

Developing Interventions for Cancer-Related Cognitive Dysfunction in Childhood Cancer Survivors

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Survivors of childhood cancer frequently experience cancer-related cognitive dysfunction, commonly months to years after treatment for pediatric brain tumors, acute lymphoblastic leukemia (ALL), or tumors involving the head and neck. Risk factors for cancer-related cognitive dysfunction include young age at diagnosis, treatment with cranial irradiation, use of parenteral or intrathecal methotrexate, female sex, and pre-existing comorbidities. Limiting use and reducing doses and volume of cranial irradiation while intensifying chemotherapy have improved survival and reduced the severity of cognitive dysfunction, especially in leukemia. Nonetheless, problems in core functional domains of attention, processing speed, working memory and visual-motor integration continue to compromise quality of life and performance. We review the epidemiology, pathophysiology and assessment of cancer-related cognitive dysfunction, the impact of treatment changes for prevention, and the broad strategies for educational and pharmacological interventions to remediate established cognitive dysfunction following childhood cancer. The increased years of life saved after childhood cancer warrants continued study toward the prevention and remediation of cancer-related cognitive dysfunction, using uniform assessments anchored in functional outcomes.

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Cancer-related cognitive dysfunction (referred to hereafter as “cognitive dysfunction”) affects one third or more of the estimated 350 000 childhood cancer survivors in the US (1–9). Cognitive dysfunction is a symptom complex characterized by decline in full scale intelligence quotient (FSIQ) and/or impairment in core functional domains of attention, vigilance, working memory, executive function, processing speed, or visual motor integration (9–14). These core deficits can compromise social and academic performance and quality of life (HRQOL), even when FSIQ falls within average range (4,9,15–22). Patient, parent, and teacher reports describe children spending excessive time on homework yet having poor acquisition and retention (17,23–27), especially in reading, spelling and mathematics (28,29). Self-monitoring skills and peer relationships can be compromised (4,17,18,27,30–37), and post-traumatic stress is common (38,39).

Cognitive dysfunction varies in severity. It is most common in survivors of brain tumors or acute lymphoblastic leukemia (ALL). However, it can affect any child treated with head and neck irradiation, repetitive neurotoxic chemotherapy, or hematopoietic stem cell transplantation (HSCT) (10,11,13,14,40–45). Cognitive dysfunction complicating childhood cancer appears to be more frequent and severe than “chemo brain” of adults (46–48). Compared to controls, childhood brain tumor survivors are less likely to marry (49,50), complete high school (51), maintain employment (52–54), or receive appropriate health care (55,56). Brain tumor survivors face additional problems related to motor,

sensory, and behavioral disturbances, often culminating in social isolation and failure to attain independence (4,10,52,57,58). Cognitive dysfunction presents at or soon after diagnosis of the cancer, but deficits often emerge insidiously years later. Over the past 40 years, clinical trials modifying cancer treatment have improved overall survival in ALL and central nervous system (CNS) tumors and reduced severity of cognitive dysfunction (4,5,9–11,13,27,44,59–62). This review examines the impact of modern cancer treatment on the epidemiology and pathophysiology of cognitive dysfunction, considers ongoing attempts to monitor outcomes through targeted and feasible neurocognitive assessments, and describes pharmacologic and nonpharmacologic interventions to remediate established cognitive dysfunction. We propose earlier intervention, use of novel intervention approaches, and ways to address accrual and retention to facilitate more robust trials.

Methods

We used PubMed to identify relevant English-language articles published between 1990 and December 2012. In alignment with best practices in search methodology, we aimed to retrieve a comprehensive set of relevant studies using combinations of search terms such as: cancer therapy, brain tumor, leukemia, cognition, cognitive deficits, radiation therapy, chemotherapy, methotrexate, neoplasms, intervention, remediation, and pediatric. We limit citations to seminal reports, primary studies and reviews of the

past two decades, and publications of remediation trials and those concerning new strategies. A total of 257 studies were selected for inclusion from 622 searched.

Epidemiology of Cancer-Related Cognitive Dysfunction

Prevalence

Prevalence estimates are derived from a composite of a few prospective longitudinal studies and many cross-sectional observational studies. The latter are characterized by small sample size, heterogeneous tumors, varied control populations, absence of power calculations, disparate assessment tools, and assessment intervals ranging from months to decades after treatment (4,9). Despite methodological limitations, a remarkably consistent picture emerges: prevalence and severity of cognitive dysfunction has declined over the last 50 years. To date, the impact of treatment modification is more noticeable in ALL than in brain tumor survivors.

The prevalence of cognitive dysfunction in ALL survivors, measured solely by decline in FSIQ, fell from an estimated 10% to 40% for patients treated in the 1970s and early 1980s to 5% to 10% in the 21st century (62–64). However, deficits in core functions continue to compromise HRQOL and performance for many (5). In contrast, the prevalence of cognitive dysfunction in survivors of childhood brain tumors ranges from 40% to 100% (3–5,65). Risk factors involve interaction among standard variables of host, tumor, and treatment (Figure 1). Risk must be interpreted in the context of the timing and type of assessment used to define cognitive dysfunction: longer follow-up and more detailed and sensitive assessments are likely to find deficits of varying functional importance.

Pathogenesis of Pediatric Cancer-Related Cognitive Dysfunction

Host-Related Risk Factors

In children, cognitive dysfunction primarily affects new learning (65). Younger age at treatment is the most important host-related risk factor (Figure 1), explained by the concurrence of cancer injury with critical periods of brain development (66). Basic motor, language, problem-solving and social skills are acquired early in life. By three months of age, a full complement of neurons populates the brain; thereafter, most neuronal proliferation arrests and differentiation of neurons begins within specific germinal centers (67). Synapses reach their maximum number by two years of age, gray matter development peaks at age four, and white matter development continues into the third decade. As the child ages, axons are myelinated, and synaptic contacts are established and refined by waves of overproduction and pruning in varying parts of the growing brain, with the tempo related to gains in cognition (66,68).

Female sex is a risk factor for cognitive dysfunction in some studies of ALL (69–71). There is no clear pathophysiological explanation for observed gender differences, and they are not reported in survivors of other tumors.

Conditions antecedent to the cancer diagnosis also contribute to cognitive dysfunction. Forty to 50% of children with CNS tumors

have cognitive impairment or developmental delay pretreatment, and 6% have cognitive abilities in the borderline to extremely low range with IQ < 70 (72). Physical disability and impaired fine motor skills associate with worse performance on neuropsychological assessment (32,73,74). Comorbidities that associate with cognitive dysfunction include seizures, hydrocephalus, meningitis, ventriculitis, cerebrovascular accidents, impaired hearing and/or vision, motor problems (eg, paresis, paralysis, ataxia, and imbalance), behavioral abnormalities, and antecedent learning difficulties or developmental delay (4,57,75).

Genetic risk factors include cancer predisposition syndromes such as neurofibromatosis type 1, tuberous sclerosis, and basal cell nevus syndrome, where underlying cognitive delays or autism confound attribution of effects to tumor and treatment (76). Polymorphisms in the MTHFR gene correlate with risk of inattention in survivors of childhood ALL treated with systemic or intrathecal folate antagonists (77,78). The association between cognitive dysfunction and gene polymorphisms involved in the metabolism of homocysteine (79), methionine synthase glutathione S-transferase, monoamine oxidase, and apo-lipoprotein E4 await confirmation (80).

A limited number of reports of cognitive dysfunction address socioeconomic factors; however, low maternal educational attainment is a consistent association (12,81,82).

Treatment-Related Risk Factors

Radiation Therapy. Dose and field of cranial irradiation are highly associated with subsequent development of cognitive dysfunction (4,9,12,25,33,44,83). Somnolence syndrome increases the risk of cognitive dysfunction (84). Radiation to temporal regions is associated with problems in memory, social function and general health—radiation to frontal areas with limitations in general health and physical performance (85). In animal models of cranial irradiation therapy (CrRT), spatial learning and memory deficits associate with alterations in glutamate receptors (86,87).

Leukoencephalopathy, a subacute degeneration of white matter, may contribute to radiation-associated cognitive dysfunction (88). Oligodendrocytes and their progenitor cells, the most radiosensitive glial cells, produce myelin. Death of oligodendrocytes, endothelial cell loss, and neural progenitor depletion initiate the release of oxygen species by astrocytes. This elicits an inflammatory response, thereby impairing neurogenesis (88,89). Irradiated rodents show increased hippocampal apoptosis, decreased stem cell numbers and reduced adult neurogenesis (90–92). Even low total doses of radiation can damage the pool of proliferative progenitor cells (93). Vascular injury manifesting five or more years after therapy can also contribute to cognitive dysfunction (88,94). Chronic ischemia or infarcts within the radiation field implicate both large and small caliber arteries (95). Pediatric brain tumor survivors have a 40-fold higher risk of stroke compared to siblings (96,97). Cerebral telangiectasia, cavernomas and aneurysms are recognized long-term complications of CrRT in children (98,99).

Total white matter volume accounts for some of the variance in the relationship between age at radiation therapy and cognitive dysfunction in survivors of ALL (100,101). In brain tumor survivors, disappearance of normal white matter and histologic

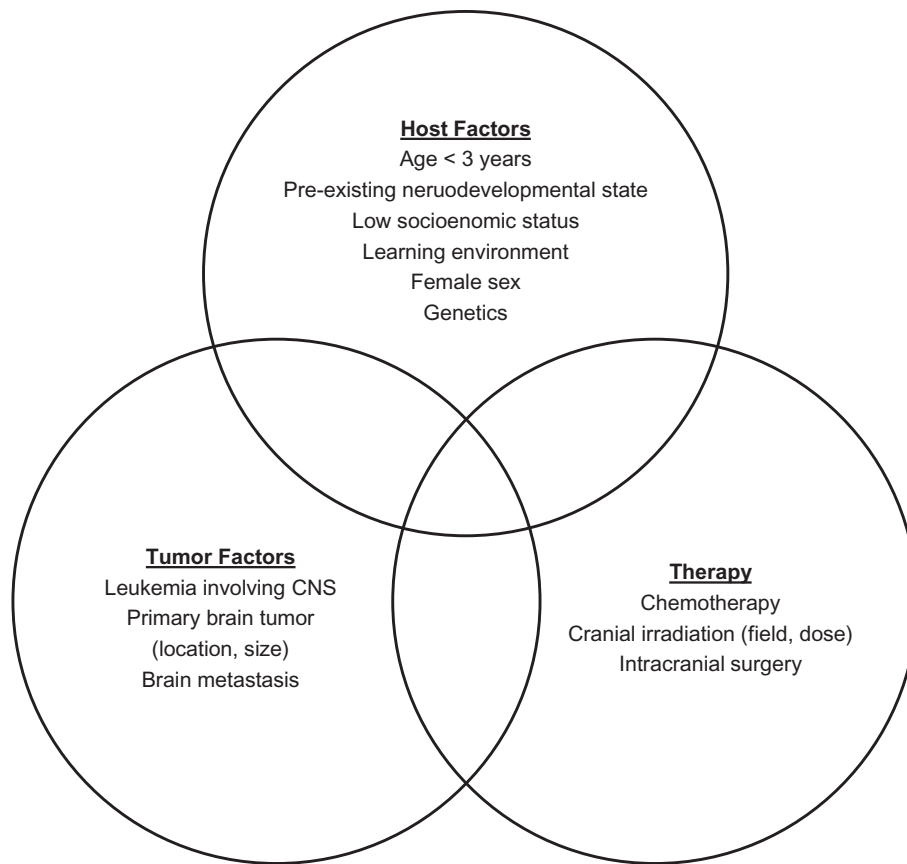


Figure 1. Factors contributing to risk of cancer-related cognitive dysfunction in childhood cancer survivors. Risk of impairment varies by timing of assessment relative to diagnosis and treatment, and by the assessment battery used. CNS = central nervous system.

evidence of demyelination and white matter necrosis on MRI correlate with decreased IQ, executive function deficits, problems with working memory, and overall academic achievement (28,102). Magnetic resonance spectroscopy (MRS) or diffusion tensor imaging (DTI) or tractography detect abnormalities in regions that do not demonstrate changes on conventional MRI (103), as shifts in metabolite ratios may reflect neuronal loss and glial proliferation after injury. Reductions in white matter fractional anisotropy in the corpus callosum or inferior frontal-occipital fasciculus on DTI correlate respectively with reduced processing and motor speed in survivors (104). Hippocampal atrophy and altered signaling in the hippocampus and elsewhere during unsuccessful encoding exercises correlate with impaired memory in survivors of ALL (105).

Chemotherapy. Neurocognitive sequelae of chemotherapy are less well documented than radiation effects (106). As childhood cancer treatment relies on combinations of drugs, attributing causality to specific agents other than methotrexate is difficult (107). Table 1 lists chemotherapeutic agents commonly associated with complications that may contribute to cognitive dysfunction, including seizures, transient ischemic attacks, encephalopathy, myelopathy, ataxia, posterior reversible leukoencephalopathy, and metabolic encephalopathy. Indirect complications of chemotherapy include infection, neuropathy, coagulopathy, vascular disorders, and polypharmacy (including antiemetics, analgesics, anxiolytics, and other agents that can compromise mental status). Notably, the risk of

neurotoxicity and cognitive dysfunction from new molecularly targeted biological therapies is unfolding, and likely related to penetration of the blood-brain barrier as well as the specificity of the target (107).

The folic acid inhibitor methotrexate is associated with cognitive dysfunction. Folic acid is essential for normal brain development and for DNA synthesis and repair throughout life. Methotrexate penetrates the blood-brain barrier in doses achievable with parenteral, intrathecal, or intraventricular administration (108). Dose, schedule, and route of methotrexate administration correlate with incidence and severity of cognitive dysfunction (6,109–112).

Although multiple systematic reviews and meta-analyses in ALL survivors associate dexamethasone with more cognitive declines than prednisone (113–115), recent primary reports have not confirmed this (82,116,117). In comparing outcomes between CNS prophylaxis with triple intrathecal therapy (ie, methotrexate, cytosine arabinoside, hydrocortisone) vs intrathecal methotrexate alone, the latter has a higher prevalence of processing speed dysfunction (118).

Neurosurgery. Surgical resection of CNS tumors provides histopathologic specimens and reduces tumor burden. Tumor location determines extent of resection and risk for complications, including altered mental status, stroke, infection, paresis or paralysis, seizures, sensory disturbance, incoordination, and cranial nerve deficits (18,107,119,120). Upon recovery from these events, long-term deficits can persist. While total resection increases the chance

Table 1. Chemotherapy in pediatric cancer associated with cognitive dysfunction*

Chemotherapy	Acute / subacute CNS effects	Potential long-term CNS effects
Methotrexate (systemic or intrathecal)	Seizures Leukoencephalopathy Myelopathy Aseptic meningitis	Attention deficits Processing speed deficits Seizures
Cytosine arabinoside	Cerebellar ataxia Aseptic meningitis Myelopathy Meningismus	Cognitive deficits Hemiparesis
AraG (Compound 506)	Somnolence Seizures	Unknown
Steroids	Sleep disturbance Mood/behavioral disorder PRES Transient psychosis	Cognitive deficits
5FU	Cerebellar ataxia	Unknown
Ifosfamide	Acute encephalopathy Hallucinations/delirium Aseptic meningitis Cranial nerve palsy Movement disorder Seizure	Cognitive deficits
Asparaginase	Thrombotic stroke Encephalopathy	Unknown
Cyclosporine	Leukoencephalopathy	Unknown
Cisplatin	Ototoxicity Peripheral neuropathy	Sensorineural hearing loss
Vincristine	Peripheral neuropathy Autonomic/cranial Neuropathy	Peripheral neuropathy
Angiogenesis inhibitors	Hypertension	Unknown
	Stroke/bleeding	

* This table is not intended to be comprehensive. Novel targeted agents more recently introduced into practice have not been included. CNS = central nervous system; PRES = posterior reversible encephalopathy syndrome.

of long-term survival, the benefits of aggressive resection must be weighed against risks of disability.

The cerebellum, the most common site of pediatric CNS tumors, is important for cortical development and high-level cognition (121,122). The tumor and its resection disrupt neural circuits connecting prefrontal, superior temporal, posterior parietal, and limbic regions (123). Comparison of preoperative and postoperative neuropsychological function demonstrates that deficits correlate with brainstem infiltration and involvement of the dentate nucleus and are often present preoperatively (48,124). Children with cerebellar low-grade gliomas treated with surgery alone are at increased risk for cognitive, affective, and adaptive deficits (65,125–131). Twenty percent are at risk of postoperative cerebellar mutism syndrome characterized by early onset of mutism, ataxia, hypotonia, and emotional lability. The symptoms of this syndrome diminish with time, but are associated with lasting effects on cognitive dysfunction (126–131). Childhood survivors of infratentorial tumors experience more difficulty than those with supratentorial tumors, attributable to ongoing motor dysfunction and impairment of executive function (128,132,133).

Pre- and postoperative tumor assessment with MRI, use of dissecting microscope, robotic technology, third ventriculostomy, and greater referral to pediatric neurosurgical oncology specialist are improving the therapeutic margin of surgery for pediatric brain tumors (134–136).

Prevention of Cancer-Related Cognitive Dysfunction by Cancer Treatment Modification

With evidence that use of CrRT in ALL was causally related to decline in FSIQ, the dose of prophylactic CrRT was systematically reduced from 2400 cGy in all children with leukemia in the 1980s to abandonment of CrRT for the majority of children in the current era (62,63). While FSIQ for ALL survivors is now within the average range, mean FSIQ is often lower than predicted or lower than those of controls (74,113,115). Review of long-term outcomes demonstrate that some combination of attention, executive function, verbal working memory, processing speed, and fine motor skills are below those of control groups. While replacement of CrRT (with systemic and intrathecal methotrexate) in contemporary therapy has reduced the severity of cognitive dysfunction, the prevalence of attention deficits remains high as 67% (117); 3% to 28% of survivors experience deficits in other domains. Prevalence is consistently higher in those receiving therapy for high risk ALL (82,117,137,138).

In childhood brain tumors, the majority of reports derive from survivors of low-grade gliomas (LGG) or medulloblastoma, the most frequently observed tumors with high survival rates. Among children with CNS tumors, recent meta-analysis reveals severe cognitive dysfunction compared to norms with substantial effect

size of -0.83 for FSIQ, -0.93 to -1.22 for core functional domains and -0.45 to 0.63 for academic domains (139). Strategies to reduce cognitive dysfunction in LGGs have included: 1) use of chemotherapy to prevent or postpone the need for cranial irradiation in young children; 2) reducing the field of CrRT with conformal radiation or proton beam radiation therapy; or 3) expectant observation of clinically asymptomatic tumors, especially in children with neurofibromatosis type 1. Sequential assessments of LGG show baseline FSIQ at the low end of average and unchanged six years later (140,141). Age at diagnosis remains the principal predictor of FSIQ (79 in those under the age of five; 96 in older patients). Even when mean FSIQ is normal, twice the number of survivors score one standard deviation below the mean than expected (120). Prospective assessment in children with pilocytic astrocytoma treated with modern therapy reveals that the majority experience progressive deficits in sustained attention and processing speed over time; the most striking deficits occur in children under the age of three and those treated with CrRT (65). While conformal radiation therapy for LGG promises less neurocognitive and neuroendocrine injury (83), its role in younger patients remains to be determined.

Cerebellar medulloblastoma comprises 20% of pediatric CNS tumors. Following curative craniospinal radiation therapy, FSIQ is less than 90 in 90% of survivors (4,5,142–148). The impact of dose reduction of whole brain CrRT from 3600 to 2340 cGy to 1800 cGy remains to be determined. A single-arm study of 2340 cGy shows declines in FSIQ (4.2 points per year) similar to historical controls, with steep declines in children under the age of seven (70). A small study shows preservation of FSIQ one to three years after 1800 cGy (149). Risk stratification, assigning a lower dose to younger children, has not necessarily decreased cognitive dysfunction as the effects of young age at the time of treatment confound assessment of lower-dose CrRT (150). Neither intensity modulation CrRT to the tumor bed (151) nor hyperfractionation of dose has reduced the risk of future cognitive decline (142).

Eliminating CrRT or limiting the field to the tumor bed in infantile tumors of all histologic subtypes is the most encouraging alteration (152,153). Objective assessment at four years shows average cognition similar to those in the HeadStart initiative (154). However, survivors of neonatal tumors continue to fare poorly, with over half having IQ under 70 (155).

Remediation of Established Cognitive Dysfunction

Broad strategies to remediate cognitive dysfunction include both education interventions and pharmacologic treatment. Education interventions encompass school remediation programs, cognitive behavior therapy, training in social skills or specific subjects, and use of computerized cognitive training (Table 2). Historically, pharmacological approaches consisted mostly of classical stimulants, such as methylphenidate, but are evolving to include other classes of drugs (Table 3).

Educational Interventions

Provider and parent advocacy is essential to access educational resources such as individualized educational plans (IEP), or

classroom and testing accommodations (504 plan) as part of school reintegration. The monograph “Learning and Living with Cancer” (156) educates parents about their options and informs parents and educators about anticipated deficits and need for structured reintegration during and after therapy. The Children’s Oncology Group (COG) and the Task Force on Neurocognitive/Behavioral Complications maintain a comprehensive list of resources for parents, teachers, and school counselors (10,157–159).

School reintegration programs are ubiquitous in North America because legislation mandates educational and special services to minimize gaps in instruction and promote positive academic progress during school absenteeism (53,128,133,134,158,160). However, reintegration programs in the US vary widely in scope and resources as they are administered by the states. Hospital-based programs have largely replaced workshops for peers and educators (160). A pilot study using structured interviews of parents and teachers to compare home-bound, hospital-based, and community-based reintegration concluded that adolescents minimally engaged in school before their cancer diagnosis did best in hospital-based programs and least well in home-based programs. In contrast, high-achieving adolescents engaged in school activities prior to diagnosis did well in all three settings (161).

The proposed standard is staged programs organized by a counselor-liaison to advocate for and interpret neuropsychological evaluations, and to coordinate resources in the community, home and hospital (14,162). Advocacy for vocational rehabilitation and school tracking in courses of study appropriate to a survivor’s cognitive capacity can also facilitate success for adolescents and young adults left with varying levels of cognitive impairment. While studies of school reintegration are needed, they are limited by challenges engaging patients and families even when optimal resources are provided (133).

In addition to attention to academics, neuropsychologists frequently emphasize the importance of training in social skills, especially among children with CNS tumors (37,50,163–166). Four trials on social skill training (Table 2) demonstrate benefit in this survivor population (37,164,166,167).

In a randomized comparison of standard school reintegration vs reintegration plus social skills training in children with non-CNS malignancies, patients in the intervention group perceived higher classmate and teacher social support. Parents reported reduced behavioral problems and improved competence (164). Subsequent follow-up interventions demonstrated improvement of social skills and function with small to medium effect sizes (166,167). In a study where brain tumor survivors received instruction on building self-confidence, making friends, cooperation, managing teasing and bullying, conflict resolution, empathy, and assertion, parents reported benefits (37). Preintervention, parents rated social skills and quality of life lower, while survivors rated themselves as normal. Postintervention, parents reported improvements in self-control and quality of life, although performance had not changed on objective tests. Explanations for the discordance include instrument limitations and that parents’ hopes for improvement are reflected in their evaluation of outcomes (37,166,168).

Cognitive remediation therapy is a structured intervention that uses metacognitive training in problem solving and managing complex tasks through individualized self-monitoring of effectiveness

Table 2. Non-pharmacologic interventions following cancer therapy in childhood survivors

Intervention	Patient population*	Study design and duration of intervention	Measures	Response	Reference
Cognitive remediation program	Cancer survivors Age range: 6–22 y (N = 31)	Pilot: single center Intervention vs control	Primary: CPT, Digit Span Secondary: WRAT sentence memory and arithmetic	Improved CPT scores	(26)
Cognitive remediation program	Brain tumors, ALL, bone marrow transplant/ total body irradiation, or non-Hodgkin's lymphoma ≥ 1 y off therapy Age range: 6–17 y (N = 20)	Multicenter randomized clinical trial Intervention vs control Two-hour cognitive remediation sessions—over 4–5 mo 4–5 mo therapy	Primary: academic achievement; focused attention; working memory; memory recall; vigilance Secondary: parent/teacher report on attention; participant self-report	Improved academics: 0.53; Improved attention by parent Conners' ratio, but not by teachers; no change in attention, memory, recall or vigilance	(178)
Cognitive remediation program	Brain tumors, ALL ≥ 6 mo off therapy Age range: 7–19 y (N = 12)	Pilot-Single Center Open 15-session, clinic-based training program over 3–6 mo	Primary: Digit span; CPT; CVLT-C; WRAT3/WJR; CBCL; SSRS	WJR writing sample and SSRS improved; low participation rate	(179)
School-based math intervention	Children on maintenance phase of treatment for ALL Mean age: 6.7 y (intervention); 6.5 y (standard care) (N = 57 enrolled; 32 completed)	Two Institutions Intervention vs control 40–50 h direct instruction on math concepts	Primary: FSIQ, processing speed working memory; visual-motor integration; fine motor speed and dexterity; academic achievement	Improved targeted math skills and visual working memory in intervention group vs decline in the comparison group	(181,251)
Compensatory memory device	Brain tumors Age range: adolescent (N = 1)	Memory notebook with log and calendar, orientation + training	Primary: WRAT, memory	Improved academic achievement; Persistent memory deficits	(252)
Computerized training / Captain's Log †	Brain tumors; ALL > 1 y off therapy Age range: 10–17 y (N = 9)	Pilot- Single Institution: Open 50 min a week for 3 mo	Primary: WISC-WMI; CPRS	Improved working memory on Digit-Span forward; improved inattention	(132)
Cogmed RM	Brain tumors; ALL > 1 y off therapy Age: 8–16 y (N = 20)	Pilot: single institution Intervention (CogmedRM) vs control group (non-adaptive program) 25 training sessions on home-based computerized cognitive training program: 3 months	Primary: CPRS, WRAML2	Improved visual working memory; decreased learning problems by CPRS	(182)
Group skills therapy	Brain tumors Age range: 8–18 y (N = 32)	Single institution: Open Eight, 2-h weekly group sessions targeting specific skills	Primary: SSRS, PedsQLCancer; CBCL; CDI	Improved self-control, social skills, quality of life at 6 months	(37)
Group skills therapy	Male brain tumor survivors not on active treatment Age range: 10–14 y (N = 8)	Sixteen, 1 h group sessions focused on development of social skills Single institution: Open Child and parent intervention	Primary: Child and parent survey on social skills	Improved social skills	(167)
Social skills intervention	Brain tumors ≥ 6 mo off therapy Age range: 8–14 y (N = 13)	Single institution: Open Three sessions with group social skill training Child and parent intervention	Primary: SSRS, CBCL, Miami Peds quality of life, IQ Secondary: Program evaluation	Small/medium effect sizes on social competence, total competence and problem behaviors	(166)
Social skills	Pediatric cancer - newly diagnosed Age range: 5–13 y (N = 64)	Two institutions Intervention vs control Several specific 60-min social skills training vs Standard school reintegration services	Primary: CDI, CBCL, SSSC	Higher perceived class-mate and teacher social support, decreased internalizing/externalizing behaviors	(164)
Psychological intervention	Newly diagnosed leukemia/lymphoma, solid tumors, or brain tumors Median age: 5 y (N = 19)	Pilot Intervention vs control Pre- and 2-mo postintervention	Primary: anxiety, post-traumatic stress disorder	Reduced anxiety and parental post-traumatic stress disorder symptoms	(253)

* In many studies, more patients than reported here were screened for eligibility; however, for consistency, we report on only those patients included in the final analysis.
 ADD = attention deficit disorder; ALL = acute lymphoblastic leukemia; CDI = child development inventory; CPRS = Conners Parent Rating Scale; CPT = Conners Continuous Performance Test; CTRS = Conners Teacher Rating Scale; CVLT = California Verbal Learning Test; CVLTC = California Verbal Learning Test, Children's Version; DKEF = Delli-Kaplan Executive Function Test; FSIQ = full-scale intelligence quotient; IQ = intelligence quotient; SSRS = Social Skills Rating System; WRAT = Wide Range Achievement Test.

† Captain's Log (<http://www.braintrain.com>); SSSC = Social Support Scale for Children; WRAML2 = Wide Range Assessment of memory and learning 2nd edition; WISC-WMI = Working memory Index.

Table 3. Pharmacologic interventions following cancer therapy in childhood survivors

Pharmacologic intervention	Patient population*	Study design and		Response	Reference
		duration of intervention	Measures		
Methylphenidate	Children with brain tumors or ALL (N = 12) Age not reported	Open label 6 mo to 6 y (median 23 mo)	Primary: attention; concentration; memory; handwriting; organizational ability; behavior; hyperactivity	75% “good response” 10% “fair response” 10% “poor response”	(254)†
Methylphenidate 0.6mg/kg, 20mg max	Brain tumors (N = 25) or ALL (N = 7) ≥ 24 mo off therapy Age range: 6 mo to 17.5 y	RDBPC 90 min	Primary: attention - CPT Secondary: CVLT, VAL	Improved score on CPT (errors of omission and overall index)	(186)†
Methylphenidate 0.3 or 0.6mg/kg (both doses divided daily)	Brain tumors (N = 51) or ALL (N = 55) ≥ 12 months off therapy Age range: 7–8 years	RDBPC crossover 3 wk	Primary: attention – CPRS, CTRS Secondary: SSRS	Improved attention and concentration; No advantage to higher dose; Response better in subset with preexisting issues	(255)† (256)†
Methylphenidate 0.6mg/kg, 20mg max	Brain tumors (N = 61) or ALL (N = 61) ≥ 12 mo off therapy Age range: 6–18 y	RDBPC crossover 2 d	Primary: CPT, Stroop Secondary: CVLT, VAL, WRAT	Improved Stroop performance	(1)†
Methylphenidate 0.3mg/kg divided daily dose	Brain tumors (N = 6) ≥3 y off therapy Age range: 8–20 y	RDBPC crossover 2 wk with a 2 wk washout in between arms	Primary: RAVL, Trail A, Trail B, CPT	No effect on attention and/or memory	(257)†
Donepezil	Brain tumors (N = 11) ≥ 12 mo off therapy Age range: 9–17 y	Single center, open label 24 wk	Primary: DKEFs, quality of life	Improved executive function	(211)
Growth hormone	Young adult survivors of childhood leukemia with reduced bone mineral density and/or insulin-like growth factor-1 (N = 20) Age range: 20–29 y	Single center Pre- and 1- and 2- y postintervention	Primary: FSIQ, attention, Trail A, Trail B, Digit Span	Improved sustained attention and visual-spatial memory; Worsened verbal memory	(214)

* In many studies, more patients than reported here were screened for eligibility; however, for consistency, we report only those included in the final analysis. ADD = attention deficit disorder; ALL = acute lymphoblastic leukemia; CPRS = Conners Parent Rating Scale; CPT = Conners Continuous Performance Test; CTRS = Conners Teacher Rating Scale; CVLT = California Verbal Learning Test; DKEF = Dellis-Kaplan Executive Function Test; FSIQ = full-scale intelligence quotient; IQ = intelligence quotient; RAVL = Ray Auditory Verbal Learning Test; RDBPC = randomized, double-blind, placebo-controlled study; SSRS = Social Skills Rating System; VAL = Visual Auditory Learning Test (subtest from the Woodcock-Johnson battery); WRAT = Wide Range Achievement Test.

† References 1, 186–190 all describe the results of the primary trial of methylphenidate in childhood cancer at differing time points and for different trial outcomes.

followed by self-correction. Evidence supports the beneficial effects in children after traumatic brain injury or stroke (169–171). Because effects of the overlap in age and the spectrum of progressive disabilities in traumatic brain injury with those observed in cancer-associated cognitive dysfunction, cognitive remediation therapy was investigated in childhood survivors (172–177). A feasibility trial in survivors and caregivers showed statistically significant improvement in focused attention but not in arithmetic computation (26). A follow-up, multicenter randomized trial demonstrated a statistically significant improvement in academic achievement in the cognitive remediation therapy group following a five-month intervention, compared with controls randomized to a wait list (178). Results are tempered by an equivalent improvement in neurocognitive functioning in the control arm, attributed to practice effect. Objective performance scores showed gains pre-intervention to postintervention in all areas, with improvement in

social skills and writing. Parents and patients perceived benefits of the intervention. Cognitive remediation therapy demanded substantial time commitment for therapists, parents, and patients, a limiting factor in studies where only 30% of eligible patients participated and only 60% of participants in the intervention arm completed the entire regimen (179). Importantly, cognitive remediation is variably covered by insurance; hence out of pocket cost limits access.

A feasibility study enrolled three survivors of medulloblastoma to participate in a condensed version of the Swedish Memory and Attention Re-Training (SMART) program, which teaches cognitive skills for the survivors and coaches both parents on stress management (180). Aspects of attention and memory performance improved from pre- to post-training assessment; survivors reported enhancement of social relations and self-image. After training, the stress level of mothers was lower and that of fathers remained low.

To test the hypothesis that mathematics training improves executive function, children with ALL were randomized to intensive individualized training in solving math problems or standard care while on treatment. While the standard care group had higher scores in applied mathematics at baseline, the intervention group improved such that it performed statistically significantly better in applied mathematics and visual memory at the end of intervention and at six-month follow-up. The standard care group did not improve in any area, and declined in seven of 11 domains, illustrating the natural history of cognitive decline. This study shows that early intervention is feasible, beneficial, and durable (181).

A trial of computerized brain training enrolled nine survivors with cognitive dysfunction in a home-based program designed to improve memory, attention, concentration, listening skills, and self-control in people aged six years and older (<http://www.brain-train.com>) (132). Following the intervention, participants exhibited statistically significant increases in working memory, and parents reported reduced problems in attention. Improvements persisted three months later (132,182). A randomized trial of a home-based computerized training program is currently in evaluation as a feasibility study in childhood brain tumor patients following CrRT (NCT01503086).

Pharmacologic Interventions

Current evidence focuses on deficits in attention as a modifiable domain in cognitive dysfunction (183). While some aspects of cognitive dysfunction resemble those of children with attention-deficit disorder (ADD), many survivors lack the typical profile for inattention and/or hyperactivity. The piperidine derivative methylphenidate, a mixed dopaminergic-noradrenergic agonist, enhances function of the fronto-striatal attentional network and is the most studied medication in pediatric ADD.

Because it demonstrates strong dose-response relationships on measures of vigilance, sustained attention, and reaction time in ADD (184,185), methylphenidate and other stimulant medications have been investigated in several studies of childhood cancer survivors with cognitive dysfunction (Table 3). While a single dose of methylphenidate improved attention 90 minutes later (186), a three-week cross-over trial demonstrated improved teacher and parent report of attention with no differences in a 0.3 and 0.6 mg/kg dose (187). Male gender, older age at treatment, and higher intellectual functioning at baseline predicted better outcomes. Despite statistically significant improvement in sustained attention, social skills and internalizing and externalizing psychopathology, methylphenidate had no impact on academic productivity (187). An open label trial for patients who demonstrated initial response showed sustained responses among participants after 12 months of continuation therapy, compared with those of nonparticipants (60). Parental, teacher, and patient assessments were aligned in the treatment group, but not in the control group, where parents reported improvement, and teachers and patients did not (60). Based on these studies, the authors conclude that methylphenidate should be the standard of care for children with cognitive dysfunction who show measurable improvement after short-term methylphenidate. Limitations of methylphenidate studies include cohorts that mix brain tumor and ALL survivors and short half-life of the drug. Importantly, a 5% rate of dose-limiting side effects was noted with

poorer tolerance in survivors of brain tumors compared to those with leukemia (3,186–189). A COG randomized trial comparing the long-acting methylphenidate with extended-release amoxetine (ACCL0422A) was closed prematurely because of poor accrual, attributable in part to the appearance of black box warnings around the use of methylphenidate.

Modafinil, a dopaminergic central nervous system stimulant, is an alternative to methylphenidate in ADD. Although not Food and Drug Administration (FDA)-approved in children under the age of 16, it is used off-label to treat narcolepsy, excessive daytime sleepiness, and ADD (190–198). Modafinil improves digit span, visual memory and spatial planning capacity among adult volunteers with cancer, with enhanced benefit among those with lower cognitive capacity at baseline (199–201). A randomized clinical trial using modafinil in breast cancer survivors resulted in improved attention and speed of memory; modafinil improved cognition, mood and fatigue in adults with CNS tumors (201). A randomized trial comparing methylphenidate and modafinil in 24 adult survivors of CNS tumors showed benefits of both drugs, with a trend for improved attention with methylphenidate and improved processing speed with modafinil. However, this trial closed after five years for failure to accrue the necessary 75 patients (202). COG is currently evaluating modafinil in a randomized trial among survivors of pediatric CNS tumors (NCT01381718).

Donepezil is an acetylcholinesterase inhibitor with beneficial effects on cognitive, behavioral, and functional symptoms in Alzheimer's and vascular dementias (203). While donepezil is FDA-approved for Alzheimer's disease, there are off-label indications for its use in cognitive impairment associated with multiple sclerosis, Parkinson's disease, multi-infarct dementia, and traumatic brain injury. Donepezil has also been beneficial in improving global function and expressive language in adults with Down syndrome (204,205) and demonstrated promising initial results in children with Down syndrome (206) or autism spectrum disorders (207,208). In a phase II, 24-week, open-label trial of 34 adults with primary brain tumors, donepezil (10 mg/day) resulted in improved attention, concentration, language function, verbal and figure memory, and mood (209,210). These results formed the basis of an ongoing phase III trial in survivors of adult brain tumors (NCT00369785) and a feasibility trial in childhood brain tumor survivors (NCT00452868). Pilot data in the latter trial indicate good tolerance of the drug, with efficacy in improving executive function and memory over a six-month, open-label trial (211).

Recombinant human growth hormone (GH) may also have benefits on cognitive function. GH deficiency is sometimes associated with abnormal white matter anisotropy on functional MRI (212) and impaired neural stem cell and myelin generation in rodent models (213). Children with ALL treated with or without CrRT are at risk of GH deficiency (214). Although a meta-analysis found insufficient evidence for beneficial cognitive effects of GH (215), recent observational (216,217) and randomized (218,219) trials report improved cognition in pediatric and adult patients with GH deficiency, adults following traumatic brain injury, and adults with mild cognitive dysfunction with or without GH deficiency. Thirteen young adult survivors of ALL who had either GH deficiency or diminished bone mineral density were treated with two

years of GH. Assessment pretreatment and at 12 and 24 months post-treatment showed normal cognition; sustained attention and cognitive-perceptual performance improved progressively at months 12 and 24, while verbal memory declined at 12 months and returned to baseline range by 24 months (214). GH warrants further investigation in randomized clinical trials in children and adults with cancer-associated cognitive dysfunction.

Future Directions

As the childhood cancer survivor population increases, future studies will require: 1) continued refinement of CNS-directed therapies; 2) early intervention with both psychoeducational tools and novel pharmacotherapies; 3) novel pharmacologic and nonpharmacologic neuroprotective strategies during cancer therapy; 4) and resources to assess and individualize neuropsychologic intervention in the highest-risk patients. A common theme across all these is the need for consensus on less burdensome screening assessments for uniformity in practice and in clinical trials.

Assessment of Cognitive Dysfunction

Variable assessment batteries and the high burden of neurocognitive assessment (in terms of time and cost) have been barriers to evaluation of cognitive impact during and following cancer therapeutic trials in children. Although a small number of treatment centers have carried out prospective, longitudinal assessment on the children enrolled on their clinical trials (83,220). COG and other cooperative groups faced challenges in obtaining sequential assessments in multi-institutional randomized phase III trials, even when reduction in cognitive dysfunction is a secondary study aim. Practice effects of sequential testing confound studies and can be addressed by limiting intervals between tests to every six to 12 months or longer (221). Impediments to assessment in trials include cost of testing instruments, limited availability of trained neuropsychologists/psychometricians at each cooperative group participating center, and limited resources for reimbursement of neuropsychologist time. High participant attrition in trials is also a barrier. Traditional neuropsychological batteries take four to seven hours and parents, patients, and treating physicians have competing priorities. Recognizing that brevity and convenience are critical to feasibility, the COG assessment battery, ALTE07C1 (NCT00772200), applied a limited number of age-standardized measurements and is administered by psychologists in less than two hours. Use of the ALTE07C1 battery has resulted in improved compliance with neurocognitive assessments in trials for medulloblastoma, compared with the full neurocognitive battery previously recommended by COG (222). The DIGIVERT panel is also validated for screening survivors for cognitive dysfunction (223). Some screens can be administered by trained research associates rather than psychologists. The Peabody Picture Vocabulary Test can serve as a screen for FSIQ (224). The Trackwell 20-minute screen is a cognitive screening tool suitable for administration within weeks to a few months from diagnosis (225). Computerized assessments with web-based reporting of results offer inexpensive, rapid, high-throughput sequential testing of core domains (226–229). The National Institutes of Health (NIH) toolbox, still in the validation stage, contains standardized measures of neurological and

behavioral function with normative values across the lifespan and has been developed to facilitate research (230).

Patient self-report, parent-, and teacher-reported outcomes may have higher acceptance and greater clinical relevance than objective testing, especially for behavioral and social skills. Instruments developed by the NIH Patient Reported Outcomes Measurement Information System (PROMIS) initiative have sound psychometric properties for functional assessment to comparing children with cancer to population norms (231–233). Nonetheless, the sensitivity and specificity of parent- and patient-reported behavioral and neuropsychological function in the pediatric cancer population remain unclear. Overall, investigators report the most deficits, patients report the fewest, and parents tend to report improvement regardless of intervention (37,165,166,234).

While abbreviated assessments facilitate research and can trigger the need for further investigation, none suffices to trigger an individual educational plan in the school systems or replaces a comprehensive assessment. In the practice setting, compliance with neuropsychological recommendations for rehabilitation following assessment is less than 50% (235). COG recommends survivors at risk of cognitive dysfunction undergo full neuropsychological assessment one year after treatment and again at three to five years, or at a point of clinical decline (10,157). Assessment batteries can typically measure FSIQ, academic ability, core functional neurocognitive domains, psychomotor skills, language, behavior and mood. No standard assessment battery is endorsed by the childhood cancer community to date. Insurance coverage of neuropsychological testing is not uniform and educational systems vary in their ability to provide timely testing. Abbreviated computerized testing is attractive, yet its translation into academic, behavioral and functional outcome is unknown. Hence, comparison of computerized assessment with traditional neurocognitive measures remains important. Standardizing the assessments and increasing feasibility of testing and adherence to recommendations is a high priority moving forward in practice and in trials (236).

Early Intervention

Understanding of neural networks and brain plasticity in traumatic brain injury suggest that early intervention (before deficits are crystalized) achieves improved results (237). Figure 2 suggests a conceptual framework for future interventions with nonpharmacologic and pharmacologic neuroprotective approaches to minimize cognitive dysfunction. The trial of mathematical intervention in ALL patients demonstrates that declines may be partially aborted by preemptive intensive educational approaches (181). Results of trials using home-based computerized brain training programs (NCT01503086) may clarify and support the role of such approaches early in therapy.

Development of reliable blood or imaging biomarkers (238–240) of radiation-associated changes in neurotransmitters and receptors that drive synapse formation or function could facilitate both early identification of neurotoxicity and subsequent monitoring. Potential biomarkers of impending cognitive dysfunction include sequential shifts in inflammatory markers or neurotransmitters, such as phospholipid oxidation profile (241,242), or increased levels of reactive oxidant stress indicators in samples of cerebrospinal fluid (243,244). If confirmed, these biomarkers may also help

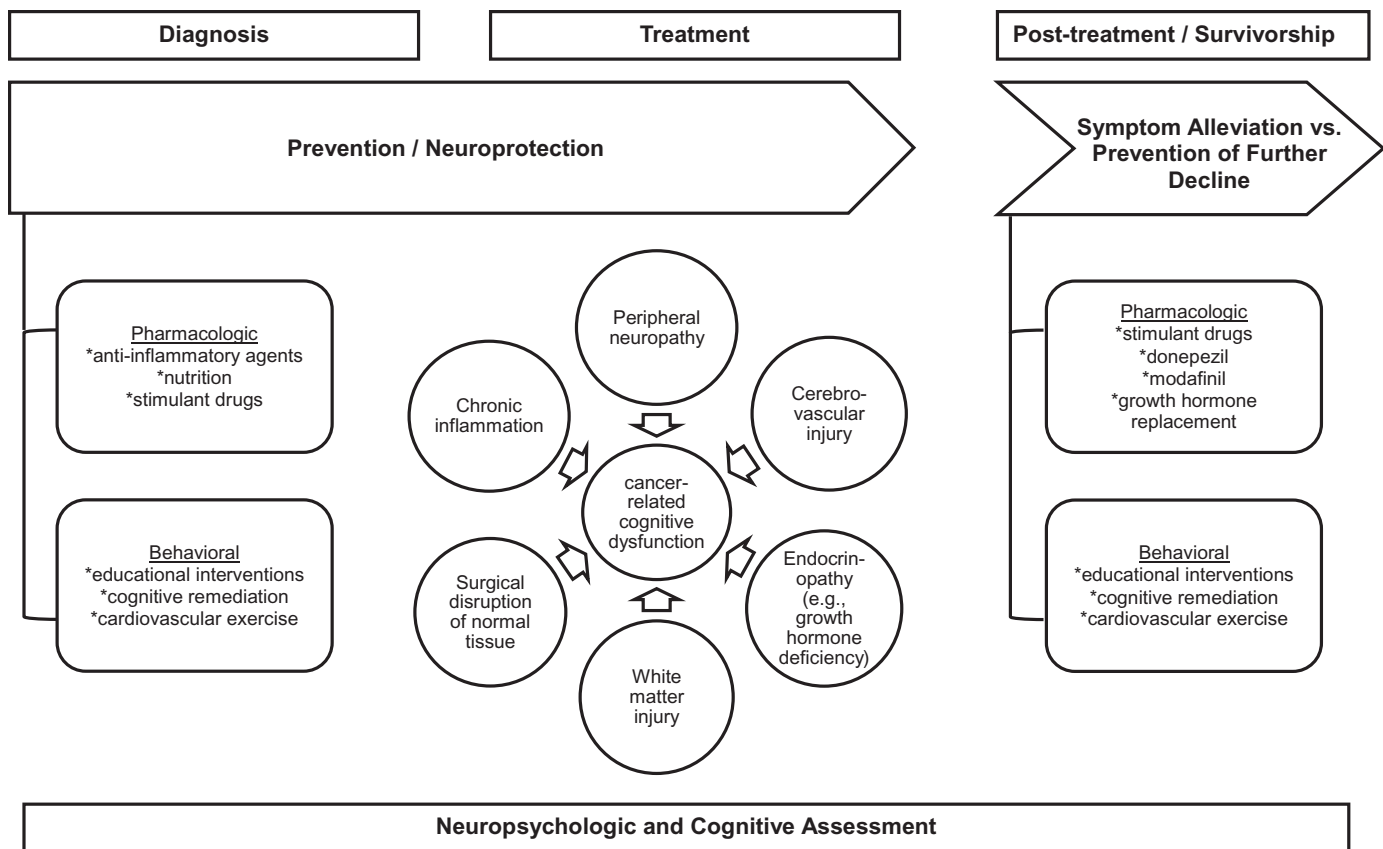


Figure 2. Conceptual approach to design of future interventions for protection and remediation against cancer-related cognitive dysfunction.

to identify patients for early pharmacologic trials of agents that approach the inflammation pathway (245).

New Approaches to Intervention

Completing and confirming studies using modafinil, donepezil, or stimulants other than methylphenidate in children should be high priority. Combining strategies may be more successful, such as the use of computerized training and methylphenidate or computerized training and cognitive remediation therapy in adult survivors of brain tumors (246,247). Cardiovascular exercise or yoga as interventions may also be important in children as in adults (248). Recent evidence of white matter changes in cognitive impairment in Hodgkin Lymphoma survivors treated with cardiotoxic therapy raises the role of cardiovascular health in maintenance of cognitive function (249).

Future interventions need to consider the inflammatory response to CrRT and evaluate anti-inflammatory agents to attenuate loss of neuronal precursor cells, impact on neurogenesis and microenvironmental changes. Strategies to attenuate reactive oxygen species and quench radiation-induced microglial inflammatory injury may provide neuroprotection prior to or during cancer treatment (245). Ultimately, elucidation of the underlying pathophysiology and refinement and streamlining of assessment tools are still required to best utilize imaging or biomarkers of subclinical injury before manifestation of cognitive dysfunction by report or neurocognitive assessment three to five years after the insult.

The design of future interventional trials needs to be robust with standardized goals and clear statistical definition of endpoints,

effect size, and accounting for practice effects of repeated testing and washout periods in cross-over studies (1). Strategies to increase compliance and participation are integral to the success of interventions beyond the cure of the tumor and are a challenge common to many areas of cancer survivorship because of study fatigue and time burden. Cooperative groups need to standardize assessment procedures for measurement of impact on cognition across disease groups.

While early intervention is a goal, even simple interventions may not be embraced by children, parents, or physicians. This is evidenced by the suboptimal feasibility of reintegration programs (133), failure of parent follow-up on recommendations for neuropsychological rehabilitation (235), and suboptimal accrual on many pharmacological-based intervention trials. This can only be addressed by education of patients and families and development of compelling clinical trials. Discussing risks of cognitive dysfunction and potential importance of early detection and early intervention should be an integral element of discussion at cancer diagnosis with parents, patients, and providers. Studies that queried parents who do not choose to participate in or drop out of studies find that most parents were too overwhelmed to take on any new responsibilities (37,133,166,250); mothers seem to be especially burdened and especially important in the decision making. Interventions that require additional time in or out of the home and/or in/out of school is a priori an increased burden to families. The whole process needs to be rendered more feasible for everyone involved.

Considerable effort has been expended to make trials in cognitive dysfunction more homogeneous, in order to validate efficacy of

a single intervention in a defined population. Exclusion criteria at times limit generalizability and negatively impact accrual. Another strategy for consideration is partnership with other pediatric subspecialties. It could increase accrual and generate more robust studies for medically complex children, in whom progressive cognitive dysfunction complicates survivorship. Radiation injury and folate inhibition are unique to cancer treatment; however, the processes underlying neuronal injury and repair in the developing brain may share features with other brain injury populations, including traumatic brain injury and sickle cell disease.

Conclusions

Ongoing cancer therapy trials aim to reduce neurotoxicity of treatment by modifying CrRT or chemotherapy or by using molecular risk stratification to target less toxic therapy for select patients (82). While large strides have been made, cognitive disabilities will persist in children with primary brain tumors, as CrRT remains a cornerstone of therapy. Therefore, the future lies in pharmacologic or non-pharmacologic interventional trials at earlier time points, in order to prevent or remediate cognitive declines associated with treatment. The overall goal remains improved HRQOL for cancer survivors with cognitive dysfunction and for their families.

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