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Cognitive Impairment in Survivors of Adolescent and Early Young Adult Onset Non-CNS Cancers: Does Chemotherapy Play a Role?

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Introduction: The development of complex cognitive functions including executive functions occurs during adolescence and early young adulthood. Survivors of cancers diagnosed during adolescence and young adulthood (AYA) may be at specific risk for chemotherapy-associated cognitive impairment; however, little data are available that specifically examine long-term cognitive outcomes in the AYA-onset cancer survivor population.

Methods: A literature search was conducted between January 1991 to December 2015 using a variety of search terms pertaining to the AYA-onset cancer population and cognitive outcomes. Articles that described cognitive outcomes in AYA-onset cancer survivors without primary or secondary central nervous system lesions diagnosed at ages 14–25 years old were examined and reported.

Results: Three articles fulfilled the inclusion criteria. All three evaluated cognitive outcomes in AYA-onset cancer survivors at varying time points after receipt of systemic chemotherapy. Target groups and neuropsychological evaluation techniques differ across studies. All studies reported increased rates of objective or self-reported cognitive impairment in AYA-onset cancer survivors.

Discussion: AYA-onset cancer survivors experience cognitive impairment. Despite the nature of normal adolescent neurodevelopment, chemotherapy exposure during the AYA years may not significantly contribute to cognitive impairment. Chronic cognitive impairment may be associated with chronic complications of cancer therapy. Large-scale standardized, prospective, and longitudinal evaluations of cognitive outcomes specific to AYA-onset cancer survivor population are needed to better understand associated risk factors.

Keywords: chemotherapy, cognitive dysfunction, health-related quality of life, late effects, survivorship

Introduction

THE ADOLESCENT AND YOUNG ADULT (AYA) cancer community encompasses a heterogeneous group of cancer survivors of ages 15–39 years.¹ Current estimates in the United States indicate that the 5-year survival for all malignant cancer types diagnosed in the AYA years is 80%–90%.¹ This growing group of survivors is at risk for significant treatment-related morbidity. Acute and chronic chemotherapy-associated cognitive impairment (CACI) is a well-described consequence of cancer treatment, affecting an estimated 15%–50% of childhood leukemia survivors; however, the impact of chemotherapy on cognition for those with other cancer types and when diagnosed during the AYA years remains poorly understood.^{2,3}

The cognitive abnormalities described in cancer survivors typically include impairments of memory, attention, processing

speed, and executive function.^{4–7} As mentioned, data regarding neurocognitive impairment in aging survivors of childhood leukemia exposed to systemic chemotherapy are established; however, these data describe survivors exposed at an average age of 4–8 years without particular focus on those receiving chemotherapy during the AYA years.^{2,8–12} In 2015, Iyer *et al.* published a meta-analysis that supports the notion of CACI in survivors of childhood leukemia.^{8,9,12} The analysis includes 10 studies reporting on a total of 509 survivors and 555 controls with a median age at diagnosis of 4 years and time since diagnosis of 8 years. They note moderate long-term neurocognitive impairment in survivors treated with chemotherapy only. Intelligence was most negatively affected; however, working memory, information processing speed, and fine motor function were also moderately impaired.⁸ Systemic and intrathecal chemotherapy such as methotrexate

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as well as corticosteroid exposure have been implicated in previous studies.^{9–14}

AYA-onset cancer survivors of noncentral nervous system (CNS) cancers may be at particular risk for cognitive impairment given the nature of normal cognitive development during adolescence. Furthermore, negative cognitive outcomes may contribute to diminished long-term vocational and social success. Adolescent brain reorganization begins during puberty and slows by age 25 years.¹⁵ This reorganization primarily involves maturation of functional connectivity of white matter networks, which is especially relevant given well-established effects of chemotherapy on white matter in childhood.^{9–16} Cortical plasticity during the adolescent period supports the development of advanced cognitive functions, particularly the executive functions including attention and emotional control, inhibition, planning, and working memory.^{15,17} This period of neural plasticity makes adolescents more vulnerable to harmful environmental influences such as illicit drug exposure and may increase susceptibility to chemotherapy.¹⁵ Quality-of-life and long-term outcomes data in the AYA population indicate that AYA-onset cancer survivors experience high rates of unemployment, low education achievement, and difficulty transitioning to independent living as compared with healthy siblings.^{15,16} Furthermore, AYA-onset cancer survivors self-report diminished quality of life, attention problems, forgetfulness, and decreased education and job attainment.^{15,16} The contribution of CACI to these outcomes may be substantial.

The aim of this article is to highlight the available data regarding cognitive outcomes specific to AYA-onset survivors of non-CNS cancers who may be at particular risk for CACI. We stress a need for systematic exploration of long-term cognitive function as it relates to chemotherapy exposure, radiation exposure, and other comorbidities experienced by survivors treated during the AYA years.

Materials and Methods

Literature search was conducted using PubMed, Web of Science, and PsychInfo databases from January of 1991 through December of 2015 using the following combinations of search terms: “neurocognitive,” “cognitive,” “cognition,” “outcomes,” “adolescent,” “young adult,” “executive function,” “memory,” “chemotherapy,” and “cancer.” According to the National Cancer Institute’s Surveillance, Epidemiology and End Results, the predominant cancer types seen in the AYA population include carcinomas (thyroid, head and neck, breast, genitourinary, and gastrointestinal), sarcomas (soft tissue and osseous), melanomas, germ cell neoplasms, lymphoma, and leukemia.¹⁸ In an attempt to capture more complete data, the terms “carcinoma,” “sarcoma,” “breast,” “testicular,” “germ cell,” “leukemia,” and “lymphoma” were included in combination with the previous search terms.

A set of inclusion criteria for article selection included (1) articles written in English, (2) articles that described cognitive outcomes per validated, standardized neuropsychiatric evaluation, and/or self-report questionnaires of perceived cognitive functioning, (3) articles that focused on survivors of AYA-onset cancers without primary or secondary CNS lesions who received systemic chemotherapy, and (4) articles reporting a median age at cancer diagnosis corresponding to adolescence and early young adulthood (~14–25 years) to target peak years of brain reorganization.

Reviews, commentaries, or qualitative articles were excluded. Primary and secondary CNS cancers and CNS irradiation are known risk factors for significant cognitive complications despite exposure to chemotherapy; therefore, this review is limited to non-CNS cancer types and excludes outcomes in survivors with primary or secondary intracranial tumors.^{19–22} In addition, survivors who received craniospinal radiation were excluded from evaluation. As already mentioned, there is a growing body of literature highlighting neurocognitive outcomes in AYA survivors of childhood-onset cancer. Although this literature is briefly discussed in this article, for the purposes of the review, these studies were not included if they did not reflect or subanalyze patients with cancer diagnosed during the target years.

A single person conducted the search in three sequential steps. First, titles were screened to exclude studies that were clearly not related to the interests of the review. Next, abstracts of articles that passed the title stage were reviewed. Finally, articles were examined to ensure they fulfilled the criteria described.

Results

In total, three articles fulfilling the inclusion/exclusion criteria were identified (Table 1). Krull *et al.* first reported on long-term cognitive outcomes in a group of 62 survivors of Hodgkin lymphoma evaluated at a mean age of 42 years. Median age at cancer diagnosis was 15.1 years (range 5.9–19 years).²³ A validated, standardized neuropsychological battery focusing on intelligence, attention, memory, processing speed, and executive function was used for testing. Survivors showed significant impairment as compared with standard norms in the areas of attention, memory, speed, and executive function.²³ Specifically, significant impairment was seen in sustained attention, new learning, short- and long-term recall, fine motor dexterity, naming speed, cognitive fluency, and working memory.²³ Furthermore, neurocognitive impairment was associated with lower educational attainment and unemployment.²³

Interestingly, the authors report a correlation between poor cognitive function and poor cardiac function, pulmonary function, and CNS pathology. They hypothesize that the cardiac and pulmonary comorbidities were related to mantle field radiation received by all subjects. Specifically, they believed the radiation contributed to delayed cerebral vascular pathology and associated cognitive impairment.²³ In their analysis, chemotherapy such as bleomycin and doxorubicin were not associated with cognitive impairment; however, because of study design, all patients received mantle radiation, thereby limiting the ability to evaluate the unique effects of these chemotherapeutic agents on cognitive function.²³ Although comorbid conditions seem to contribute to delayed cognitive impairment in AYA-onset Hodgkin lymphoma survivors, the specific effects of chemotherapy on CNS pathology and cognition were not specifically explored.

Prasad *et al.* later published a more comprehensive assessment of neurocognitive outcomes in long-term survivors of AYA-onset cancers. Outcomes for cancer survivors participating in the Childhood Cancer Survivor Study (CCSS) diagnosed at age 11–21 years were assessed at roughly 30+ years of age through a validated, self-reported neurocognitive tool entitled the CCSS Neurocognitive Questionnaire

TABLE 1. STUDIES DETAILING COGNITIVE OUTCOMES IN AYA-ONSET CANCER SURVIVORS EXPOSED TO CHEMOTHERAPY

Author	Study design	Subjects (n)	Controls (n)	Age at diagnosis, years (% study population)	Age at NC evaluation, years (% study population)	Cognitive evaluation tool	Neurocognitive outcomes
Krull <i>et al.</i> ²³	Prospective, cross-sectional	62	Population norms	5.9–19, mean 15.1	34–55.4, mean 42.2	BRIEF-Adult Version, WASI, Trail Making Test Part A, CPT-II, Digit Span Forward of WAIS-III, CVLT-II, Groove Pegboard, Stroop Color Word Test, Trail Making Test Part B, Controlled oral Word Test, Digit Span Backward of WAIS-III	Hodgkin lymphoma survivors showed poor sustained attention, variability of attention and attention span. Short-term memory recall was below expectation. Fine motor speed and naming speed performance were low. Cognitive fluency was reduced. Survivors reported problems with working memory, task completion, and fatigue.
Prasad <i>et al.</i> ²⁴	Retrospective, cross-sectional	6192	390 siblings	11–14 (48.5%), 15–21 (51.5%)	25–29 (2.4%), 30–34 (21.9%), >35 (75.5%)	CCSS Neurocognitive Questionnaire (CCSS-NCQ)	Survivors 11–21 years reported impairment in task efficiency, emotional regulation, organization, and memory. Lymphoma/sarcoma survivors aged 15–20 reported high rates of cognitive problems in task efficiency (13.9%), emotional regulation (16.8%), organization (12.7%), and memory (21.6%).
Edelmann <i>et al.</i> ²⁵	Retrospective, cross-sectional	80	39 community controls, population norms	14.2	Mean 38.9	WASI, Woodcock-Johnson III Tests of Achievement, Trail Making Test Part A/B, CVLT-II, Grooved Pegboard Test, WAIS-III	Leukemia/CNS cancer survivors had worse outcomes in task efficiency and memory; however, these patients were not subanalyzed to assess outcomes with or without cranial irradiation. Survivors showed lower reading scores ($p=0.01$), more variability in sustained attention ($p=0.002$), poorer short-term memory ($p=0.01$), slower motor processing speed ($p<0.001$), and poorer cognitive fluency ($p=0.006$).

AYA, adolescence and young adulthood; BRIEF, Behavior Rating Inventory of Executive Function; CNS, central nervous system; CPT-II, Conner's Continuous Performance Test II; CVLT, California Verbal Learning Test-II; WAIS-III, Wechsler Adult Intelligence Scale-III; WASI, Wechsler Abbreviated Scale of Intelligence.

(CCSS-NCQ). Survivors were divided into those diagnosed during adolescence at ages 11–14 years ($n=1255$) or during early young adulthood ages 15–21 years ($n=1334$). Subjects were further divided into two categories: CNS cancers/leukemia survivors or sarcoma/lymphoma survivors.²⁴ Self-reported neurocognitive outcomes were compared with matched sibling controls and with outcomes of childhood-onset cancer survivors with similar diagnoses. In general, survivors aged 11–21 years collectively self-reported higher rates of cognitive impairment in task efficiency, emotional regulation, organization, and memory than sibling controls. More specific to the goals of this article, sarcoma/lymphoma survivors diagnosed at ages 15–21 years (young adults) self-reported impairment similar to those diagnosed at ages 6–10 years and to those diagnosed at ages 11–14 years in task efficiency (13.9% vs. 13.1% vs. 14.6%), organization (12.7% vs. 13.1% vs. 13.7%), and memory (21.6% vs. 20.2% vs. 23%).²⁴ In addition, steroid exposure was associated with difficulties in task efficiency and memory for both the adolescent group and young adults. Outcomes for the CNS tumor/leukemia survivors showed significant impairment similar to those diagnosed at younger ages; however, receipt of cranial irradiation for all patients in this treatment group was likely a large contributor to the similar outcomes. Finally, educational and vocational outcomes were analyzed in context with reported cognitive outcomes. Impairment with task efficiency increased risk for unemployment (odds ratio [OR] 2.93), less than college educational attainment (OR 1.31), and dependent living (OR 2.82). Memory impairment increased the risk of attaining less than college education (OR 1.42) for those diagnosed with cancer at >11 years of age.²⁴ Although the data suggest that cranial radiation therapy and corticosteroids may play a contributory role in cognitive impairment, the role of other chemotherapeutic agents was not specifically explored.

Finally, Edelman *et al.* reported on a retrospective cohort of 80 osteosarcoma survivors in the St. Jude Lifetime Cohort Study treated at a median age of 14.2 years and tested at a median age of 38.9 years.²⁵ As compared with community controls and population normative data, childhood osteosarcoma survivors did demonstrate significant impairment in attention, memory, processing speed, executive function, and academics. Cognitive impairment did not correlate with cumulative dose or pharmacokinetic indices of high-dose methotrexate.²⁵ The authors consider the addition of intrathecal therapy in leukemia treatment, the difference in age at time of exposure for leukemia patients, the extended time between treatment and testing in this study, and the influence of genetic polymorphisms as potential explanations for lack of association with high-dose methotrexate in the osteosarcoma group. Furthermore, the group hypothesizes that the potential influences of nonantimetabolite chemotherapeutic agents and chronic illness on cognition could be contributory.²⁵

Discussion

A variety of agents used systemically to treat AYA-onset cancer types (cisplatin, methotrexate, cyclophosphamide, carmustine, 5-fluorouracil, and cytarabine) have been examined in the preclinical setting and are associated with direct neurotoxicity and memory impairment.^{4,5,26} An understanding of the toxicity of these medications, when administered during the AYA years, is lacking in both the pre-clinical and

clinical setting. CNS-penetrating chemotherapy, particularly high doses of systemic and intrathecal methotrexate used in pediatric acute lymphoblastic leukemia (ALL) treatment regimens, can cause chronic leukoencephalopathy and has been implicated in CACI.^{8,9,12} ALL diagnosed in the AYA years is often treated with pediatric-inspired chemotherapeutic regimens or other intense regimens that include methotrexate and intrathecal chemotherapy.²⁷ It is reasonable to suspect that some cognitive deficits seen in childhood leukemia survivors may translate to AYA-onset leukemia survivors. Furthermore, other cancer types such as germ cell cancers and sarcomas occur at increasing rates during the AYA years, and common treatment regimens include agents such as high doses of methotrexate, but also cyclophosphamide and cisplatin.^{18,26,28} The effects of nonantimetabolite chemotherapeutic agents on the developing adolescent brain may more specifically impair executive functions because of direct neuronal toxicity during periods of significant brain white matter reorganization.

To date, only three studies exist that specifically explore cognitive outcomes in the young AYA-onset cancer population. All three studies were completed by the same research group and included data collected for the St. Jude Lifetime Cohort Study or the CCSS.^{23–25} Unfortunately, limited data and significant variability in study design including difference in timing of cognitive testing after chemotherapy, difference in type of cognitive testing used (objective vs. self-reported), different disease target groups, and differing primary study aims limit our ability to make solid conclusions regarding cognitive outcomes, especially as they relate to chemotherapy exposure.^{23–25}

Although the available literature suggests that some survivors of cancers diagnosed during young adulthood experience impairment in a variety of cognitive realms including intelligence, memory, attention, and executive functions, chemotherapy may not be an important risk factor causing cognitive impairment in this population. Instead, comorbid conditions associated with cancer and cancer therapy may be a major contributing factor.^{23–25} The pathophysiology of CACI is thought to be multifactorial, involving microvascular injury, secondary inflammation, metabolic changes, and direct damage to neurons, neuronal stem cells, and hippocampal dendrites.^{4,5,26,29,30} Many of these changes may also be attributed to chronic systemic complications of cancer therapy. Although cognitive impairments may be significant and correlate with structural changes in the brain as well as diminished academic and vocational achievement, the cause for these changes is likely multifactorial and may most strongly be associated with chronic health complications associated with extensive cancer treatment.^{23–25}

Future directions

In an attempt to solve some of the problems associated with methodological variability seen in current cognitive outcomes research, the International Cognition and Cancer Task Force published recommendations in 2011 for the standardization of research in the field.³¹ The current recommendations promote larger studies with longitudinal evaluation, multiple control types, and with thoughtful and specific study goals in mind.³¹ The International Cognition and Cancer Task Force also promotes the standardization of

cognitive testing to specific validated testing, particular for memory, processing speed, and executive function.³¹ Challenges with participation and long-term follow-up for aging survivors of AYA-onset cancers may hinder our ability to investigate the incidence and magnitude of CACI in this population; however, well-designed longitudinal clinical trials directly assessing cognitive function in relation to chemotherapy exposure and other contributors during the AYA years are necessary.³² A more standard approach to cognitive testing is imperative to build power across studies.

In addition, the integration of new investigational modalities to the science of cognitive testing is crucial in developing a more comprehensive understanding of the pathophysiology contributing to cognitive impairment across varying ages, cancer types, and exposures. Although available studies are small and investigate specific cancer survivor groups, a growing body of data seems to correlate imaging abnormalities with objectively documented neurocognitive changes in some cancer survivor populations.³³⁻⁴¹ More expansive studies exploring the correlation between functional and structural imaging abnormalities and cognitive impairment may help to better describe subtle differences in impairment seen in different groups of cancer survivor populations and pinpoint the cause for these subtle changes. Various modalities such as functional magnetic resonance imaging, positron emission tomography scanning, neurophysiologic profiling, and serum biomarkers such as brain-derived neurotrophic peptide may complement neuropsychological testing.^{42,43}

Ultimately, a more systematic approach to research and focused attention to AYA-onset cancer survivors will help in understanding the impact of cognitive impairment in this survivor group. Delineating the causes for cognitive impairment is challenging, but may allow for future development of targetable interventional strategies to improve functional outcomes in this growing survivor population.

Author Disclosure Statement

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