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Topical Review

How Cancer Harms the Developing Brain: Long-Term Outcomes in Pediatric Cancer Survivors

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Abstract

Survival rates for pediatric cancer are improving, resulting in a rising need to understand and address long-term sequelae. In this narrative review, we summarize the effects of cancer and its treatment on the developing brain, with a focus on neurocognitive function in leukemia and pediatric brain tumor survivors. We then discuss possible mechanisms of brain injury and management considerations.

Introduction

Approximately 15,000 children and adolescents are diagnosed with cancer each year in the United States.[1] With improved molecular diagnostics, targeted therapies, and better supportive care, survival rates for pediatric cancer have risen dramatically in recent decades. The five-year survival rates for pediatric cancer now exceed 80%.[2] As children with cancer live longer, there is a rising need to understand the long-term consequences of cancer and cancer treatment.

Both intrinsic and extrinsic factors determine the biobehavioral impact of cancer on brain development.[3] Intrinsic factors include the patient's neurodevelopmental stage at the time of diagnosis and treatment, the tumor site and characteristics, and genetic predisposition to treatment-related toxicity. Extrinsic factors include the patient's psychosocial milieu; specific treatment modalities employed to treat the cancer—namely, chemotherapy, immunotherapy, radiation, and surgery; and the quality of supportive care during and after treatment. Here we present two representative histories of patients experiencing long-term consequences of cancer treatment to illustrate the complex interaction between these factors.

Patient 1 is a 19-year-old female with a history high-risk B-cell acute lymphoblastic leukemia (ALL). She was diagnosed at age 10 years after presenting to her pediatrician for weight loss, fatigue, and easy bruising. She underwent treatment for high-risk disease with chemotherapy including intrathecal methotrexate. Her treatment was complicated by methotrexate leukoencephalopathy, manifesting with acute hemiparesis and altered mental status. Two years after her diagnosis, she had a central nervous system (CNS) relapse and

received 18-Gy cranial radiation and additional chemotherapy. The following year she had a second relapse and was treated with CD19-targeted chimeric antigen receptor (CAR) T-cell therapy, which was complicated by self-limited seizures. She is now three years progression-free and is off of antiseizure medications. In school, she had an individualized education plan for extra time on assignments due to impairments in attention and processing speed. Owing to frequent medical absences, she is still working on her high school diploma. She lives with her mother and carries out her activities of daily living independently but struggles with fatigue and depression. Her brain magnetic resonance imaging shows global volume loss (Fig A).

Patient 2 is an 18 year-old male with history of medulloblastoma. He was diagnosed at age six years after presenting to his pediatrician for headaches and gait instability. He underwent gross total resection of the tumor, which was clustered with the Group 3 subtype on methylation analysis. Postoperatively, he developed pediatric cerebellar mutism syndrome characterized by speech impairment and emotional lability (Fig B). He received multiagent intensive chemotherapy and 23.4-Gy craniospinal photon radiation with a boost to the posterior fossa for a cumulative dose of 54Gy. He has remained progression-free since initial treatment but has significant impairments, including sensorineural hearing loss, ataxia, multiple endocrinopathies, and neurocognitive deficits. He is in eleventh grade in separate special education classes and ambulates with a walker. He bathes and dresses himself independently, but requires help with more complex tasks like cooking due to executive function impairment.

Although each patient's experience with cancer is unique, our two patients' clinical courses represent common themes in pediatric oncology survivorship. Both were exposed to the major components of contemporary cancer treatment. Both patients remain cancer-free in adulthood but will always carry with them the sequelae of their cancer journeys. In this narrative review, we summarize the long-term effects of cancer and its treatment on the developing brain, with a focus on neurocognitive function. We then discuss putative mechanisms of brain injury and management considerations.

Section snippets

Challenges in cancer neurocognitive and developmental outcomes research

As is apparent from the two cases above, it can be difficult to disentangle the many factors affecting the neurodevelopment of pediatric patients with cancer, both when approaching the individual patient and in research settings.[4] Treatment regimens shift over time, making long-term outcome studies difficult to interpret. The effect of specific treatments must be carefully distinguished from confounding factors, such as *a priori* risk differences in cancer molecular subgroups, age at diagnosis,…

Neurocognitive outcomes in pediatric ALL

ALL survivors are a large, relatively homogeneous group with a long track record of high-quality neurocognitive and developmental outcome studies. Approximately one in 1000 people in the United States will be diagnosed with ALL at age less than 20 years, and most will be cured of their cancer.[6] The five-year survival for pediatric patients with ALL <15years old at diagnosis is over 90%. Over 80% are cured of the disease, thanks to prolonged intensive chemotherapy regimens that have been…

Neurocognitive outcomes in pediatric brain tumors

The CNS is the most common site for solid tumors in children. Although brain tumors are relatively common as a group, they are heterogeneous in terms of CNS site, histology, clinical features, and molecular

characteristics. Five-year survival rates are similarly varied, ranging from well over 90% for certain low-grade glial tumors to less than 10% for diffuse midline glioma.[1,13]

Brain tumors and their treatment fundamentally alter patients' developmental trajectory. Like patients with childhood…

Radiotherapy

Although the toxic neurodevelopmental effects of CNS radiotherapy are well known, radiation continues to play an essential role in many pediatric cancer treatment regimens. Patients like our two representative cases pay for their improved chance of survival with a concomitant decrease in their lifetime ability to care for themselves and achieve their goals. Thus, there has been a focus on understanding the mechanisms of radiotoxicity to the developing brain, with the goal of minimizing this…

Hearing impairment

Irreversible hearing loss is an important adverse effect of commonly used chemotherapy drugs, particularly platinum-based agents, and can also occur with radiotherapy, direct tumor involvement of critical structures, and surgical intervention. Although hearing testing is typically included in standard follow-up regimens for high-risk patients, it is likely that a subset of patients has unaddressed hearing loss, or suboptimal interventions and support services.[75] In turn, hearing impairment is…

Risk reduction

The highest-yield strategy for reducing neurocognitive impairment in pediatric cancer survivors has been to delay or reduce exposure to radiation. Focal radiation has replaced craniospinal radiation in certain brain tumors such as atypical teratoid/rhabdoid tumors without a concomitant decrement in survival.[89] For patients younger than four years with medulloblastoma, intensive chemotherapy with stem cell transplant is used as a radiation-sparing measure. For older children, efforts at…

Conclusions

As child neurologists, our expertise is in the care of the developing brain. Survivors' cancer experience fundamentally alters their developmental trajectory in ways that may lead them to our clinics and consultive services. In this review, we have highlighted the myriad ways in which cancer and its treatment can affect long-term neurocognitive function. In the cases of our two representative patients, we have also taken the perspective of the individual's experience to illustrate how…

CRediT authorship contribution statement

Benjamin I. Siegel: Conceptualization, Writing – original draft, Writing – review & editing. **Juliane Gust:** Writing – review & editing, Conceptualization, Writing – original draft.…

Declaration of competing interest

Dr. Siegel and Dr. Gust declare no competing interests.…

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