor population. However, only 4 studies were identified that directly measured physical performance. Three of these studies only evaluated cardiopulmonary fitness. The fourth used field testing measures to characterize fitness, rather than “gold standard” or ideal direct measures of muscle strength and cardiopulmonary fitness. Few of these studies included survivors who had survived for 10 or more years since transplantation. Direct and comprehensive measures of physical performance may help further clarify the proportion of individuals who have subclinical problems amenable to intervention before apparent functional loss becomes a problem. There is a need to include longer term survivors in such an assessment.

In addition, some obvious chronic problems, including GVHD, second cancers, and heart disease, are potentially associated with physical performance limitations. The paucity of information that directly identifies risk factors for poor performance outcomes is likely because many of the study sample sizes were very small or because pretransplant therapy for the original cancer diagnosis was unknown. Identification of risk factors for poor physical performance outcomes is important so that persons at the greatest risk for loss can be identified, and so that potential interventions can be applied to prevent impairment before it appears.

NEUROCOGNITIVE OUTCOMES

Introduction

HCT survivors are thought to be at risk for late neurocognitive deficits as a result of the intensity of their treatment and exposure to a number of potentially neurotoxic agents [46,47]. Among the agents used in pretransplant conditioning, total-body irradiation (TBI) has been the primary focus of those assessing neurocognitive sequelae, but other cytotoxic conditioning agents, such as busulfan and other high-dose ablative chemotherapies are potentially neurotoxic as well [48,49]. Central nervous system toxicities also are associated with agents (eg, cyclosporine) commonly used for the prophylaxis and/or treatment of GVHD [50], although there is speculation regarding direct effects of GVHD on the central nervous system [51,52].

Study of neurocognitive and academic outcomes in pediatric HCT has been hindered by methodologic challenges, including the relatively small samples of survivors at any single institution [53]. Longitudinal studies, considered the gold standard in this setting, have been few, and present additional challenges, including necessary changes in test instruments as patients age. To more comprehensively address these questions, multisite studies are in order, but to date, none has been reported. A small literature on neurocognitive outcomes in HCT has developed, but most studies remain limited by small sample sizes, retrospective designs, or other methodologic difficulties. The findings reported thus far have been contradictory, but a consensus is beginning to emerge (still challenged by some) that points to a relatively benign outcome [53].

Current State of Knowledge

The currently available studies on neurocognitive outcome are not sufficient to allow for meta-analysis, but a review suggests a smaller number of studies that report declines in cognitive function following HCT [54-59]. Those studies reporting declines tend to include samples with a high percentage of very young children. However, the preponderance of studies report normal neurodevelopment, with no evidence of decline [60-68]. Kramer and colleagues [56] reported a significant decline in IQ in their cohort at 1 year post-HCT, and these deficits were maintained at 3 years post-HCT [55]. Theirs was a very young sample, with the majority of patients under 5 years of age at the time of transplant. Similarly, studies from Sweden have reported deficits in visual-spatial domains and executive functioning in very young children who were transplanted with TBI [58,59].

In contrast, Phipps et al. [64-66] have reported on the largest longitudinal cohort to date, with follow-up through 5 years posttransplant, describing remarkable
stability in global cognitive function and academic achievement over that time frame. Phipps et al. [64-66] reported poorer outcome in patients undergoing unrelated donor transplant, in those who received TBI, and in those who experience GVHD, but these effects were small, compared with the much larger effects seen based on differences in socioeconomic status [66]. The majority of studies report similar outcomes. Simms et al. [68] reported normal cognitive function and academic achievement in a cohort of 47 patients followed prospectively through 2 years post-HCT. Likewise, Kupst et al. [62] noted stable cognitive function in a large cohort followed from pre-transplant to 2 years post-HCT. In smaller studies, Arvidson et al. [60] and Llach et al. [63] have reported similar normal functioning and absence of declines over time in HCT survivors. Barrera and colleagues [61] reported that HCT survivors did not differ from their siblings in cognitive and academic function, with the exception that survivors performed better than siblings on measures of perceptual organization. Based in these findings, we have concluded that HCT poses low to minimal risk for late cognitive and academic deficits in survivors.

Gaps in Current Knowledge

Although the above conclusion is reasonably supported by currently available data, it must be considered tentative with several caveats. We would highlight 3 areas that clearly call for additional research. First, the literature to date has been focused on global cognitive outcomes such as IQ and academic achievement, and there has been minimal attention to specific neuropsychological functions, such as attention, processing speed, or working memory. Current research examining cognitive outcomes in children treated for acute lymphoblastic leukemia and brain tumors has highlighted the need to move from global to specific functions, which is important in understanding mechanisms which might point to targets for intervention [69,70]. It will be important to examine specific neuropsychologic functions in HCT survivors, focusing on the most likely candidate domains (executive functions, processing speed) to ensure that more subtle difficulties are not being missed. The second gap involves identifying the most important subgroups at potential risk. The subgroup continues to pose the greatest potential risk are the youngest children who receive TBI. This group poses a challenge because some executive functions are more difficult to assess in very young children, or are assessed differently over time as children age. Development of an accepted standard approach to assessment of the youngest children in this setting is needed. Subsequently, it will be necessary to accrue much larger numbers of patients in this age range, requiring multisite studies. Finally, and we believe, most importantly, data are needed from patients as they move beyond 5 years posttransplantation. Little or nothing is known regarding cognitive functions in such long-term survivors. We cannot assume that the relative stability observed through 5 years will be maintained indefinitely. Evidence is accumulating that brain tumor survivors continue to show declines many years following completion of therapy [69], and thus it is possible that the relatively benign outcomes observed to date in HCT survivors may be followed by declines much later in the survival trajectory.

Emerging New Data

Given the remaining questions, it is concerning that there has been no new data reported in recent years. Several reports were published in early 2008 [57,59,61,66], but to our knowledge, not a single empiric paper examining neurocognitive outcomes in HCT has been reported in the 3 years since then. Recent research with acute lymphoblastic leukemia and brain tumor populations has been focusing on the development of interventions to prevent or remediate cognitive late effects, and could be applied to HCT survivors as well. These interventions comprise 3 different approaches: (1) traditional cognitive remediation approaches including massed practice [71], (2) pharmacologic interventions with medications such as stimulants [72], and (3) computerized interventions targeting working memory [73]. There are pros and cons to each of these approaches, but at present, the computerized interventions appear to hold the most promise and are the most widely studied, with several new clinical trials just getting underway [69,70,73].

Screening and Management

The available data suggest that comprehensive neuropsychologic assessments obtained intermittently are no longer necessary as a standard of care. An interview assessment of the child’s school performance, supplemented by parental questionnaire data should be sufficient in most cases. Well-validated survey instruments such as the Behavioral Assessment Scale of Children [74] or the Behavioral Rating Inventory Executive Function [75] provide much relevant information for the clinician. Exceptions to this approach might be made for children who were younger than 5 years at the time of transplant, particularly if they received TBI, and those for whom cognitive problems have already been identified. For those children, and those for whom problems are identified via interview or questionnaire, referral for more comprehensive psychologic assessment would be indicated.
SUMMARY AND RECOMMENDATIONS FOR FUTURE RESEARCH

The absence of research reports in this area over the past 3 years suggests some investigators may feel the major questions have been answered. However, it is clear that little or no data on outcomes beyond 5 years posttransplantation have been obtained, and clinicians working with this population remain concerned regarding the cognitive functions of these survivors. Thus we suggest the area of highest research priority at this time is a focus on very long-term HCT survivors. Such a study should include both performance-based measures and survey approaches, and include assessment of specific neuropsychologic functions as well as global outcomes. This would be best approached in a multisite study to generate a sufficient sample within a reasonable time frame.

CONCLUSIONS

These 3 areas—HRQL, functional outcomes and neurocognitive outcomes—are important issues for pediatric HCT survivors, and future research in these domains should be a priority. We need to conduct large multicenter studies which follow children post-HCT longitudinally and obtain direct measures of function. Very long-term follow-up is an important issue. We need to start to consider the issue of concurrent medical events to better understand who is at greatest risk for poor outcomes. Finally, we need to begin to plan and develop interventional trials for those at the highest risk of poor outcomes.

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