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Neurocognitive Dysfunction in Hematopoietic Cell Transplant Recipients: Expert Review from the Late Effects and Quality of Life Working Committee of the Center for International Blood and Marrow Transplant Research and Complications and Quality of Life Working Party of the European Society for Blood and Marrow Transplantation

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Abstract

Hematopoietic cell transplantation (HCT) is a potentially curative treatment for children and adults with malignant and nonmalignant diseases. Despite increasing survival rates, long-term morbidity after HCT is substantial. Neurocognitive dysfunction is a serious cause of morbidity, yet little is known about neurocognitive dysfunction after HCT. To address this gap, collaborative efforts of the Center for International Blood and Marrow Transplant Research and the European Society for Blood and Marrow Transplantation undertook an expert review of neurocognitive dysfunction after HCT. In this review we define what constitutes neurocognitive dysfunction, characterize its risk factors and sequelae, describe tools and methods to assess neurocognitive function in HCT recipients, and discuss possible interventions for HCT patients with this condition. This review aims to help clinicians understand the scope of this health-related problem, highlight its impact on well-being of survivors, and help determine factors that may improve identification of patients at risk for declines in cognitive functioning after HCT. In particular, we review strategies for

preventing and treating neurocognitive dysfunction in HCT patients. Finally, we highlight the need for well-designed studies to develop and test interventions aimed at preventing and improving neurocognitive dysfunction and its sequelae after HCT.

Keywords

Neurocognitive dysfunction; Cognition; Cognitive function; Bone marrow transplantation; Hematopoietic cell; transplantation; Hematology oncology

Introduction

According to the Worldwide Network for Blood and Marrow Transplantation [1] and the World Health Organization, over 1 million hematopoietic cell transplants (HCT) have been performed worldwide and approximately 50,000 HCT procedures are performed annually [2,3]. By 2030 an estimated half-million HCT recipients in the United States will be long-term survivors [4]. These survivors are at risk for late effects that may adversely affect their quality of life and increase morbidity and mortality [5,6]. Neurocognitive dysfunction, including symptoms such as memory impairment, impaired concentration, and difficulty in performing multiple tasks simultaneously, has been recognized as a common complication in cancer patients [7,8]. Neurocognitive dysfunction can significantly impact the early and late post-HCT course, and it has emerged as a major cause for post-transplant morbidity and mortality [9].

In adult HCT survivors, an incidence of neurocognitive dysfunction of up to 60% has been documented at 22 to 82 months post-HCT [10-12]. Neurocognitive dysfunction is associated with risk factors such as pretransplant chemotherapy, use of total body irradiation (TBI) in conditioning, immunosuppressive therapies, length of hospital stay, and graft-versus-host disease (GVHD) [10,12-16]. For children undergoing HCT, special considerations include the presence of nonmalignant disorders that impact neurocognitive function even without transplant (e.g., sickle cell anemia) and prior intense chemotherapy or radiation for malignant diseases during developmentally vulnerable periods that lead to language and speech delays [17].

Current gaps exist in our characterization of neurocognitive dysfunction after HCT and include an operational definition, neurocognitive issues in adults and children, risk factors, assessment, and interventions. To address this gap the Late Effects and Quality of Life Working Committee of the Center for International Blood and Marrow Transplant Research (CIBMTR) and the Complications and Quality of Life Working Party of the European Group for Blood and Marrow Transplantation provide an expert review to characterize the state-of-the-science of neurocognitive dysfunction after HCT and to build on these data with general recommendations for clinical practice and future areas of research.

Definitions

Neurocognitive Function Domains

Neurocognitive function refers to the activities of the brain that generate the complex behaviors of day-to-day life. Although a large number of brain structures may be involved in generating these behaviors, unique neurocognitive functions can be described most comprehensively by evaluating 8 domains (Table 1) [22]. Notably, neurocognitive evaluation in children may also include an assessment of academic achievement and global intelligence.

Neurocognitive Dysfunction in HCT

Neurocognitive dysfunction describes a negative change in neurocognitive function that is independent of normal aging and may affect activities of daily living, including social interactions, complex behaviors, and occupational or academic functioning; this change may have a profound effect on quality of life [22]. Neurocognitive dysfunction may be assessed in relation to a subject's prior abilities, if known, or in relation to a normative population.

Characterization of Neurocognitive Dysfunction Challenges

A variety of issues hamper the ability to characterize and understand neurocognitive dysfunction after HCT. First, it is unclear whether self-appraisals of neurocognitive dysfunction correlate with objective neurocognitive test results, and most studies do not include an analysis of the patients' perspectives. In the few studies that have performed this analysis, correlations between the patient's perspective and the test results varied [10,23-25] Second, the heterogeneity in study designs, testing methods, and cut-offs makes it challenging to identify the neurocognitive domains most affected by HCT. Furthermore, definitions of neurocognitive dysfunction vary between studies, and analysis and interpretation of longitudinal data can be hampered by the practice effect of repeating tests over time and the high attrition rate due to adverse medical outcomes [23,26]. Neurocognitive testing also depends on the patient's ability to communicate in English or the local language of the healthcare providers, thereby excluding minorities that may be less proficient in these languages. Finally, cultural differences and contextual understanding of neurocognitive function may impact neurocognitive testing, bias results, and lessen the validity of findings [27].

Neurocognitive Issues in Adults

A recent survey performed in a heterogeneous group of more than 400 survivors and caregivers by a patient advocacy group (www.bmtinfonet.org) showed that finding information about neurocognitive dysfunction was the top concern for patients and second most important concern for caregivers (personal communication). Moreover, Bevans et al. [28] studied 171 adult survivors of allogeneic HCT and found that difficulty with concentration was 1 of the most prevalent physical symptoms reported by 3-year survivors. Historically, HCT has not often been an option for individuals over age 55 years; however, with advances in treatment options such as reduced-intensity regimens and supportive care measures, patients aged ≥ 65 years are now candidates for HCT. There is a scarcity of

evidence regarding neurocognitive dysfunction and older HCT recipients. In the few studies that have reported findings in this population, results suggest that regardless of age HCT survivors have more neurocognitive dysfunction than healthy individuals [29]. Further, age was not associated with outcomes such as GVHD, nonrelapse mortality, or overall survival [29].

Despite the demand for information about neurocognitive dysfunction, assessment is complicated because many patients have neurocognitive dysfunction before transplant (Table 2). Indeed, when neurocognitive function was evaluated before HCT, up to 58% of adults had some level of neurocognitive dysfunction. In a multi-institutional study, Scherwath et al. [13] followed 102 adult allogeneic HCT recipients and found that before HCT 4% to 24% of patients demonstrated scores consistent with neurocognitive dysfunction across various domains, including verbal fluency, fine motor function, and verbal memory.

In addition to this confounding factor, only a limited number of researchers have examined the course of neurocognitive dysfunction after HCT. Thus far, studies have revealed that among adults neurocognitive function declines in the first few months after HCT in a subset of patients and then partially recovers over time (Table 2). For example, Syrjala et al. [36] prospectively assessed neurocognitive function among 92 allogeneic HCT survivors at a single center. Their results showed that by the end of the first year after HCT the neurocognitive functioning of most survivors recovered to pretransplant levels in most domains, excluding grip strength and motor dexterity [13]. Importantly, pretransplant impairment on each test was identified in 15% to 32% patients [15].

In another study, Scherwath et al. [13] found that at 1 year post-HCT 41% of patients demonstrated neurocognitive dysfunction on at least 1 domain assessed compared with 47% of patients who experienced neurocognitive dysfunction at baseline. Also, 56% of survivors demonstrated decline at both day + 100 and 1 year post-HCT, and 17% of survivors developed cognitive decline starting at 1 year. Finally, in a systematic review conducted by Phillips et al. [37], researchers failed to identify a statistically significant change in neurocognitive function after HCT. Although this review included 11 studies and 404 patients, the authors highlighted important methodologic limitations including heterogeneous samples, no control groups, small sample sizes, and a high prevalence of neurocognitive dysfunction before HCT [37]. These studies also failed to differentiate neurocognitive dysfunction from “chemo brain” or “chemo fog,” which is experienced by patients undergoing treatment for cancer [38,39].

In cases where neurocognitive functioning does not recover, evidence suggests that neurocognitive dysfunction may persist in the long term and negatively affect the quality of life of survivors. Indeed, Syrjala et al. [16,36] documented that 41.5% of survivors compared with 19.7% of control subjects continued to demonstrate at least mild neurocognitive dysfunction at 5 years post-HCT. Many patients with neurocognitive dysfunction have a poor self-image and are often unable to resume pretransplant activities, such as attending work or school. In fact, nearly half of patients remain on disability or sickness benefits after HCT because of multiple factors, including neurocognitive dysfunction [10]. Not surprisingly, higher incidences of anxiety, fatigue, depression, emotional distress, and poor

physical and social functioning have also been reported among HCT survivors with neurocognitive dysfunction [10,25]. These side effects may lead to difficulty with medication management, including dosing errors and noncompliance, in the early period after HCT [40].

The aforementioned data support the notion that neurocognitive dysfunction is a prevalent complication after HCT in adults. Moreover, it is of the upmost importance among adult HCT survivors. The demonstration of neurocognitive dysfunction before HCT among adults suggests that it may be a result of the disease itself as well as previous treatments.

Despite limited data, results also suggest that neurocognitive dysfunction may occur across the continuum of HCT survivor care and may also be associated with decrements in physical, emotional, and social health. Unfortunately, these decrements in well-being may also have important ramifications with respect to treatment compliance and subsequent increased risk for morbidity and mortality after HCT.

Neurocognitive Issues in Children

Neurocognitive dysfunction and associated decrements in intelligence quotient (IQ) have been noted in children when comparing pre- and post-HCT scores [41-43]. For example, Shah et al. [42] found domain-specific alterations, including lower verbal and performance IQ scores, at 5 years post-transplant; however, other researchers found no significant changes in these areas of neurocognitive function [44-50]. Although Simms et al. [46] found that parent ratings of their child's academic ability were lower than those of a normative sample, other investigators [45,47,51] found academic achievement of children post-HCT to be within normal limits. Barrera and Atenafu [48] noted deficits in academic achievement and found that family (e.g., cohesion) and clinical factors (e.g., diagnosis) were predictors of neurocognitive function. Evidence suggests that other domains may also be impacted by neurocognitive dysfunction, including adaptive skills such as activities of daily living (e.g., dressing one's self) and diminished social competence, self-esteem, and emotional well-being in the first year after HCT [24,26,32].

Notably, studies have shown that younger age at diagnosis and treatment are associated with the most significant declines in neurocognitive function [43,45,46,52]. Although IQ and academic achievement may remain within normal ranges for younger children post-HCT [44,51], they may experience deficits in executive functioning skills, such as sustained attention, inhibition, response speed, and visual-motor integration skills [51]. Research has indicated that younger autologous HCT recipients experience neurocognitive dysfunction, including impairment in visual memory and visual-motor skills [53]. In addition, deficits in fine motor skills appear to be more pronounced in HCT recipients who received cranial irradiation at a younger age than those who received cranial irradiation at older ages [15,41,45].

To date, prospective longitudinal data in this area of research are limited. Longitudinal evaluation of neurocognitive functioning is important because it may elucidate differences over time as well as among specific domains. For example, Shah et al. [42] found that some

patients develop domain-specific declines that eventually improve (e.g., visual motor skills), whereas other patients develop domain-specific declines that are progressive and chronic (e.g., verbal skills). Significantly, patients in this study were unable to acquire new skills at a rate comparable with age-matched healthy peers, although this may have been due to changes in the sample across time as well as the unreliability of small sample sizes. The necessity for longitudinal evaluation in children is also evident when focusing on academic achievement. As an example, lower academic achievement has been noted, particularly as time since transplant increases [49,54].

To date, literature reporting neurocognitive function of children post-HCT is inconclusive, conflicting, and often focused on specific domains such as IQ and academic functioning. Notably, studies of neurocognitive dysfunction have suggested that age at the time of diagnosis and HCT is a potentially important moderating variable such that younger age may be deleterious. Despite a need for additional longitudinal data, results also suggest that neurocognitive dysfunction may occur across the continuum of HCT survivor care for children as well.

Risk Factors

Reported risk factors associated with neurocognitive impairment after HCT are presented below.

Conditioning Regimen

Transplant conditioning includes the administration of chemotherapeutic agents, TBI, or both before stem cell infusion. Chemotherapeutic agents that cross the blood–brain barrier and TBI have a direct cytotoxic effect on the brain. Table 3 displays the most common agents used in transplant conditioning regimens and their side effects. A TBI dose of 12 Gy is the mainstay treatment of myeloablative conditioning regimens for acute lymphoblastic leukemia [66,67], and the neurotoxic effects of this treatment have been studied in adults and children. Neurotoxic effects with the use of reduced-intensity conditioning regimens have been documented [37]. For example, fludarabine, a common component of reduced-intensity conditioning regimens, may be associated with neurotoxic effects in both adults and children. It may be important therefore to tailor individual conditioning regimens that balance potential neurotoxic effects of the administered agents in the context of desired overall and disease-free survival.

Although researchers have demonstrated that TBI and chemotherapy are neurotoxic, the specific effects of TBI and chemotherapy on the patients' neurocognitive functioning in the peritransplant period are unknown. Different techniques of administering TBI between centers make data analyses complex; as a result, conclusions are elusive. For example, Harder et al. [11] found mild to moderate late neurocognitive dysfunction in 60% of the patients who had received high-dose chemotherapy with TBI up to 12 Gy compared with healthy population norms. Others report no systematic effects of conditioning intensity on neurocognitive function [14,68], and a meta-analysis found no significant associations between TBI and neurocognitive dysfunction [37].

The potential adverse effect of myeloablative doses of TBI on neurocognitive function has been reported in young children with leukemia [14,16,69]. The addition of cranial or craniospinal irradiation, which may be added to TBI, may further impact neurocognitive function [50]. Other data in children reveal that the effects of TBI and cranial irradiation on neurocognitive function are relatively modest and variable [44-49]. Notteghem et al. [53] evaluated 76 children with extracranial solid tumors after autologous HCT using chemotherapy-only conditioning and found that the percentage of children falling into the below average range for IQ was greater than that of children in the general population and over a third of participants had severe reading or writing difficulties. Research has also shown executive function and visual-spatial skills to be below age level in children who received busulfan [52].

GVHD and Immunosuppressive Therapies

Allogeneic HCT recipients who develop GVHD may need immunosuppressive therapy for extended periods of time. These include calcineurin inhibitors such as cyclosporine and tacrolimus, which are known to have neurotoxic effects that include tremor, posterior reversible encephalopathy syndrome (PRES), and thrombotic microangiopathy. Studies have shown that subgroups of children who received unrelated al-logeneic HCT and developed GVHD demonstrated increased risk of neurocognitive dysfunction [42,47]. Despite potential association between GVHD and neurocognitive dysfunction, at present we are limited to conjecture regarding the possible effects.

Infections

Immune defects post-HCT and immunosuppressive therapy used during allogeneic HCT increases the risk for viral infections, including cytomegalovirus, Epstein-Barr virus, and human herpesvirus-6. These infections may specifically affect nonverbal memory functions, attention, and speed of cognitive performance [70-75]. Mild neurocognitive dysfunction associated with viral infections may not be identified by clinical or cognitive screening [70-73,76,77].

Primary Disease

Unlike patients with hematologic malignancies, patients with nonmalignant disease may have neurocognitive dysfunction that is often related to their primary disease. For example, patients with adrenoleukodystrophy have disease-specific neurologic dysfunction before HCT. These patients may have lesions in their central nervous system (CNS) that can affect both their physiologic and psychological functioning. Similarly, patients with sickle cell disease often experience cerebral ischemic events before HCT that can affect their overall neurocognitive functioning. Finally, patients with severe combined immunodeficiency due to adenosine deaminase deficiency may have neurocognitive dysfunction before HCT that is a result of their disease [74,75].

Other Risk Factors

Risk factors for neurocognitive dysfunction after HCT include female gender, younger age, higher body mass index, absence of a social partner, allogeneic HCT, extensive chronic D,

higher intensity pre-HCT cancer treatment, and use of narcotics, corticosteroids, tricyclic antidepressants, and sedatives [14,78,79]. In some studies pre-HCT functioning [51,53] and socioeconomic status are strong predictors of neurocognitive function after HCT [80]. However, other researchers have failed to find similar associations [48]. Behavioral problems such as sleep deprivation, fatigue, and depression may adversely affect neurocognitive function [80,81]. Finally, researchers have noted a negative relationship between pre-HCT anxiety and post-HCT neurocognitive function [51]. Collectively, the evidence indicates many factors could impact neurocognitive dysfunction and need to be examined for possible interventions targeting modifiable factors.

Assessment

Both subjective and objective measures have been used to assess neurocognitive function in HCT. However, no standard recommendations exist for the timing or types of measures to assess neurocognitive function in either adults or children. Table 4 summarizes tests for specific neurocognitive domains, applicable age ranges, average administration times, and general descriptions for each assessment tool. These tests are common in the published literature and address the domains most affected by neurocognitive dysfunction. All commonly used neurocognitive tests are standardized measures that are psychometrically validated and widely available in multiple languages [33,82-98].

Neurocognitive Testing

Adults—Researchers and clinicians currently use the following instruments to assess the neurocognitive function of adults before and after HCT: the Mini Mental State Examination, the Cognitive Abilities Screening Instrument, the Cognitive Assessment Screening Test, the Cambridge Neuropsychological Test Automated Battery, and the Repeatable Battery for the Assessment of Neuropsychological Status [87]. However, the use of these screening tools is controversial. The National Comprehensive Cancer Network does not recommend these screening tools for use in cancer patients, including HCT patients [99], likely because these screening tools were developed for patients with dementia and may not be sensitive enough to address the subtle neurocognitive dysfunction found in HCT patients. Given the drawbacks of these assessments, it may be more applicable for researchers and clinicians to assess patients based on identified risk factors; thus, future research should focus on the development of a standardized risk factor profile for patients who may be at risk of poor neurocognitive functioning post-HCT.

Children—Researchers and clinicians may consider assessing neurocognitive function of children before HCT, 1 year after HCT, and then at the beginning of each new stage of education. It should be noted that some children can be challenging to assess because they may not be old enough to perform specific assessments. As a result, deficits in neurocognitive function may only appear in the long term along with increasing age and tasks that require higher executive functioning. In addition, to date, researchers have not developed assessment tools that can reliably predict future neurocognitive deficits in more complex domains (e.g., math, reading and executive function) in children. Clinicians should consider the impact of other factors, such as protective isolation, missed schooling, and socialization with peers, when assessing the neurocognitive function of children post-HCT.

These factors are difficult to measure but may have a significant impact on the neurocognitive function and development of children over time.

Self-Report Measures and Interview

Because the sole use of objective measures does not provide clinicians with a complete picture of the patient's level of daily functioning, it is important to include self-report measures and a clinical interview in the assessment process. Self-report measures capture the patients', parents', or teachers' assessments of neurocognitive function and serve as an additional tool to screen for neurocognitive dysfunction. Similarly, the clinical interview collects information, including previous education, occupation, medical and psychiatric history, and cognitive history [68,100], to guide intervention for patients with neurocognitive dysfunction [101].

One self-report measure, The Childhood Cancer Survivor Study-Neurocognitive Questionnaire [102], addresses specific self-reported concerns about neurocognitive function in long-term survivors of childhood cancer, and it can be used with patients' post-HCT. The Childhood Cancer Survivor Study-Neurocognitive Questionnaire, which was developed in conjunction with the Behavior Rating Inventory of Executive Function—Adult Version, uses similar items and includes novel items specific to outcomes in survivors of childhood cancer [102]. Versions for younger children are also available— the Brief-Pre (for preschool children), the Brief-P (for school age children), and the Brief-SR (for older children). To ensure the most accurate findings, a qualified neuropsychologist who is aware of the relationship between mental health and subsequent neurocognitive assessment should administer the assessment tools, interpret the results, and provide a report to clinicians [103-111].

Correlates

In addition to the use of subjective and objective measures, neurologic specific biomarkers of CNS injury, neuroinflammation, and neuroimaging should be examined as potential tools to evaluate neurocognitive dysfunction after HCT. Biomarker discovery is a promising area of inquiry that may facilitate a deeper understanding of the impact of HCT on the CNS. From a clinical perspective, biomarkers may help define risk and identify protective factors for neurocognitive dysfunction as well as help monitor patient response to treatment. Biomarkers may also help elucidate the potential relationship between distressing symptoms, such as sleep deprivation, anxiety/depression, and infection, and neurocognitive dysfunction, leading to better care and quality of life for patients after HCT.

Biomarkers of CNS Injury and Neuroinflammation

Biomarkers of neurologic injury have been historically studied in stroke patients and patients with brain metastasis [30,112-115]. Previous studies have identified associated biomarkers of neurocognitive function such as O6-methylguanine–DNA methyltransferase [116], neuron-specific enolase [117], S100B [118], and neurotransmitters such as glutamate and γ-aminobutyric acid. However, to date, these biomarkers have not been studied in patients with CNS damage caused by chemotherapy or radiation [119,120]. Chemotherapy and radiation

used in HCT conditioning may result in the stimulation of inflammatory pathways and associated elaboration of various cytokines, adhesion molecules, and chemokines from leukocytes, fibroblasts, and endothe-lial cells. Preclinical models have shown that chemotherapy and radiation regulate expression of tumor necrosis factor-α, intracellular adhesion molecule-1, and IL-1 [121]. These inflammatory markers have been detected in the blood of patients who received radiation [122]. Similarly, serum levels of inflammatory cytokines have been measured in stroke patients [123,124] and correlated with neurocognitive dysfunction among newly diagnosed breast cancer patients [125]. Markers of oxidative stress have been associated with neurocognitive dysfunction among childhood leukemia patients, but similar studies have not been conducted among HCT recipients [126]. Among HCT survivors, Sharafeldin et al. [127] characterized various single nucleotide polymorphisms in combination with neurocognitive assessment tools. The results of these studies underscore the need for additional longitudinal studies in HCT patients evaluating select blood-based biomarkers in combination with imaging modalities and neuropsychological assessment tools.

Neuroimaging Biomarkers

Magnetic resonance (MR)-based imaging and positron emission tomography techniques, including structural and functional MR imaging, diffusion tensor imaging, and MR spectroscopy, may play an important role as biomarkers for neurocognitive dysfunction after HCT. In multiple previous studies, researchers have used these techniques to detect neurocognitive dysfunction after the diagnosis and treatment of cancer. For example, Cao et al. [128] evaluated dynamic contrast-enhanced MR imaging as a biomarker to predict radiation-induced neurocognitive dysfunction. MR changes including reduced neuroanatomic volumes have also been associated with neurocognitive dysfunction among survivors of childhood leukemia; however, similar studies have not been conducted among HCT survivors [129].

Building on this work among HCT recipients, Correa et al. [130] used neuroimaging techniques and neuropsychological testing to study 28 adult HCT recipients conditioned with TBI and high-dose chemotherapy or high-dose chemotherapy alone. They noted gray matter loss and a concomitant increase in ventricular volume in patients 1 year after HCT and no corresponding changes in healthy participants in the control group. Despite the noted changes in neuroimaging, statistically significant differences in rates of neurocognitive dysfunction were not found.

Other Correlates

Physical and psychological symptoms associated with cancer and cancer treatment may also be associated with neurocognitive dysfunction. In this area of research most studies have focused on fatigue and depressive symptoms [10,23,39,40]. For example, 1 longitudinal study examined cancer-related symptoms associated with neurocognitive dysfunction and found significant relationships over time among several domains of neurocognitive function and symptoms such as fatigue, depression, and perceived stress [131]. Another study examined patients with multiple myeloma who completed autologous HCT and found similar associations between neurocognitive function and symptoms (e.g., depression) [23].

In 2002 Harder et al. [10] focused on neurocognitive dysfunction of patients receiving HCT within the past 22 to 82 months and found that neurocognitive dysfunction was present in 60% of participants and that fatigue was a strong predictor of neurocognitive dysfunction; however, a correlation with depression was not reported in this study. Similarly, Mayo et al. [40] noted significant relationships between fatigue and depression and neurocognitive dysfunction in a cohort of patients at least 6 months after HCT. However, it should be noted that 2 studies found no significant relationship between fatigue or depression and neurocognitive dysfunction [23,39] and that 2 other studies found anxiety to be significantly associated with neurocognitive dysfunction [40,131].

Interventions

Awareness of neurocognitive dysfunction in HCT recipients is important for timely introduction of psychosocial support and other interventions, but there is a significant void in high-quality data to assess interventions in this area. Several approaches aimed at prevention or reduction of neurocognitive dysfunction have been studied in patients receiving systemic chemotherapy and/or radiation therapy, but to date no prospective studies have been conducted and relevant interventions still need to be evaluated in HCT patients. Four potential strategies to mitigate the risks or improve outcomes of neurocognitive dysfunction after HCT are listed below and in Table 5.

Strategy 1: Interventions to Minimize Therapy-Related Neurocognitive Toxicity

To reduce neurocognitive dysfunction, clinicians may consider reducing the use of neurotoxic therapies such as prophylactic cranial radiation, TBI, or neurotoxic agents [144,145] or the substitution of busulfan for TBI-based conditioning during treatment [15]. Similarly, in cases where the patient does not need radiation to control disease (e.g., non-malignant diseases), clinicians may choose to reduce or eliminate neurotoxic agents given concerns for long-term sequelae.

Strategy 2: Management of Acute CNS Toxicities after Allogeneic HCT

TBI has been associated with CNS complications within the first 100 days in adults, and those patients with known seizure history may experience increased seizures [134]. PRES occurring in the first 100 days after allogeneic HCT is associated with neurocognitive dysfunction [134] and requires careful management strategies [31]. Identification of PRES and tight control of hypertension as well as a careful search for and removal of the etiologic agent remains a mainstay of management. For example, sirolimus, cyclosporine, or tacrolimus have been associated with PRES and may be withdrawn if they are believed to be contributing to the development of PRES [34]. Thrombotic microangiopathy and genetic susceptibility to thrombotic microangiopathy [132] can also be associated with neurocognitive dysfunction and also require prompt identification and management [133].

Strategy 3: Nonpharmacologic Interventions

For adults, re-education or job training may be beneficial. For children, approaches include cognitive remediation strategies and educational interventions [35,135]. Establishment of school re-entry programs that involve teachers early, tutoring in the immediate period after

HCT, enlisting the school system to provide an individualized educational plan, and accommodations based on a patient's individual deficits should be considered [54,135]. Poor recruitment and compliance with these educational programs remain a challenge and require improvement in accessibility and convenience for children and their families [136].

Cognitive rehabilitation for childhood cancer survivors in the form of intensive therapist-delivered training such as the cognitive remediation program has shown encouraging initial results [35]. The application of computer-based techniques to support optimal neurocognitive function may also be considered in children and adults. The systematic use of computer-based cognitive training is associated with significant improvements in working memory attention problems and processing speed in childhood cancer survivors with attention and working memory deficits [137,138].

Integrative therapies may also be useful to improve neurocognitive function (e.g., strategies to improve diet, exercise, and stress management) after HCT. For example, nutraceuticals such as vitamin therapy and other supplements may improve neurocognitive function and need to be examined before any conclusions can be made regarding their efficacy in HCT patients. Campbell et al. [146] found aerobic exercise improved neurocognitive function in cancer patients. Current investigation is ongoing to examine the potential benefit of exercise on neurocognitive dysfunction (NCT02533947) in adults. Finally, health behaviors such as abstinence from tobacco use and consuming alcohol in moderation may support healthy neurocognitive functioning after HCT.

Strategy 4: Pharmacologic Interventions

Pharmacologic interventions include therapies with a variety of pharmacologic agents such as stimulants; however, data in HCT recipients are lacking. Therapy with methylphenidate is associated with short- and long-term improvements in attention, concentration, executive function, and memory in childhood cancer survivors with neurocognitive dysfunction [135,137,139]. However, rebound symptoms (psychosis, depression, and attention problems) may arise with long-term use [140]. With perceived effects in social skills and behavior, further study focusing on the impact of methylphenidate on academic functioning is warranted.

The acetylcholinesterase inhibitor, donepezil, was studied in adult patients with primary brain tumors and showed improved attention, concentration, language function, verbal and figure memory, and mood [141]. Breast cancer patients taking modafinil have shown improvement in memory and attention [142]. Administration of recombinant human growth hormone may be associated with improved cognition; sustained attention and cognitive-perceptual performance in young adult survivors of childhood cancer [143].

Future research and Clinical Practice

Several significant gaps in our knowledge support our proposed recommendations for future research, and the general recommendation for clinical practice shown in Table 6. Current practice recommendations are difficult to suggest because of the lack of adequately powered randomized controlled trials; however, the literature suggests a burden of neurocognitive

dysfunction in HCT recipients and their caregivers. There is no evidence supporting standard drug or other intervention prophylaxis in all or even in currently definable subgroups of patients. There are also limited data to justify choice of conditioning based on predicted neurocognitive effects, and therefore conditioning treatments should be guided by primary disease. However, clinicians need to balance the need for high-intensity conditioning regimens and disease control with short- and long-term sequelae of these therapies.

Clinicians may inform and counsel their patients of the signs of neurocognitive dysfunction before HCT, such as difficulty concentrating or remembering important dates, and conduct appropriate assessments at each follow-up visit to enable early intervention. Supportive treatment may be considered based on dominating symptoms. Moreover, referral for a neuropsychiatric consult may be also considered. Awareness of the risk factors and likelihood of neurocognitive dysfunction after HCT is important for counseling patients pretransplant but also to help earlier identification of emerging toxicities to guide referrals to appropriate specialist and help management.

Conclusions

This review examined extant literature in key areas to characterize the state of the science regarding neurocognitive dysfunction in patients who have completed HCT. Several significant gaps in our knowledge support our proposed recommendations for future research and the general suggestions for clinical practice. Future studies focusing on specific populations including various pediatric populations and older adult populations are needed to delineate neurocognitive dysfunction after HCT and to define potential risk and protective factors for patients who suffer from the condition and represent unmet needs. In addition, researchers should focus on the development and validation of a sensitive screening tool for neurocognitive dysfunction that can be used by clinicians who treat patients after HCT. Moreover, the combination of a wider application of neurocognitive assessments with newly developed biomarkers may prove to be a powerful combination of tools used to define at-risk HCT recipients. These data can then be used to develop and evaluate precision interventions focused on prevention and amelioration of neurocognitive dysfunction. With properly designed studies, appropriate interventions and practice guidelines can be developed. Emerging knowledge on evaluation and intervention may lead to better neurocognitive outcomes.

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Table 1
Domains of Neurocognitive Function in Adults and Children

Domain	Alternative Names	Subdomains	Characteristics
Attention and concentration	• Attention	• Arousal • Focused attention • Divided attention • Vigilance or sustained attention	Alertness sufficient to the completion of tasks. Ability to focus and sustain attention throughout tasks (distractibility). Aspects of attention include the level of alertness or arousal of an individual, which is maintained by the reticular activating system [18]. Object recognition. Ability to recognize where objects are located in space. The ventromedial occipital parietal tract aids in the identification of objects, whereas the dorsolateral occipital parietal pathway serves to determine their location in space [19]. Learning is the capacity to store and recall new information [20]. Working memory is used to describe the capacity to hold, process, and manipulate information.
Perceptual processing	• Sensory-perceptual • Sensory-motor • Visuospatial and constructional processing	• Agnosia • Visual-spatial cognition	
Learning and working memory	• Visual learning and memory	• Verbal • Visual • Working memory • Short- and long-term recall recognition	
Abstract thinking and executive function	• Executive function	• Initiation and planning • Cognitive flexibility • Self-regulation	Ability to reason beyond given information to arrive at an interpretation or understanding, or a course of action consistent with goals. Many executive functions are served by the frontal lobes [21].
Language		• Reception • Repetition • Self-expression	Ability to use written or spoken communication to understand or convey information.
Information processing speed			Ability to rapidly process simple and complex information. Information processing speed is a measure of the efficiency of cognitive function and is necessary for motor function.
Motor function	• Motor speed and strength • Fine motor		Ability to perform tasks rapidly, precisely and in a smooth, coordinated way
Emotions	• Inhibition • Mood, thought content, personality, and behavior • Motivation/ symptom validity	• Speed • Dexterity • Coordination • Behavioral • Perceptual	Ability to suppress actions that interfere with goal-driven behavior.

Table 2
Reported Prevalence and Kinetics of Neurocognitive Change before and after HCT

Reference	Baseline (%) (n/N)	Time Assessment of Neurocognitive Dysfunction (%) (n/N)	Study Design	Population
[28]	46% (26/56)	Day 100: 38% (19/50) 6-8 months: 29% (12/42)	Single center Prospective Observational Longitudinal study	Recruitment: 2012-2013 58 adults AlloHCT 100% (58) Various diseases
[18]	47% (25/53)	1 month: 49% (20/41) showed decline compared with baseline evaluation Day 100: 48% (14/29) *Additional finding:* Showed decline compared to baseline evaluation	Single center Prospective Observational Longitudinal study	Recruitment: 2008-2011 53 adults AutoHCT 100% (53) Only multiple myeloma
[30]	21% (2/28) compared with 10% (1/10) healthy control subjects	1 year: Rates of decline/ improvement over 1 year did not differ between patients and control subjects *Additional finding:* Reduction in regional gray matter and ventricular enlargement 1 year: 41%	Multicenter Prospective Interventional (imaging) Longitudinal study with healthy control group	Recruitment: N/A 28 adults AutoHCT: 43% (12/28) AlloHCT: 57% (16/28)
[12]	47%		Multicenter Prospective Observational Longitudinal study	Recruitment: 2005-2008 102 adults AlloHCT
[15,24]	15-32% (expected rate = 16%)	Day 80: 27-63% 1 year: 15-46% 5 years: 40%	Single center Prospective Observational Longitudinal study	Recruitment: N/A 142 adults up to 1 year, 92 adults up to 5 years. AlloHCT 100% (142/142)
[31]	30% (10/33)	6 weeks: 47% (15/32) *Additional finding:* Showed reliable decline on at least 1 test 28 weeks: 33% (5/15) *Additional finding:* Showed further decline on at least 1 test	Single center Prospective Observational Longitudinal study	Recruitment: N/A 117 adults AutoHCT 50% (59/117) AlloHCT 48% (56/117) Missing: 2% (2/117)
[20]	Not reported	5 months: 51% (compared with 16% in the general population)	Single center Cross-sectional study	Recruitment: 1997-1999 65 adults All adults AutoHCT: 81% (53/65) AlloHCT 19% (12/65)
[32]	5-26% (1/19-5/19)	Day 100: 5-42% (1/19-8/19)	Single center Prospective Observational longitudinal study	Recruitment: N/A 39 adults AlloHCT 100% (39/39)
[33]	6% (16/269)	1 month: 4% (5/124)	Single center	Recruitment: N/A
		Day 100: 2% (2/83)	Prospective Observational longitudinal study	388 adults AutoHCT 79%(306/388) AlloHCT 21% (82/388)
[11]	58%	14 months: 51%	Single center Prospective Observational longitudinal study	Recruitment: 1996-1998 71 adults Auto/Allo ratio N/A
[19]	Not reported	1.6 years: 32%	Single center Cross-sectional study	Recruitment: N/A 40 adults AutoHCT: 100% (40/40) Only breast cancer
[34]	Not reported	36 months: 37%	Not reported	Recruitment: Not reported 66 Autologous 11% (7/66) Allogeneic 89% (59/66)
[21]	20%	8 months: 20%	Single center Cross-sectional study	Recruitment: Not reported 61 AutoHCT: 31% (19/61) AlloHCT: 69% (42/61)
[35]	56%	Not reported	Single center Cross-sectional study	Recruitment: 1989-1991 55 Auto/ Allo ratio N/A

Baseline assessment was before HCT. Allo indicates allogeneic; Auto, autologous.

Table 3
Reported Factors Associated with Risk of Neurocognitive Dysfunction after HCT

	Manifestations
Conditioning regimen	
TBI	Headache, fatigue.
Busulfan	Reversible encephalopathy with some somnolence, confusion, decreased alertness, myoclonus, hallucinations; seizures.
Carboplatin	Ototoxicity in patients with neuroblastoma.
Carmustine	Variable degrees of optic disc and retinal microvasculopathy with variable degrees of visual loss [55,56].
Cytarabine arabinoside	Pancerebellar syndrome ± diffuse encephalopathy with lethargy, confusion, and seizures [57].
Etoposide	Confusion, somnolence, and seizures, which resolve spontaneously [58].
Fludarabine	Neurological decline, blindness, leukoencephalopathy.
Ifosfamide	Encephalopathy with lethargy, confusion and seizures in 10-40% of the patients. Visual or auditory hallucinations, myoclonus, or muscle rigidity have been reported, which is often self-limited, but there are reports of progressing to coma [59,60].
Thiotepa	Chronic encephalopathy with progressive declines in cognitive and behavioral function and memory loss.
Immunosuppressive therapy	
Cyclosporine A Tacrolimus Sirolimus	TMA, PRES [61-63]
Steroids	Psychosis, myopathy
Antithymocyte globulin	Neurotoxicity, seizures
Cyclophosphamide	Neurotoxicity
Methotrexate	Leukoencephalopathy
CNS infections	
Human herpesvirus 6	Encephalitis, AMS [64,65]
Herpes simplex virus	Meningoencephalitis, seizures
Varicella zoster virus	Encephalitis, postherpetic neuralgias, zoster ophthalmicus
JK	Altered mental status, encephalitis
Epstein-Barr virus	Post-transplant lymphoproliferative disease
Cytomegalovirus	Vision loss, cytomegalovirus retinitis, meningoencephalitis
Toxoplasma gondii	Mild to severe encephalopathy

TMA indicates thrombotic microangiopathy; PRES, posterior reversible encephalopathy syndrome; AMS, alerted mental status.

Table 4

Abbreviations, Names and Description of Commonly Used Neurocognitive Tests

Test	Age (yr:mo)					
	<2:0	**2:0-4:11**	**5:0-5:11**	**6:0-16:11**	**17:0-17:11**	**18:0+**
Intelligence						
Bayley-III (90 min) *	X† (0:0 to 3:6)					
WPPSI-IV (VCI, PRI) (60 min)		X‡ (2:6 to5:11)				
WISC-IV (VCI, PRI) (60 min)				X		
WAIS-IV (VCI, PRI) (60 min)					X	X
Processing speed/attention						
WPPSI-IV (Symbol Search, Coding) (10 min)		X (4:0 to < 6:0)				
WISC-IV (Symbol Search, Coding) (10 min)				X		
WAIS-IV (Symbol Search, Coding) (10 min)					X	X
TEA-Ch (15 min)				X (6:00 to <16:00, 17:00 to 16:11 norms pending)	X (17:00 to > 18:00 norms pending)	
TEA (15 mins)						X
CPT-K (15 min)		X (4:00 to 4:11)	X			
CPT-CA (15 min)				X§ (8:00 to 16:11)	X	X
TMT						X
Memory CMS (Story Memory I & II) (10 min)			X	X		
WISC-IV (Digit Span, LN Sequencing) (5 min)				X		
WAIS-IV (Digit Span, LN Sequencing (dropping					X	X
Arithmetic) (5 min)						
WMS-III (Logical Memory I & II) (10 min)					X	X
CVLT-C (20 min)			X	X		
CVLT-II (30 min)				X (16:00 to 16:11)	X	X
HVLT-R (30-35 min)					X	X

Test	Age (yr:mo)					
	<2:0	**2:0-4:11**	**5:0-5:11**	**6:0-16:11**	**17:0-17:11**	**18:0+**
CFT (30 min)					X	X
Educational achievement						
WIAT-III		X (4:00 to 4:11)	X	X	X	X
Verbal fluency and word-finding						
COWAT (10-15 min)				X	X	
Fine motor speed						
Groove Pegboard Test (5 min)				X	X	
Finger tapping task (5 min)				X	X	
Executive functioning						
BRIEF-Pre (parent/teacher) (15 min)		X	X			
BRIEF-P (parent/teacher) (15 min)			X	X	X	
BRIEF-SR (self-report) (15 min)				X (11:00 to >18:00)	X	
BRIEF-A (adult) (15 min)						X
CCSS-NCQ (adult childhood cancer survivors) (15 min)						X
SCWT (5 min)			X	X	X	X
WCST (25 min)				X	X	

Abbreviation	Name of Measure	Description of Measure
Bayley-III	Bayley Scales of Infant and Toddler Development, Third Edition	Examines all facets of a young child's development
BRIEF-P	Behavior Rating Inventory of Executive Function for children—Parent/teacher Version	Assesses executive functioning behaviors in the school and home environments in school-age children
BRIEF-A	Behavior Rating Inventory of Executive Function—Adult Version	Assesses executive functioning behaviors in the work and home environments in adults
BRIEF-Pre	Behavior Rating Inventory of Executive Function for Pre-School children—Parent/teacher Version	Assesses executive functioning behaviors in the school and home environments in preschool-age children
CCSS-NCQ	Childhood Cancer Survivor Study-Neurocognitive Questionnaire	Assesses executive functioning behaviors in the school and home environments in adult survivors of childhood cancer
CFT	Rey Complex Figure Test	Measures visual memory and organization
CMS	Children's Memory Scale	Measures memory function in children
COWAT	Controlled Oral Word Association Test	Measures verbal fluency

Test	Age (yr:mo)					
	<2:0	2:0-4:11	5:0-5:11	6:0-16:11	17:0-17:11	18:0+
CPT-CA	Conner's 3 Continuous Performance Task, Child and Adult		Assesses attention and control in children and adults			
CPT-K	Conner's 3 Continuous Performance Task, Kiddies		Assesses attention and control in very young children			
CVLT-II	California Verbal Learning Test second edition		Measures episodic and verbal learning in adults			
CVLT-C	California Verbal Learning Test (child and teen)		Measures episodic and verbal learning in children and teenagers			
GIT-V	Finger tapping task Groginger Intelligence Test, short form		Assesses motor speed/dexterity Measures general intelligence; has 3 subtests: spatial ability, abstract reasoning, arithmetic			
HVLT	Grooved Pegboard test Hopkins Verbal Learning Test-Revised		Assesses motor speed/dexterity Assesses verbal learning and memory			
SCWT	Stroop Color Word Tests		Measures executive functioning and selective attention			
TEA	Test of Everyday Attention in Adults		Assesses attentional capacity in adults			
TEA-CH	Test of Everyday Attention in Children		Assesses attentional capacity in children			
TMT	Trail-making Tests Part A and B		Assesses motor speed and attention			
WAIS-IV	Wechsler Adult Intelligence Scale, 4th Edition		Measures cognitive ability in older teenagers and adults			
WIAT-III	Wechsler Individual Achievement Test, 3rd Edition		Assessment of academic achievement			
WISC-IV	Wechsler Intelligence Scale for Children, 4th Edition		Measures cognitive ability in children			
WMS-IV	Wechsler Memory Scale, 4th Edition		Measures memory function in older teenagers and adults			
WPSSI-IV	Wechsler Preschool and Primary Scale of intelligence, Fourth Edition		Measures cognitive development for preschoolers and young children			

*Bailey-III administered in lieu of all tests of cognition for children > 2:6,or >3:6 in the case of evidence of developmental delay.

†For patients >3:6 and evidence of developmental disability: administer Bayley Scales.

‡For patients >4:0: administer Receptive Vocabulary, for patients ≥4:0: administer Vocabulary.

§No CPT available for 6:00 to 7:11.

Table 5

List of Potential Interventional Strategies to Mitigate the Risks or Improve Outcomes of Neurocognitive Dysfunction after HCT

Category	Interventional Strategy (References)
Reduction of neurotoxic effects of therapy associated with HCT	• Avoidance of prophylactic cranial irradiation, TBI (especially in those with prior seizure history), and/or certain cytotoxic agents during conditioning regimen [15] [117-119]
	• Gender-and age-specific changes in motor speed and eye-hand coordination in adults: normative values for the Finger Tapping and Grooved Pegboard Tests
Management of post-HCT complications	• Management of TMA [132,133]
resulting in CNS effects	• Management of PRES [31,34,134]
	• Treatment of infectious complications
Nonpharmacologic interventions	• Cognitive remedial approaches, school programs, cognitive behavioral therapy, social skills training [35,54,135,136]
	• Computerized (web- or smartphone-based) cognitive training [137,138]
	• Use of smartphone or another device for note taking; list making
Pharmacologic intervention	• Methylphenidate [135,139,140]
	• Donepezil [141]
	• Modafinil [142]
	• Recombinant human growth hormone [143]

Table 6
Proposed Recommendations for Future Research Opportunities and for Clinical Practice

Recommendation	Explanation
Recommendations for research	
Study design and measures	• Conduct prospective longitudinal studies
	• Include sufficient sample size (conduct multisite studies)
	• Use cooperative research groups to support large future studies, harmonize methods Include normative data and (matched) control groups (healthy control and disease-specific groups)
	• Conduct comprehensive neuropsychological assessment
	• Use sufficiently sensitive measures
	• Assess specific cognitive domains in addition to global functioning
	• Evaluate (fine-)motor function
	• Use both performance-based measures and surveys
	• Include self-report measures of neurocognitive function
	• Include measures of health-related quality of life to understand the functional consequences of observed deficits
Measurement time points	• Include precondition therapy baseline
	• Assess patients early after immediate post-transplant period (approximately day 100)
	• Conduct longer follow-up periods (>5 years), focus on very long-term survivors
Statistical analysis	• Consider influence of attrition
	• Improve clinical utility by using individual-level analysis (Reliable Change Index)
	• Control for pre-HCT treatment
	• Include concurrent medical events as covariates
	• Determine standard criterion for cognitive impairment
Risk factors	• Identify risk factors for and predictors of poor cognitive outcome
	• Identify risk factor at various time points before and after HCT
	• Consider disease-specific features
	• Identify biologic and genetic contributors using global techniques such as metabolomics and proteomics
	• Identify psychosocial contributors
Rehabilitation/intervention	• Identify the cognitive profile of patients
	• Develop and evaluate specific cognitive rehabilitation strategies
	• Evaluate the effectiveness of cognitive rehabilitation strategies developed for other populations
	• Investigate the usefulness of intervention programs developed to reduce symptom burden
	• Study the utility of stimulant and centrally active anticholinergic drugs for this condition
Impact of cognitive impairment	• Evaluate the possible consequences on academic achievements, return to work, and quality of life
	• In younger patients consider longer term impact on academic and vocational attainment, ability to live independently, enter and maintain social relationships
Recommendations in clinical practice	
Routine	• Provide vocational counseling
	• Provide psychosocial support
	Take patients' concerns seriously
	• Monitor patients
	• Evaluate neuropsychological function in patients with cognitive complaints at 1 year after HCT

Recommendation	Explanation
Rehabilitation/intervention	• Implement an integrated rehabilitation concept • Treat patients individually