Neurological Complications of Cancer and Cancer Therapies in Long-Term Survivors

34

Isabel Arrillaga

Introduction

The advent of improved cancer therapies has increased patient survivorship and with it the need to better understand the long-term sequelae of cancer and cancer therapies. With earlier detection methods and improved treatments, the number of cancer survivors by the year 2020 is estimated to reach approximately 20 million [1]. As this number increases, so does our awareness of the long-term neurological complications of cancer treatments. Among several cancer treatment-related side effects, neurotoxicity can be particularly severe and impact quality of life and overall functioning [2–4]. Given the inherent susceptibility of the developing nervous system to toxicity and an estimated high survival rates of up to 80% [5, 6], survivors of childhood cancers are affected disproportionately. Much of what we know about the long-term neurological complications of cancer and cancer therapies has been learned from research on survivors of childhood cancers.

This chapter will focus on several common long-term neurological side effects of cancer and cancer treatments, with some emphasis on CNS toxicity in long-term survivors of pediatric cancers. Some of the most common CNS complications to be discussed below include impaired cognition, seizures, cerebrovascular events, and peripheral neuropathy. A discussion of these complications in acute and subacute treatment settings can be found in earlier chapters of this text.

Cognitive Impairment

Cognitive impairment is a potentially long-lasting and late side effect of cancer and cancer treatments that can greatly impact quality of life and overall functioning [7]. Pediatric oncology patients are particularly vulnerable to the damaging effects of radiation and chemotherapy on the developing brain, and cognitive dysfunction has been reported in up to 40% of childhood cancer survivors. Neurocognitive difficulties have also been reported in adult cancer survivors [8–16]. Various cognitive domains can be impacted including attention, memory, and processing speed [17, 18].

Cognition in Survivors of Pediatric CNS Tumors

About 20% of pediatric tumors arise in the CNS. The 5-year overall survival of pediatric primary brain tumor patients has been estimated at more than 75% [5], with many survivors at risk of pervasive neurocognitive impairment decades after diagnosis and treatment [19–27]. Pediatric brain tumor patients experience up to a 20-fold increased frequency of severe impairment compared to the general population 20 years after diagnosis [28], and cognitive declines of 20–40 IQ points are not uncommon [20, 23, 29]. Importantly, subjective cognitive complaints do not mirror objective declines in cognition, despite significant functional implications. In one study, fewer than 10% of survivors reported severe cognitive impairment despite 50% being severely impaired in performance-based measures [28], highlighting the need for clinical assessment in addition to patient-reported outcomes when assessing cognition in this population. Despite subjective awareness of deficits, the functional implications of severe cognitive decline are tremendous, with observed reduced attainment of expected adult developmental milestones including education, employment, independent living [28], and possibly a lower socioeconomic attainment [20].

Cranial and craniospinal irradiation have been a well-known risk factor for impairment in cognition in children and adult survivors of pediatric brain tumors [5, 24, 30–33], particularly in areas of memory and executive functioning [34–37]. There is a correlation between radiation

I. Arrillaga (✉)
Department of Neurology/Neuro-Oncology, Massachusetts General Hospital, 55 Fruit Street, Yawkey 9E, Boston, MA 02114, USA
e-mail: iarrillaga@mgh.harvard.edu

D. Schiff et al. (eds.), *Cancer Neurology in Clinical Practice*,
DOI 10.1007/978-3-319-57901-6_34

dose and IQ [38, 39]. Moreover, it is estimated that, when irradiated at age less than 7 years, nearly 100% of children require special education; after 7 years of age approximately 50% of children require special education [33]. The temporal lobe is particularly vulnerable to effects of radiation; higher dose levels to this region are associated with higher risk for memory impairment [21]. Newer treatment techniques have been aimed at minimizing dose and target volume, though the long-term benefit of these techniques has yet to be established.

While the precise mechanisms underlying radiation-induced cognitive dysfunction remain elusive, damage to hippocampal neurogenesis may be involved. Studies in animal models have demonstrated that therapeutic doses of cranial irradiation virtually ablate neurogenesis and that this inhibition of neurogenesis correlates with impaired performance on hippocampal-dependent memory tests [33, 40, 41]. Surprisingly, irradiation does not simply deplete the stem cell population, but rather disrupts the microenvironment that normally supports hippocampal neurogenesis [40, 42]. This microenvironmental perturbation is due largely to irradiation-induced microglial inflammation and anti-inflammatory therapy with the non-steroidal anti-inflammatory agent indomethacin partially restores hippocampal neurogenesis and function in rodents [42]. Additional possible mechanisms underlying radiation-induced cognitive dysfunction include white matter dysfunction, altered regional blood flow due to microvascular disease and acute and chronic oxidative stress and inflammatory responses [43–45].

Cognition in pediatric brain tumor survivors is also affected by factors other than radiation. In survivors with no exposure to radiation, there exists a 17-fold increase in the prevalence of impaired cognitive flexibility, and a fivefold increase in the prevalence of impairments in short- and long-term memory. Additionally, up to 37% of these survivors are severely impaired on at least one measure of processing speed [28].

Treatment of pediatric brain tumors may include cranial irradiation and/or cytotoxic chemotherapy; both have been implicated in the pathophysiology of cancer treatment-induced cognitive decline. Additional factors that have been associated with neurocognitive outcome include tumor site [46], age at diagnosis [47], history of seizures and hydrocephalus with shunt placement [20, 28]. After adjustment for exposure to cranial irradiation, Brinkman and colleagues found that seizures conferred a 50% increase in the risk of cognitive impairment [28]. This may be related to the use of anticonvulsant medications or the cumulative neurobiological and physiologic consequences of recurrent seizures. Likewise, the same group reported that a history of hydrocephalus with shunt placement conferred 40% increased risk of memory impairment [28], possibly related to hippocampal vulnerability to hydrocephalus [48].

Cognition in Survivors of Non-CNS Pediatric Cancers

Pediatric survivors of non-CNS cancers are also at risk of developing clinically significant impairment in neurocognitive functioning [6]. The incidence of impairment in at least one cognitive domain has been reported as high as 21% [49]. Most of these data have been derived from studies on survivors of childhood leukemias [50–56] and lymphomas. These studies suggest that cranial irradiation, chemotherapy (in particular high dose systemic and intrathecal) [57], stem cell transplant [58], and other treatments such as corticosteroids [55, 58] may be involved in the etiology of cognitive dysfunction in these patients. Additional factors associated with neurocognitive outcome in this patient population include age at diagnosis and female sex [49, 57, 59–62].

Acute lymphoblastic leukemia (ALL) represents the largest diagnostic group of survivors of childhood cancers, and the best studied. Neurocognitive impairment in this population is pervasive and long lasting, being reported up to 26 years after diagnosis, well into adulthood [53, 63]. Deficits in attention, memory, intelligence, processing speed, and executive functioning have been reported [53, 59, 64–66]. Until recently, these impairments had been largely attributed to prophylactic cranial irradiation [50, 53].

Cranial irradiation affects cognition in a dose-dependent manner [53], and, in this population, dose thresholds remain debatable. Recent reports suggest that a dose of less than 18 Gy may reduce risk [31, 67]. Withholding radiation and treating with chemotherapy alone may further reduce risk [31, 67] and has been an impetus for the omission of radiation therapy for most patients with childhood ALL. Instead, systemic and intrathecal chemotherapy is used to establish CNS prophylaxis.

Chemotherapy also has a significant impact on cognition in this population [6, 18, 60, 68–72]. Krull et al. [53] recently demonstrated that significant cognitive impairments were common among survivors of childhood ALL treated with chemotherapy only. Likewise, a recent meta-analysis assessing long-term neurocognitive functioning after chemotherapy-only regimens among survivors of childhood ALL revealed significant moderate impairment across multiple neurocognitive domains, with intelligence most affected [56]. Additional information is needed on the functional

implications of these impairments though certainly patient and families should be provided with appropriate educational planning and surveillance.

Imaging correlates to neurocognitive outcomes in ALL survivors have been discovered, providing an understanding of some of the mechanistic underpinnings of late cognitive deficits and suggesting a role of white matter changes in neurocognitive changes secondary to cancer treatments. Specifically, smaller brain white matter volumes have been associated with larger deficits in attention, memory, intelligence, and academic achievement [73–75]. Additionally, fractional anisotropy (a measure related to degree of myelination) has been associated with IQ in childhood survivors of ALL.

Though limited, additional data exist to suggest that cognition is affected in childhood survivors of other non-CNS cancers. Intriguingly, some of these reports suggest that cognition can be affected by indirect mechanisms of treatment and not by direct CNS toxicity. Krull et al. [76] reported that adult long-term survivors of pediatric Hodgkin disease (HD) were at significant risk for neurocognitive decline. Importantly, this finding was associated with cardiopulmonary dysfunction attributable to standard care treatment with thoracic radiation and anthracyclines or bleomycin. Cardiopulmonary morbidity was further linked with cerebrovascular pathology as evidenced by multifocal leukoencephalopathy and hemosiderin deposits in the brain. This notable CNS finding was sixfold higher in HD survivors than in comparable cohorts and suggests a mechanism whereby pulmonary and cardiac dysfunction may lead to cognitive decline in this population. Primary prevention strategies have been sought and include reduction or omission of mantle field radiation, though these patients likely remain at risk given known cardiopulmonary side effects of anthracyclines and bleomycin.

Cognitive outcomes in long-term survivors of childhood osteosarcoma have also been evaluated [77]. Pediatric osteosarcoma has a 70% survival rate, largely due to advances in treatment including adjuvant chemotherapy with intravenous methotrexate. In addition, historical treatment regimens have incorporated anthracyclines, bleomycin, and alkylating agents, all chemotherapies known to affect cardiopulmonary function. The prevalence of cognitive decline in this population was found to be high, and this was not completely related to treatment with methotrexate. Maximum plasma concentrations, median clearance, and median/cumulative exposure to systemic methotrexate were not associated with cognitive impairment. Instead, any grade 3 or 4 adverse chronic conditions such as cardiac, pulmonary, or endocrine dysfunction were associated with poorer memory and slower processing speed. These results suggest that chronic health conditions related to cancer and cancer treatment can have a significant impact on cognition, in some cases more so that direct toxicity from treatment itself.

Cognition in Survivors of Adult Cancers

The incidence of post-treatment cognitive impairment in survivors of adult cancers ranges from 15 to 61% [78] and may be among the most frequently reported post-treatment symptoms of cancer survivors [79]. Effects can be worse immediately after treatment with some improvement over time [78] or with little recovery, leading to long-lasting impairment [10, 16, 80, 81]. Alternatively, patients may develop symptoms months to years following treatment [14]. Deficits in memory, executive function, processing speed, and attention appear most frequently [82]. Age [83, 84] and baseline cognitive reserve [83] have been identified as risk factors to neurotoxic effects of chemotherapy.

The mechanisms underlying effects of chemotherapy on the brain remain elusive, but may involve direct neurotoxic injury of hippocampal progenitor cells [85–87]. Such effects on hippocampal neurogenesis may help explain the delayed impact of treatment on cognition. Chemotherapy-induced increases in oxidative stress [88], white matter damage [86, 89], and reduced brain vascularization [78] may also be involved. Imaging studies have provided additional information about the structural and functional pathology associated with chemotherapy exposure. Reductions in hippocampal and frontal white and gray matter have been documented in cancer patients treated with chemotherapy [90, 91]. Advanced imaging studies using functional MRI, PET, and diffusion tensor MRI have provided additional albeit limited understanding of the pathophysiology of cognitive changes associated with chemotherapy [78].

Cerebrovascular Events

Numerous studies have shown that cancer survivors are at increased risk for stroke. The potential consequences of a stroke can be devastating leading to overt physical and cognitive disabilities, but can also be subtle and worsen cognitive impairment related to other factors. Cranial irradiation, in a dose-dependent fashion, is a particularly strong predictor of stroke risk [92–97]. The cumulative stroke risk in survivors treated with 50+ Gy has been estimated at 12% between 10 and 30 years of post-diagnosis [96]. Importantly, the elevated stroke risk conferred by cranial irradiation in childhood persists into early adulthood and continues to increase decades after treatment [96, 98, 99].

Radiation increases risk of arteriopathies such as moyamoya. Arteriopathies can lead to small and large vessel necrosis and has been identified as the most common risk factor for recurrent stroke in cancer survivors [100]. They typically occur shortly after completion of radiation, with one report estimating a median of 55 months from the time of radiation to discovery [101]. Since stroke risk persists decades after treatment, a second mechanism for delayed arteriopathy may exist.

Atherosclerosis is a more common cause of stroke in all comers and has also been linked with radiation [102–105]. The cumulative risk of stroke in survivors of childhood cancer treated with cranial irradiation increases fourfold for patients with additional atherosclerotic risk factors such as hypertension, diabetes, or black race [96], but is not solely dependent on these additional factors. A better understanding of the role of arteriopathy and atherosclerosis in the mechanism of stroke in cancer survivors would have significant implication for primary prevention, in particular in childhood cancer survivors. As it stands, the increased risk of stroke in cancer survivors suggests that frequent screening for modifiable stroke risk factors needs to be considered.

Seizures

Seizures are a common occurrence in both adults and children with brain tumors with an incidence near 30% [2]. The incidence of ongoing seizures in long-term survivors of pediatric brain tumors is as high as 14–25% [19, 106]. Seizures in this population are recognized as one of the most significant neurological complications of childhood brain tumors as they can occur frequently and at any time from diagnosis to years later. Moreover, they negatively impact quality of life [107]. Tumor pathology, extent of tumor resection and tumor recurrence are all risk factors [106]. In addition, treatment such as surgery, radiation, and chemotherapy can increase risk for seizures. In an analysis of a large cohort of survivors through the Childhood Cancer Survivor Study, patients with a history of radiation dose greater than 30 Gy to a cortical region of the brain had twofold risk of developing seizure as a late effect of treatment [19]. In this population, concurrent use of medications such as antidepressants and antibiotics, as well secondary medical complications such as infection or bleeding, can also lower seizure thresholds and increase risk [106].

Survivors of pediatric non-CNS cancers are likewise at increased risk for seizure as reported in a study assessing neurological morbidity in survivors of childhood ALL, which reported seizures in 11% of study participants [4]. History of CNS involvement of disease was associated with seizures, but additional factors such as cranial irradiation and chemotherapy likely also played a role [4].

Seizures themselves can be quite burdensome to cancer survivors, limiting functionality and quality of life in many cases, and affecting brain function in some. Moreover, additional side effects from the treatment of seizures with antiepileptic drugs (AEDs) can be equally as disturbing. Many of these agents have been associated with fatigue, and cognitive impairment, in addition to many non-neurological side effects. Thus, even infrequent seizures can impact overall medical health and quality of life.

Peripheral Neuropathy

Chemotherapy-Induced Peripheral Neuropathy

In comparison with the central nervous system, the peripheral nervous system (PNS) has better regeneration capacity. Notwithstanding, peripheral nerve toxicity, typically related to chemotherapy (chemotherapy-induced peripheral neuropathy, CIPN), can be debilitating, long lasting, and sometimes permanent [108, 109]. Until recently, this type of toxicity had remained an underestimated and under-recognized clinical problem in cancer survivors [110], perhaps because the accepted paradigm was that of a reversible condition. The evidence of long-term persistence of symptoms is now clear, in part due to the availability of large cancer registries such as Patient-Reported-Outcomes Following Initial Treatment of Long Term Evaluation of Survivorship (PROFILES) [110]. This has led to increased attention to this topic, so much so that the National Comprehensive Cancer Network recently expanded its guidelines for survivorship to address CIPN [111]. The hope is that with the increased attention, research in this field will continue to expand.

Most of the evidence supporting long-term CIPN in cancer survivors comes from studies of patient with breast, colorectal, and ovarian cancers who are typically exposed to neurotoxic agents. In one study of patients treated with oxaliplatin, 79% reported ongoing peripheral neuropathy after a median of 29 months from treatment [112]. Another study reported that over 25% of patients treated with oxaliplatin had NCI-CTC grade 3 symptoms 2 years after treatment. More compelling have been results from analysis of PROFILES data that revealed the persistence of CIPN up to 11 years post-treatment [113]. Cumulative dose was associated with worse outcomes [114].

Additional reports have revealed that CIPN can result in functional impairment. In a recent study, 89% of cancer survivors treated with oxaliplatin reported at least one symptom of neuropathy at 7 years from completion of therapy [115]. Importantly, due to their peripheral nerve symptoms, up to 24% of these survivors had difficulties driving, and 60% reported difficulties with exercise [115].

Functional consequences are further evidenced by reports that reveal an increased propensity to falls, with some series reporting up to 20% of patients with cancer and CIPN reporting falls [116, 117]. Motor neuropathy associated with taxanes use in breast cancer has been most strongly associated with increased propensity for falls [117]. Importantly, while clearly prevalent in cancer survivors, CIPN remains underreported by patients [118], suggesting that practitioners must be vigilant for symptoms and be educated to recognize early signs of the condition.

CIPN is also prevalent in adult survivors of pediatric cancers. In patients treated with either vinca alkaloids or platinum agents, the prevalence at a median of 25 years from diagnosis can be as high as 20 and 17.5% for long-term motor and sensory impairments, respectively [119]. In platinum-treated testicular cancer survivors, 22% had detectable peripheral neuropathy 23–33 years after therapy, and 6% had disabling neuropathy up to 22 and 15 years out from treatment, respectively [120, 121]. Clinical evidence for peripheral neuropathy as measured by EMG/NCS has also been reported in nearly 30% of survivors of childhood ALL at a mean of 7.4 years post-treatment [122]. CIPN in this population likely increases the risk for functional performance limitations, as evidenced by objective decreases in mobility and poor performance on a walk test and a timed "up and go" test [119].

Unfortunately, there are no proven preventive therapies for CIPN. There are data to support the role of duloxetine in the treatment of neuropathic pain related to CIPN, though relief is typically incomplete. No convincing data exist to support the use of other agents such as tricyclic antidepressants, gabapentine, or topical lidocaine, despite data supporting their utility in other neuropathic nerve conditions. Practitioners will often try these agents regardless of their success in these other conditions. Additional research with these agents is needed. Although no protective or curative agents exist, early detection of symptoms is important, in particular for children, as rehabilitative services and equipment may improve symptoms and provide strengthening and joint protection which in the long run could minimize functional limitations. For a compete discussion of CIPN including pathogenesis, clinical features, and evidence for treatment, please refer to Chap. 15 of this text.

Radiation-Induced Peripheral Neuropathy (RIPN)

Radiation-induced peripheral neuropathy (RIPN) is a less well-recognized, studied phenomenon, largely because it is more rare than its counterpart CIPN. The functional implications, however, can be equally severe [123]. RIPN has long been considered irreversible [124] and is associated with fibrotic changes to the nerves. The pathogenesis may be related to progressive fibrosis driven by reactive oxidative species and inflammatory mediators, ultimately resulting in demyelination, direct axonal injury, and nerve ischemia [125, 126].

A classic example of this type of neuropathy is a brachial plexopathy that can occur when radiation is directed at the chest, axillary region, thoracic outlet, or neck [127]. The incidence has decreased over the past six decades due impart to better radiation techniques and decreased doses. In the 1950s, the incidence was close to 65%, while now the incidence is only 1–2% [125], with 40–75% of cases resulting from radiation for breast cancer [128, 129]. Timing of symptom presentation varies widely, ranging anywhere from one year to decades after completion of treatment [130]. Presentation also varies ranging from mild sensory symptoms to debilitating pain and motor dysfunction. For a complete discussion of RIPN including pathogenesis, clinical features, and evidence for treatment, please refer to Chap. 14 of this text.

Summary

Neurological complications of cancer and cancer therapies are common in survivors of both adult and childhood cancers. Common complications often include cognitive deficits, strokes, seizures, and peripheral neuropathy. Importantly, these side effects are often associated with limitations in normal functioning, and impairment in quality of life. Much remains to be learned about the pathophysiology underlying many of these complications. This knowledge will ideally aid in the discovery of preventive and curative strategies, where currently there are none. Early recognition of these complications and risk for complications is crucial to provide both functional and psychological support to survivors and their families.

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