Neurocognitive Risk Factors and Current Intervention Strategies for Survivors of Pediatric Acute Lymphoblastic Leukemia

Abigail Lee Taber

A Senior Thesis submitted in partial fulfillment
of the requirements for graduation
in the Honors Program
Liberty University
Spring 2020

Acceptance of Senior Honors Thesis

This Senior Honors Thesis is accepted in partial
fulfillment of the requirements for graduation from the
Honors Program of Liberty University.

_____

Kimberly A. Mitchell, Ph.D.
Thesis Chair

_____

Gary Isaacs, Ph.D.
Committee Member

_____

Marilyn Gadomski, Ph.D.
Honors Assistant Director

_____

Date

Abstract

The improved survival rate for pediatric cancer patients is one of the greatest triumphs of recent medicine, but the late effects faced by these survivors have been uncovered through this new population of survivors. Many survivors of pediatric acute lymphoblastic leukemia (ALL) experience cognitive deficits in areas such as attention, memory, processing speed, and academic achievement following cancer treatment. Recent research has pointed to chemotherapeutic agents, host risk factors, and genetic predispositions as perpetrators of these deficits, although other factors are also under investigation. Consequently, the search for appropriate interventions for the amelioration of these deficits has dominated the literature in recent years. Due to the individualized and multi-faceted nature of the late effects, universally effective remediation methods are still nonexistent. However, pharmacological, non-pharmacological, and computerized cognitive intervention methods have all shown considerable promise for counteracting these cognitive deficits.

Cognitive Deficits Faced by Survivors of Acute Lymphoblastic Leukemia, Risk Factors for Cognitive Deficits, and Current Intervention Methods

Modern pediatric cancer treatment practices have improved significantly in recent decades, and the survival rate for these patients has skyrocketed as a result. While this development is considered one of the greatest feats in medical history, it has also revealed the late effects these survivors face (Marusak et al., 2018). Most of these late effects involve the child's executive functioning capabilities, especially in areas of attention, memory, and processing speed. Cognitive dysfunction following pediatric cancers occurs in about 15-75% of survivors (King & Green, 2015; Kuśmierek et al., 2020) and has led researchers to name the phenomenon "chemobrain" (Simó, Rifà-Ros, Rodriguez-Fornells, & Bruna, 2013). Generally, there are two classes of risk factors that contribute to cognitive deficits: host risk factors and treatment risk factors. Host risk factors include qualities such as female sex, young age at diagnosis, and certain genetic polymorphisms. Treatment risk factors mainly include issues such as chemotherapeutic neurotoxicity, white matter volume changes, and oxidative stress. (Buizer, de Sonneville, & Veerman, 2009; Simó et al., 2013). In many cases, it is a combination of multiple risk factors that causes the presentation of cognitive deficits in survivors.

Acute lymphoblastic leukemia (ALL) is the most common cancer diagnosis for children in the US (Reddick et al., 2006), and most ALL cases are seen in children between 1 and 6 years old (Zeller et al., 2013). The origin of ALL is in the bone marrow, but this form of leukemia spreads to many other parts of the body through the bloodstream, including the central nervous system (CNS). The acute quality of this cancer means that it has a quick progression and will likely lead to death if not treated promptly after diagnosis (ACS, 2019). Although the standard treatment protocol for pediatric ALL has shifted drastically over the past few decades, most

practitioners provide treatment in alignment with that outlined by the American Cancer Society (ACS). ALL is optimal for studying the cognitive deficits in pediatric cancer survivors due to the prevalence of this form of cancer as well as the extensive volume of literature on cognitive late effects seen in ALL survivors (Cheung & Krull, 2015).

The cognitive deficits faced by ALL survivors have long-reaching effects on the individual's quality of life and can even negatively affect the individual's performance in academic and work settings. The necessity of appropriate cognitive intervention strategies and methods is clear. Pharmacological, nonpharmacological, and computerized cognitive intervention strategies have all been studied in an effort to find the most efficacious method to combat cognitive deficits, and although research has only shown modest improvements following those interventions thus far, this area of research still shows ample promise for the future (Olson & Sands, 2016).

Standard Pediatric Cancer Treatment

History of Treatment Protocol for Pediatric ALL

The landscape of pediatric cancer treatment protocol has shifted dramatically over the past few decades. In the 1970s, combination CNS-directed chemotherapy became the leading method for treating childhood leukemia. At the time, a major component of all treatment was cranial radiation therapy (CRT) at a high dosage of 24 Gy. In many cases, this was combined with intrathecal methotrexate (MTX); in this form of treatment, the chemotherapeutic drug is administered through a lumbar puncture and directly injected into the cerebrospinal fluid (CSF). The idea was that the intensification of chemotherapy would lead to less CNS relapse and higher survival rates. Although the adjustment did, in fact, lead to those two outcomes, it was quickly evident that the change came with some significant consequences. The toxicity of CNS

irradiation was linked to secondary malignancies, physiological complications, and significant cognitive late effects. This led to the reduction of the radiation dosage from 24 Gy to 18 Gy (and even 12 Gy in some cases), but the effects of irradiation remained the same even when used in smaller doses (Buizer et al., 2009).

Practitioners soon discovered that irradiation could be completely removed from treatment and that CNS relapse could still be staved off using a chemotherapy-only protocol. This final shift in treatment became the prevailing standard of treatment that is still used today (Buizer et al., 2009). By replacing CNS irradiation with chemotherapy-only protocols, the neurocognitive late effects were reduced but not completely eliminated (Reddick et al., 2006); these patients still displayed cognitive deficits in areas of visual and motor processing, attention, and executive functioning (Cheung & Krull, 2015; Moore, 2005). Rates of attentional deficits for chemo-only survivors are still listed with an incidence as high as 67%, and other cognitive processes have displayed rates up to 28% (Marusak et al., 2018). However, this shift from radiation to chemotherapy-only did result in an increase in academic performance and preservation of white matter volume, which is the brain tissue that is important for neural connectivity and processing speed (Reddick et al., 2006). More importantly, the transition into chemotherapy-only treatment (specifically with the use of intrathecal MTX) increased the survival rate for pediatric ALL patients. While CRT was averaging an 80% survival rate for ALL patients, a chemotherapy-only protocol yields patient survival rates as high as 93.5% (Cheung & Krull, 2015).

Current Standard Treatment Protocol for Pediatric ALL

The battle for finding the most effective treatment strategy for ALL patients has now become an issue of balancing acceptable levels of neurotoxicity with high-efficacy protocols

(Moore, 2005). Treatment of ALL is individualized to each patient depending on the severity of the condition at the time of diagnosis, but the protocol outlined by The ACS is the general standard (ACS, 2019). The first stage of treatment, remission induction, is generally the most intensive segment. The aim of remission induction for leukemia is to completely eliminate any leukemia cells from the bone marrow and restore normal blood counts (Butler & Mulhern, 2005). Standard-risk ALL patients usually receive a 3-drug combination of chemotherapeutics including L-asparaginase, vincristine, and a steroid drug (like dexamethasone or prednisone). High-risk ALL patients additionally receive daunorubicin; the greater intensity of chemotherapy ensures that residual cancer will not remain in the system following induction (ACS, 2019).

The second stage, CNS preventative therapy, aims to eradicate any leukemia cells that moved into the CNS. This usually takes the form of intrathecal or systemic chemotherapy (Butler & Mulhern, 2005). Intrathecal therapy typically consists of high-dose methotrexate alone or, in the case of high-risk children, a triple intrathecal form consisting of methotrexate, cytarabine, and hydrocortisone (Buizer et al., 2009). For extreme cases of ALL wherein the leukemia already displays a significant presence in the CSF at the time of diagnosis, radiation therapy to the brain may still be implemented, although high-dose MTX is preferable and shows equal efficacy (ACS, 2019; Buizer, de Sonneville, van den Heuvel-Eibrink, Njiokiktjien, & Veerman, 2005).

Once remission is achieved, the patient enters the third stage, consolidation. This is a continuation and intensification of the chemotherapy meant to eradicate any remaining leukemia cells that may have survived initial chemotherapeutic treatment. Children in this stage are treated again with a combination of chemotherapy drugs including any of the following: MTX, 6-

mercaptopurine (6-MP), vincristine, doxorubicin, cyclophosphamide, etoposide, L-asparaginase, cytarabine, dexamethasone, or prednisone (ACS, 2019).

Once the leukemia reaches sustained remission, the patient enters the final stage, maintenance, in order to stave off any undetected leukemia remaining in the body (Butler & Mulhern, 2005). This stage only includes low-dose chemotherapy using MTX and 6-MP in the form of pills taken regularly over a period of time (ACS, 2019).

Host Risk Factors for Cognitive Deficits

Age As a Risk Factor

One of the greatest predisposing factors for late effects involving neurocognitive deficits is a younger age of the patient at the time of diagnosis and treatment. For children undergoing cancer treatment in early childhood—the most formative and critical years of the brain's development—any invasive condition or procedure can lead to detrimental effects in neurocognitive development. In the first three months of development, a child's brain consists of nearly all of the neurons needed (Castellino, Ullrich, Whelen, & Lange, 2014). During the first few years of life, the brain remains in a period of rapid, dynamic development where levels of gray and white matter fluctuate and differentiate according to the different needs in the areas of the brain (Moore, 2005). By age four, the volume of gray matter in the brain peaks and is subsequently modified through apoptosis of unnecessary neurons and connections (Castellino et al., 2014; Moore, 2005). White matter continues to increase in volume well into early adulthood, and it is this proliferation of white matter that stages the brain tissue for possible damage due to radiation or chemotherapy treatment at a young age (Moore, 2005). During white matter proliferation, neuronal myelination also occurs at a high volume, which continues into early adulthood. The newly formed myelin at this stage has high levels of activity coupled with high

levels of instability, making it highly susceptible to damage from the toxicity of the cancer treatment (Reddick et al., 2006). Also, the three fundamental aspects of executive functioning—attention shifting, inhibition, and working memory—are the building blocks for higher level thinking such as problem-solving; the preservation of these fundamental skills in the early stages of life is imperative to the intellectual development of these pediatric cancer survivors (Benzing et al., 2018).

Sex As a Risk Factor

Female sex has been shown to be a risk factor for cognitive deficits in ALL survivors; female leukemia patients have been shown to be at a higher risk for cognitive late effects following chemotherapy treatment (Olson & Sands, 2016). Although the exact mechanism of this is unknown, some theorize that this could be attributed to developmental differences between males and females in the early years of life (Buizer et al., 2009). White matter volume is known to mature more slowly in girls than boys during childhood, which could make girls more susceptible to chemotherapy-induced neurotoxicity (Schmithorst, Holland, & Dardzinski, 2008).

Genetic Polymorphisms

In addition to physiological changes linked to cancer treatment as risk factors for cognitive function, there are several genetic polymorphisms—particularly with genes involved in neural plasticity and repair—that have been associated with increased cognitive dysfunction in ALL patients. Some of the greatest risks faced by cancer patients are the neurotoxicity and oxidative stress that occur as consequences of such intense chemotherapy and radiation. Several genes have crucial roles that, when disrupted, can compound any of those issues that are already present following treatment. Understanding the role of genetics in the presentation of future

cognitive deficits has important implications for how interventions can effectively counteract these risks by gene targeting methods (Seigers & Fardell, 2011).

Brain-derived neurotrophic factor (BDNF) gene. BDNF is a protein that is responsible for the development and differentiation of new neuronal cells and the survival of existing neuronal cells (Jones & Pattwell, 2019). In addition, it aids in long-term memory storage through the preservation of long-term potentiation (LTP) in the hippocampus (Seigers & Fardell, 2011). This gene is most highly expressed in the cortices, hippocampus, cerebellum, and limbic system structures of the brain (Thomason, Yoo, Glover, & Gotlib, 2009). The most common single nucleotide polymorphism (SNP) in the gene BDNF is BDNFVal66Met; in this mutation, a methionine group is substituted for valine at codon 66 (Jones & Pattwell, 2019). Previous studies have found that mice containing the $BDNF_{Met}$ polymorphism display decreased hippocampal volume, impaired memory, and modified memory processing (Jones & Pattwell, 2019; Thomason et al., 2009). A recent study found that BDNF-knockout (deletion of the BDNF gene) mice exhibited compromised spatial memory and processing (Jones & Pattwell, 2019). However, after injection with BDNF into the hippocampus, mice exhibited significant improvement on the Morris water maze, a neurological test observing spatial memory (Seigers & Fardell, 2011). The receptor for BNDF, TrkB, is also involved in LTP in the hippocampus, and malfunction of this receptor has been linked to deficits in learning (Jones & Pattwell, 2019). On a larger scale, abnormal functioning of the BDNF gene or its receptor in human individuals has been linked to psychiatric disorders such as schizophrenia, dementia, anxiety, post-traumatic stress disorder (PTSD), and depression (Jones & Pattwell, 2019; Seigers & Fardell, 2011).

In an important study by Thomason et al., the researchers observed the role of BDNF in functional connectivity of the brain through the use of fMRI scanning with a specific focus on

the default-mode network (DMN), the executive network (EN), and the salience-emotion network (SEN) (Thomason et al., 2009). The DMN is active in task-negative scenarios (when the brain is not focused on a task), but the EN becomes activated when there is a specific task at hand. The SEN is the link between the two, and it decides which stimuli are salient, or important enough to be integrated in order to alter behavior (Goulden et al., 2014). This study was completed in a group of children and adolescents with roughly half of the group containing the met allele SNP and the other half with a normal genotype. The researchers observed reduced connectivity in the hippocampal, parahippocampal, and cortical brain regions at rest in all three of the networks being studied for individuals with the met allele, indicating that BDNF plays a crucial role in neuronal connectivity throughout the brain (Thomason et al., 2009).

Apolipoprotein E4 gene (APOE4). APOE4 is responsible for fat metabolism through the regulation of lipid uptake and distribution (Anderson & Kunin-Batson, 2009). This gene also plays a role in neural plasticity and repair (Simó et al., 2013) as well as cognitive processes such as learning and memory (Jones & Pattwell, 2019). One of the gene's alleles, E4, has been recently linked to Alzheimer's disease (AD; Anderson & Kunin-Batson, 2009). In a study of cognitive performance in individuals with and without the E4 allele, Ahles and associates (2003) found that the E4 allele primarily interacted with chemotherapy in the spatial and visual cognitive domains (Ahles et al., 2003). Other studies have shown deficits in episodic memory and executive functions in E4 carriers (Small, Rosnick, Fratiglioni, & Bäckman, 2004). It can be concluded that APOE4 may be a genetic marker for cognitive decline induced by chemotherapy (Ahles et al., 2003).

Catechol-o-methyl transferase (COMT) gene. COMT is an enzyme responsible for multiple processes throughout the brain. One of its most crucial roles is to inactivate

neurotransmission by breaking down catecholamines like dopamine (DA) and norepinephrine (NE) via methylation. The most common polymorphism associated with this gene is a SNP that occurs at codon 158 resulting in a codon change from valine to methionine (McAllister et al., 2004). The Val158Met polymorphism has been associated with reduced enzymatic activity (Cole et al., 2015); the methionine allele is less active than the valine allele by four-fold. This change in enzymatic mechanisms has important implications of DA breakdown, as the methionine allele metabolizes much less DA in comparison to the valine allele (Cole et al., 2015; McAllister et al., 2004). Previous research has established a relationship between the prefrontal cortex and DA; if there is too much or too little DA signaling, working memory can be negatively affected (Farrell, Tunbridge, Braeutigam, & Harrison, 2012). Furthermore, a reduced amount of methylated catecholamines is correlated with lower defense of oxygen radicals, making COMT polymorphisms a predisposing factor for additional oxidative stress when exposed to chemotherapy (Cole et al., 2015).

Methylene tetrahydrofolate reductase (MTHFR) gene. The MTHFR enzyme is responsible for the methylation of folate. For individuals possessing polymorphisms in the MTHFR gene, exposure to MTX during chemotherapy can lead to depleted folate stores and excess homocysteine levels (Anderson & Kunin-Batson, 2009). Folate is an essential component of CNS development and function. Polymorphisms that alter levels of folate in the CNS can lead to cognitive deficits in areas of attention and processing speed (Kamdar et al., 2011). Similarly, high levels of homocysteine are associated with endothelial cell injury, and they could also contribute to the vascular changes induced by the neurotoxicity associated with MTX discussed below (Shuper et al., 2002). When high levels of homocysteine or other excitatory amino acids accumulate in the system, toxic effects are exerted upon epithelial cells. This also primes neurons

for sensitivity to oxidative damage, ultimately leading to neuronal apoptosis and reduced production of myelin (Kamdar et al., 2011). Hyperhomocysteinemia is also correlated with the presentation of multiple neurological phenotypes, including schizophrenia and depression (Blom & Smulders, 2011).

Nitric oxide synthase 3 (NOS3) gene. The NOS3 gene codes for endothelial nitric oxide synthase (eNOS), an enzyme responsible for generating nitric oxide (NO) in endothelial tissue. NO acts as an antioxidant that protects against the production of radical ions such as hydroxyl (Yanar et al., 2016). eNOS is especially essential for patients undergoing chemotherapy. Chemotherapeutic agents such as MTX are known to induce oxidative stress via free oxygen radicals and increased homocysteine levels, which can subsequently cause endothelial and vascular damage; however, eNOS counteracts those effects through preservation of angiogenesis (production of new blood vessels), and protection against oxidative stress (Cole et al., 2015; Yanar et al., 2016).

The NOS3 894TT polymorphism is the most common for the NOS3 gene, and it is characterized by a Glu298Asp amino acid substitution. This polymorphism leads to decreased enzymatic activity, thus reducing the production of necessary antioxidants to protect against oxidative stress (Yanar et al., 2016). Additional research has also discovered a link between the 894TT polymorphism and increased homocysteine levels in the plasma in comparison to a healthy control group. These homocysteine levels exhibit a link with risk for cognitive decline (Ferlazzo et al., 2011). At a cognitive level, polymorphisms affecting NOS3 are associated with poor performance in Vocabulary, Block Design, Matrix Reasoning, IQ, and Digit Span intelligence tests. In a study that observed neurocognitive outcomes for carriers of mutations in

the NOS3, COMT, HFE, GTSP1, and SLCO2A1 genes, the NOS3 mutation most frequently resulted in lower IQ scores (Cole et al., 2015).

Solute carrier organic anion transporter family member 2A1 (SLCO2A1) gene. The SLCO2A1 gene encodes a prostaglandin transporter (PGT) that modulates the movement, uptake, and clearance of prostaglandins throughout the body, including at the blood-brain barrier (BBB; Cole et al., 2015). Prostaglandins have been shown to induce extra oxidative stress on an individual by way of amplifying the immune response. When cancer manifests in the body, an immune response is activated to recruit cytokines and other inflammatory factors to the site, further progressing the cancer. The cytokines then generate ROS by their mechanism of action; these ROS induce apoptosis at the injury site. Prostaglandins are produced in response to the expression of inflammatory cells and ROS, and they, in turn, enhance inflammatory cytokine expression. This propagates the cycle of free radical production and subsequent oxidative stress (Federico, Morgillo, Tuccillo, Ciardiello, & Loguercio, 2007). Recent studies have found that PGT expression is highest in the cortex, cerebellum, and hippocampus during development. Also, lower levels of PGT is seen in the brains of individuals with neurodegenerative diseases such as Alzheimer's disease (Choi, Zhuang, Crain, & Doré, 2008).

Mutations in the SLCO2A1 gene can affect the clearance and redistribution of prostaglandins, which can result in oxidative stress and cognitive impairment. The neurocognitive outcomes for individuals with a variant G allele in the SLCO2A1 gene mirrors those seen in NOS3 polymorphic individuals; they scored lower on all five tests of intelligence (Vocabulary, Block Design, Matrix Reasoning, Digit Span, and IQ) and exhibited lower mean estimated IQ scores (Cole et al., 2015).

Glutathione S-transferase P (GSTP1) gene. The GSTP1 gene codes for glutathione-s-transferase P (GST-P), an important enzyme that defends against oxidative stress. GST-P's interaction with glutathione allows the antioxidant to attack products of oxidative stress and form less toxic material for excretion. In one particular experiment, the activity of GST-P was inhibited, which led to an increase in oxidative-stress-dependent apoptosis (Röth et al., 2011). As previously observed, polymorphisms in genes connected to oxidative stress or neuroinflammation are linked to poorer cognitive outcome. One of the most common polymorphisms in this gene is a change from alanine to valine at codon 114 due to a C to T transition at position 2293 (Welfare, Adeokun, Bassendine, & Daly; 1999); the GSTP1 T allele individuals scored lower on tests of Digit Span and IQ compared to their healthy counterparts (Cole et al., 2015).

ATP-binding cassette sub-family B member 1 (ABCB1) gene. In addition to genes related to oxidative stress, genes that influence BBB permeability are also key contributors to cognitive dysfunction when polymorphisms are involved. The ABCB1 gene codes for ABCB1, or P-glycoprotein, the most prevalent efflux transporter. This efflux transporter is incredibly important for the transport of xenobiotic or endogenous substances from the brain into the bloodstream (van Assema et al., 2012). It is especially important for reducing the level of brain exposure to certain chemotherapeutic agents like doxorubicin (Seigers & Fardell, 2011). This ABCB1 gene is highly polymorphic, and these polymorphisms can lead to modified P-glycoprotein function (van Assema et al., 2012). In one study, mice were injected with paclitaxel, a neurotoxic agent that is known to lead to cognitive impairment when allowed to cross the BBB. P-glycoprotein knockout mice showed ten times the amount of paclitaxel exposure in the brain in comparison with wild-type mice (Seigers & Fardell, 2011). Excess

exposure of the brain to xenobiotics greatly increases the likelihood of neurotoxicity and cognitive impairment and has been shown to have links with the onset of neurodegenerative diseases such as Parkinson's disease (Seigers & Fardell, 2011; van Assema et al., 2012).

Cystathionine beta-synthase (CBS) Gene. The CBS gene codes for the CBS enzyme, which is responsible for regulating homocysteine levels. Elevated homocysteine levels have previously been linked to endothelial cell damage and changes in vascularization (Shuper et al., 2002). In an experimental study of the relationship between CBS and homocysteine, an increase in activity of CBS directly led to the reduction of homocysteine levels in the plasma (Wang et al., 2004). Another study observed the effect of different genetic polymorphisms in cognition of ALL survivors over the course of four years following diagnosis; carriers of the CBS 844ins68 polymorphism exhibited reduced IQ scores over the four-year period (Krajinovic et al., 2005).

Treatment Risk Factors for Cognitive Deficits

In addition to host risk factors such as age, sex, and genetic polymorphisms, pediatric ALL patients encounter many treatment-related risk factors that may contribute to the onset of cognitive deficits. There are two major routes by which ALL treatment leads to deficits. First, the direct effect of chemotherapeutic agents on the brain can lead to cognitive deficits. Secondly, the occurrence of cranial complications such as oxidative stress, leukoencephalopathy, decreased vascularization, and increased membrane permeability can lead to increased neurotoxicity and cognitive dysfunction (Ikonomidou, 2018; Reddick et al., 2006; Seigers & Fardell, 2011).

Immediate Effects of Chemotherapeutic Agents

Chemotherapeutic agents can generally be divided into a few drug classes based on their mechanism of action. Alkylating agents prevent cell replication by alkylating electron-rich atoms to form covalent bonds that react with DNA bases. Two common examples of alkylating

chemotherapeutic agents are doxorubicin and cyclophosphamide (Ikonomidou, 2018; Seigers & Fardell, 2011). Antimetabolites, such as methotrexate, are responsible for disrupting the biosynthesis of nucleic acids in order to prevent the formation of new DNA or RNA, which subsequently leads to cell cycle arrest (Ikonomidou, 2018). DNA topoisomerase inhibitors interfere with the action of DNA topoisomerase, responsible for creating single- or double-strand breaks in the DNA helix during replication in order to release the torsional stress of the coil. When the inhibitors prevent this process, the supercoiled and strained DNA leads the cell to arrest, apoptosis, or necrosis (Ikonomidou, 2018; Seigers & Fardell, 2011). Alkaloids, such as vincristine, bind tubulin and effectively block the assembly of microtubules to arrest the cell in metaphase (Moudi, Go, Yien, & Nazre, 2013). Regardless of the chemotherapeutic drugs used, most results have shown that the degree of neurocognitive deficits experienced is largely dose-related (Krull et al., 2013). Recent research has established a direct correlation between intensity of cancer treatment and the severity of cognitive deficits following, with the most devastating effects seen in those who have received the highest dosages of chemotherapeutics (Buizer et al., 2009).

Methotrexate. MTX is the most extensively studied chemotherapeutic agent in terms of its neurotoxic effects. The main action of MTX as an antimetabolite is to inhibit dihydrofolate reductase, an enzyme responsible for the reduction of dihydrofolate to tetrahydrofolic acid (THF). This THF-deficiency leads to decreased purine and pyrimidine synthesis and antiproliferative effects overall (Olsen, Spurlock, & Aune, 2014). MTX also disrupts transmethylation reactions important for protein, lipid, and myelin synthesis (Shuper et al., 2002). Primarily, the neurotoxic effects of MTX include apoptotic and excitotoxic neuronal cell

death, decreased neurogenesis, reduced myelination, reduced blood flow, and increased oxidative stress (Ikonomidou, 2018; Seigers & Fardell, 2011).

Although the exact mechanisms by which each these effects are exerted are not fully established, many inferences can be drawn from the understood mechanisms of action of MTX. One proposed method by which methotrexate induces acute neurotoxicity is through inhibiting synthesis of catecholamines such as dopamine (McAllister et al., 2004); this is attributed to the interference of MTX on transmethylation reactions (Shuper et al., 2002). This conclusion was drawn from an experiment in which the use of intrathecal MTX in male rats led to decreased concentrations of norepinephrine, dopamine and serotonin in the hippocampus as well as impaired learning and memory (McAllister et al., 2004).

Another proposed theory for the neurotoxicity of MTX is based on the alteration of folate metabolism pathways. Folate and homocysteine are crucial in cellular metabolism processes such as the donation of carbon groups to purines for the synthesis of genetic material (Blom & Smulders, 2011). MTX increases levels of homocysteine and its precursor, S-adenosyl homocysteine; high levels of these two compounds are associated with endothelial cell injury (Shuper et al., 2002). Also, malfunctioning folate and homocysteine metabolism is associated with psychiatric and neurodegenerative diseases (Blom & Smulders, 2011). The demyelination caused by MTX can be attributed to its transmethylation interference that prevents the formation of myelin (Shuper et al., 2002). Finally, MTX is associated with production of excitatory amino acids, (Buizer et al., 2009) which can lead to excitotoxicity, a form of cell death caused by overstimulation of excitatory amino acid receptors (Ikonomidou, 2018).

The cognitive deficits seen as a result of MTX occur in a dose-related manner. A study by Krull and associates (2013) found that for every 1 g/m^2 increase of intravenous MTX, the risk

for slowed processing speed increased by 3% in a direct relationship while controlling for irradiation (Krull et al., 2013). Catecholaminergic and cholinergic systems also play a complementary role in attention and memory, and the interference of MTX on catecholaminergic systems likely contributes to the deficits in attention and memory seen in the survivors (McAllister et al., 2004).

Cyclophosphamide. Cyclophosphamide is an alkylating agent that plays a role in inducing apoptosis and excitotoxicity, decreasing neurogenesis, impairing long-term potentiation (LTP), and inducing oxidative stress (Ikonomidou, 2018; Seigers & Fardell, 2011). Also, in animal studies, cyclophosphamide has been associated with impaired memory retention and avoidance (Seigers & Fardell, 2011). In a study by Yang and associates (2010), it was discovered that cyclophosphamide suppresses neurogenesis in the hippocampus, which may lead to the deficits in learning and memory (Yang et al., 2010).

Vincristine. Vincristine exerts considerable neurotoxic effects peripherally and likely contributes to the sensory-motor impairments observed in ALL survivors (Buizer et al., 2005). This sensory-motor deficit is potentially a result of the axonal degeneration and decreased axonal recruitment caused by vinca alkaloids due to their prevention of microtubule assembly. However, vincristine uptake into the brain is relatively low (Moudi et al., 2013).

Doxorubicin. Doxorubicin is an anthracycline, and it acts as both an alkylating agent and a topoisomerase inhibitor. In the alkylation process, a reactive oxygen species is released, which leads to lipid peroxidation—a state known to contribute to membrane and DNA damage and oxidative stress (Thorn et al., 2011). The neurotoxic effects of this agent have also been associated with reduced hippocampal LTP, increased oxidative stress, and induced caspase-

mediated cell death—conditions that have all been linked to cognitive deficits (Alhowail et al., 2019).

Corticosteroids. Corticosteroids alter gene expression through the binding of glucocorticoid receptors, and they are responsible for inducing apoptosis, modifying oncogenes, and inhibiting cytokine production (Inaba & Pui, 2010). The most commonly used corticosteroids in chemotherapy are dexamethasone, prednisone, and hydrocortisone. Traditionally, dexamethasone is preferred to prednisone for its superior level of CNS penetrance (Buizer et al., 2005), which allows it to inhibit CNS leukemia more effectively, but the toxicity of prednisone is generally lower in comparison to dexamethasone (Inaba & Pui, 2010). Impaired executive function and attention has been seen in patients treated with dexamethasone while controlling for MTX (Krull et al., 2013). Furthermore, most corticosteroids are known to lead to adverse effects such as proximal myopathy, which may contribute to the motor problems experienced by ALL survivors (Buizer et al., 2005).

Neurotoxic effects linked to cognitive deficits

Increased permeability of the BBB. One of the physiological alterations that contributes to the cognitive deficits seen in ALL survivors is the direct assault that occurs on the CNS by the cytotoxic chemotherapeutic agents. The permeability of the BBB plays a direct role in the CNS exposure to the chemotherapeutic agents. The BBB is a semipermeable border formed by capillary endothelial cells that are linked together by tight junctions, and its function is to separate the brain from the circulating blood (Ikonomidou, 2018; Seigers & Fardell, 2011). Generally, the only molecules that are allowed to pass through the BBB are water, amino acids, and small, lipophilic molecules. In some cases, drugs that utilize an internal transport system can also pass through (Ikonomidou, 2018). In order to further guard against foreign substances

entering into the brain, the BBB is equipped with an efflux transport system that restricts the level of cytotoxic drugs that could potentially accumulate. When activity of efflux transporters becomes inhibited or decreases, an increased level of drugs can accumulate in the brain and lead to cognitive impairments (Seigers & Fardell, 2011). The use of some chemotherapeutic agents allows for much higher permeability of the BBB through peripheral mediators—such as cytokines—that are released as a result of the drug's mechanism of action. For example, MTX is known for its increase in the level of proinflammatory cytokines IL-1 and IL-6 (Olsen et al., 2014). Additionally, research has discovered a causal relationship between increased neuroinflammation and subsequent cognitive impairment. A well-supported theory for this is that the BBB becomes disrupted via cytokines, resulting in extended exposure of the CNS to chemotherapeutic drugs and amplified cognitive deficits (Wardill et al., 2016).

Altered cerebral vascularization or blood flow. Several chemotherapeutic agents are known to contribute to decreased vascularization and blood flow in certain areas of the brain. The vascular damage and reduced blood flow are associated with impaired cognition and neural functioning (Seigers & Fardell, 2011). MRI imaging techniques have revealed irregular cerebral blood flow in the frontal and cortical areas during treatment with chemotherapeutics (Österlundh et al., 2008). Previous research has found that MTX reduces cerebral blood flow and glucose metabolism (Seigers & Fardell, 2011). Additional studies have found that MTX directly leads to decreased density of hippocampal blood vessel density (Seigers et al., 2009). Multiple studies have found decreased hippocampal volume due to reduced proliferation, and it is theorized that this is a result of the combination effect of decreased vascularization and reduced proliferative signals (Seigers & Fardell, 2011). Corticosterone exposure has also been shown to induce cellular changes in the hippocampus, which are linked to worse performance on tests of

executive function, such as the Wisconsin Card Sorting Test (WCST), and are frequently associated with cognitive dysfunction in areas of visual and verbal memory (Frodl et al., 2006).

Oxidative stress. Oxidative stress is the result of disrupted mitochondrial DNA that leads to the production of reactive oxygen species (ROS; Ikonomidou, 2018). These ROS lead to mitochondrial DNA mutations and result in defective mitochondrial proteins, a malfunctioning electron transport system, and eventually, the production of more ROS (Seigers & Fardell, 2011). Chemotherapy produces ROS that go on to oxidize apolipoprotein A1 (ApoA1), which is responsible for the synthesis of TNFα. TNFα then can penetrate the BBB and induce apoptosis (Gaman, Uzoni, Popa-Wagner, Andrei, & Petcu, 2016). Although the generation of ROS is effective in the eradication of tumors and malignancies, there are many unintended consequences as a result of excess ROS species in the body, most often in the form of DNA or RNA damage, neurotoxicity, and cell death. And though the body naturally produces antioxidants that break down ROS, the brain contains a low level of these protective agents. Maintaining normal redox levels in the brain has been shown to be crucial for specific processes such as cell differentiation and preservation of normal CNS function (Gaman et al., 2016). Oxidative stress has been most highly associated with cytarabine, doxorubicin, MTX, and carboplatin chemotherapeutic agents (Ikonomidou, 2018). In addition to creating extra ROS, doxorubicin, cyclophosphamide, and MTX also activate TNFα. This further exacerbates neurotoxicity, as a known side effect of TNFα is the deactivation of glutathione, an important antioxidant (Gaman et al., 2016). In an experiment performed by Konat et al. (2008), cognitive impairment induced by chemotherapy treatment was ameliorated when an antioxidant was introduced into the rat, which led to the conclusion that oxidative stress is a key contributor to cognitive deficits in individuals who underwent chemotherapy treatment (Seigers & Fardell, 2011). This also promotes targeting

TNFα in therapy to preserve the level of antioxidants in the brain of a patient receiving chemotherapy (Gaman et al., 2016).

Leukoencephalopathy. Many studies of pediatric ALL patients have observed leukoencephalopathy—or the decrease in white matter volume in the brain—in many of the patients, especially in the frontrostriatal tract (Cheung et al., 2016). Several studies have shown that decreased white matter is directly correlated with decreased attention, intelligence, and academic achievement (Reddick et al., 2006). Lower cognitive performance occurs proportionally with decreased white matter integrity; this same trend is seen in individuals with a traumatic brain injury or with an aging disease such as dementia (Moore, 2005). White matter and oligodendrocytes also play an important role in myelination for improved impulse conduction, and this damage could be the cause of the reduced processing speed seen in chemotherapy-treated patients (Seigers & Fardell, 2011).

There are a few possible mechanisms for the white matter damage that occurs due to the chemotherapy. The first mechanism is through direct assault on the various types of brain tissue, including oligodendrocytes and microglia (Anderson & Kunin-Batson, 2009). Since oligodendrocytes are essential for myelination in the CNS, damage to these cells can lead to demyelination (Reddick et al., 2006). The second possible mechanism is through injury to the microvasculature, including obstruction of blood vessels, ischemia, and necrosis (Anderson & Kunin-Batson, 2009).

Neurogenesis. MTX and cyclophosphamide are both associated with decreased neurogenesis (Ikonomidou, 2018; Yang et al., 2010). Neurogenesis is particularly important in hippocampal proliferation, and a decrease can lead to deficits in learning and memory (Seigers &

Fardell, 2011). Decreased neurogenesis can also be a result of neuroinflammation, which is a common side effect for recipients of CNS-directed chemotherapy (Ikonomidou, 2018).

Current Intervention Strategies

Each ALL patient undergoes rigorous physical treatment during chemotherapy, but the challenges do not usually end for the individual once treatment has concluded—especially for those that develop cognitive deficits. Readjusting after cancer brings a new set of demands as the individual works to reenter school, reintegrate into his/her relationships, and acclimate to chronic pain or lifelong physiological changes due to the cancer and/or its treatment (Marusak et al., 2018). For those who develop cognitive deficits, this leads to additional difficulties in the educational and work settings (Olson & Sands, 2016). This accentuates the need for efficacious intervention programs to reduce or improve some of these deficits and improve quality of life for these individuals. Pharmacological interventions to improve executive functions such as attention have shown considerable effectiveness; however, many survivors are unable to receive them for a myriad of reasons such as parental preference, endocrinopathies, seizures, interaction with current medications, or risk of side effects (Conklin et al., 2016). As the research and healthcare field begins to look to nonpharmacological options as viable intervention strategies, solutions such as computerized cognitive intervention programs seem to show considerable promise for the future. The evolution of these programs in recent decades leads to future direction for this field.

Pharmacological Interventions

Methylphenidate. Methylphenidate chloride (MPH) is a dopaminergic and adrenergic agonist. It increases release and reduces reuptake of dopamine at synaptic terminals and also inhibits monoamine oxidase, an enzyme responsible for neurotransmitter inactivation (Conklin et

al., 2007). This increases the concentration of these neurotransmitters—and thereby, the level of functioning—in the frontostriatal tract, which is a crucial area of the brain for processes involving attention (Conklin et al., 2007; Davis, Ahlberg, Berk, Ashley, & Khasraw, 2013). MPH is most widely known for its use in treating attention deficit hyperactivity disorder (ADHD), for which is it the most commonly prescribed medication (Conklin et al., 2007). In a crucial experimental study, the efficacy of MPH as a potential pharmacological intervention for the remediation of the cognitive deficits that are experienced by ALL or brain tumor (BT) survivors was investigated. Ninety minutes after receiving a dose of MPH, the individuals underwent a series of cognitive tests for areas of attention, cognitive flexibility, verbal memory, and overall academic performance. Significant effects from MPH were seen in Stroop Word-Color Association Test (a test of impulsivity, cognitive flexibility, and selective attention), and the Continuous Performance Task (a test of attention and concentration; Conklin et al., 2007).

Unfortunately, since MPH activates such a large part of the cortical region in the brain, the individual is susceptible to more side effects from the drug. The most common side effects of MPH are anxiety, sweating, hallucinations, decreased appetite, and overactive behavior (Davis et al., 2013; Mulhern et al., 2004); however, in a study of 83 patients undergoing MPH treatment, only 5% exhibited symptoms when the dosage was decreased (Mulhern et al., 2004). Although the benefits of treated cognitive deficits in cancer survivors have not been fully elucidated, the efficacy of MPH in treating ADHD symptoms makes this a promising option as a pharmacological intervention.

Metformin. Metformin is most commonly used in treating type 2 diabetes due to its ability to control hyperglycemia. The primary mechanism by which it achieves this is through regulation of the AMP-activated protein kinase (AMPK) pathway (Chaudhari, Reynolds, &

Yang, 2020). AMPK signaling works to preserve metabolic homeostasis following synaptic transmission by regulating glycolysis and mitochondrial function (Marinangeli et al., 2018) . These pathways increase neuronal survival, differentiation, and proliferation, and preserve synaptic neuroplasticity (Chaudhari et al., 2020; Marinangeli et al., 2018). Previous studies have indicated that malfunctioning MAPK signaling is associated with cognitive impairments, as neuroplasticity is an important element in cognitive processes such as memory (Marinangeli et al., 2018). In addition to activating AMPK pathways in neurons, metformin has also been found to increase glucose metabolism and reduce apoptosis in astrocytes (Chaudhari et al., 2020).

One study evaluated the efficacy of metformin as a therapeutic agent in improving cognitive function. The researchers injected mice with cisplatin, a common chemotherapeutic agent used during the induction stage of treatment for various cancers. After injection, the mice performed a series of cognitive tests, including the Novel Object-Place Recognition Test (for memory) and the Social Discrimination Test (for recognition abilities). The mice injected with cisplatin displayed impaired performance in both tasks, signifying cognitive deficits. However, when the mice were injected with metformin in addition to cisplatin, performance on both of the cognitive tests was improved (Zhou, Kavelaars, & Heijnen, 2016). Another pilot study found improved executive function, attention, learning, and memory when metformin was administered to patients with Alzheimer's disease (AD) or mild cognitive impairment (MCI; Chaudhari et al., 2020).

Metformin has shown considerable effectiveness in protecting against peripheral neuropathy, a common consequence from chemotherapeutic agents such as vincristine and docetaxel that affects motor and sensory function (Mao-Ying et al., 2014). However, the effects

of metformin were found to be dependent on sex, age, dosage, treatment duration, and comorbidities (Chaudhari et al., 2020).

Donepezil. Donepezil is most widely used in the treatment of Alzheimer's disease. This drug is a acetylcholinesterase (AChE) inhibitor, so its main function is to increase the concentration of acetylcholine at synapses (Winocur, Binns, & Tannock, 2011). Increasing the levels of ACh results in increased cholinergic signaling and improved cognitive function, specifically in hippocampal processes such as learning and memory (Lim, Joung, Yu, Shim, & Kim, 2016; Winocur et al., 2011).

Previous research has shown that donepezil ameliorates cognitive decline in attention deficit and attention seen in patients with AD after twelve months of treatment. Links between donepezil-dependent cognitive improvement in survivors of brain tumors have also been established (Correa, Kryza-Lacombe, Baser, Beal, & DeAngelis, 2016).

In a study focused on the cognitive benefits of donepezil, a group of mice were treated with two chemotherapeutic drugs known to cause cognitive deficits, MTX and 5-fluouracil. The researchers noted that this chemotherapeutic combination led to hippocampal memory loss and impaired prefrontal executive functions, especially in areas of spatial memory, working memory, and learning. The chemotherapy-treated mice were given a dose of donepezil in concurrence with the chemo cocktail weekly for four weeks. The results revealed that the group treated with donepezil alongside the chemotherapy treatment showed significant improvement in the tests of learning and memory. Some of the improvements were so great that the level of cognitive performance nearly matched that seen in the control group of mice that were only treated with saline (Winocur et al., 2011).

Another study used PET scans to observe glucose metabolism in a group of rats treated with chemotherapeutic agents and donepezil. Preliminary PET scans following injection with chemotherapeutics doxorubicin or cyclophosphamide revealed an overall decrease in glucose metabolism in the prefrontal cortex and hippocampus. This effect was seen more significantly in conjunction with doxorubicin. After donepezil treatment in the doxorubicin group, PET scans revealed an increase in glucose metabolism in the medial prefrontal cortices, the hippocampi, and the parietal cortices. The donepezil-treated cyclophosphamide group had increased glucose metabolism in the parietal, frontal, and temporal cortices, as well as the hippocampi (Lim et al., 2016). In this same study, two behavioral tests were used to test cognitive function. The Morris Water Maze was used to study spatial and reference memory, and a passive avoidance test was used to test explicit working memory. Impairments in all three functions of memory were observed following chemotherapy treatment along with slower processing and lower memory retention. However, following injection with donepezil, the integrity of all of the tests was rescued, and cognitive improvement was observed. Overall, the cognitive improvement after donepezil administration was seen to a greater extent in the doxorubicin-treated group in comparison to the cyclophosphamide-treated group (Lim et al., 2016).

Nonpharmacological Interventions

Many of the pharmacological interventions remain moderate in their mitigation of cognitive dysfunction. Moreover, many ALL survivors are unable to receive pharmacological interventions. This has caused many individuals to turn to other ecological, psychological, and cognitive training interventions to improve the cognitive late effects.

Exercise. A simple and accessible intervention is participation in physical activity, which improves cognitive function. Although these improvements are relatively trivial in healthy

individuals, these positive effects are amplified for individuals who display disease-related cognitive deficits (Seigers & Fardell, 2011). At a cognitive level, multiple studies have shown that exercise improves aspects of executive functioning, especially working memory. An experimental study by Schmidt and associates (2015) tested aspects of executive functioning following a 6-week physical activity training program that required the use of higher cognitive functioning in the activities. The team found improved shifting processes of executive functioning in the participants after the program, indicating that physical activities that require cognitive engagement are particularly beneficial in ameliorating deficits, especially when compared to physical activity without a cognitive component (Mirko, Katja, Fabienne, Claudia, & Achim, 2015). In addition to cognitive functions, exercise also improves the physiological processes that are affected in chemotherapy treatment, such as increasing cell proliferation, improving cerebral blood flow through the production of growth factors, reducing inflammation and oxidative stress, and preserving white matter integrity (Seigers & Fardell, 2011).

School Reentry Programs. One of the most well-documented cognitive late effects recognized in pediatric cancer survivors is poor academic achievement (Krull, Hardy, Kahalley, Schuitema, & Kesler, 2018; Olson & Sands, 2016). One of the methods that has proven useful in mitigating this specific issue is the use of school reentry programs. The ideal model of this program—although not widely implemented in oncology centers yet—is that a trained employee in the pediatric oncology department would communicate with parents, teachers, and caregivers of the patient in order to provide general education about the neuropsychological effects the patient might face. Although this program would be individualized to each patient, this may include a personalized academic plan, communication with the school, or even an educational session for the patient's classmates (Thompson et al., 2015). The risk in omitting this bridge

between treatment and the child's school is that newfound deficits in areas such as attention could be misinterpreted by the teacher as noncompliance or a poor attitude. Providing teachers with training regarding various cognitive deficits that may appear can allow the teacher to make proper accommodations in the classroom and relay any changes in cognitive performance to the practitioner/parents should they arise (Krull et al., 2018).

Computerized Cognitive Training Programs. Although psychological or therapy-based interventions are utilized for some cognitive remediation, computerized cognitive training programs have some notable advantages—such as reduced cost, lack of adverse effects, and geographic reach—in comparison to clinical interventions (Conklin et al., 2016). Computerized cognitive training programs aim to target specific cognitive skills through tasks with high repetition and graded difficulty (Conklin et al., 2015; Hardy, Willard, Allen, & Bonner, 2013). The implementation of these programs began in the 1980s with programs aimed at ameliorating cognitive deficits experienced by individuals with a traumatic brain injury (TBI) and later moved into the field of pediatric oncology (Olson & Sands, 2016).

The first groundbreaking study was by Butler and Copeland (2002) when they tested a pilot intervention called the Cognitive Remediation Program (CRP; Butler & Copeland, 2002). This intervention strategy was tripartite, combining components of TBI rehab, educational psychology, and clinic-based psychological interventions. Thirty-one pediatric cancer survivors with known attentional deficits were included in the study, twenty-one of which received the intervention, while the other ten composed the non-intervention control group. The program consisted of twenty 2-hour sessions given in an outpatient setting weekly. The intervention targeted attentional deficits through three general components: 1) drill practice, 2) skills acquisition, and 3) cognitive-behavioral therapy (CBT). After the intervention was complete, the

CRP displayed significant improvement in performance on all three measures of attention (Butler & Copeland, 2002; Butler et al., 2008).

In a modified version of the previous study, Butler et al. (2008) employed the clinic-based CRP for one 2-hour session weekly for 20 sessions. However, whereas the first study was only a pilot study of the CRP program with a small group of survivors, the 2008 study was conducted as a nationwide, multicenter, Phase 3 clinical trial. The intervention group of this program showed improved academic achievement, attention, working memory, and recall.

Kesler, Lacayo, and Jo (2011) utilized a similar pilot computerized cognitive training program. This intervention consisted of forty home-based sessions 20 minutes each over the course of eight weeks. Each session consisted of six tasks: two tested working memory, two tested attention, and the last two tested cognitive flexibility. Pediatric cancer survivors that participated in this intervention displayed improved processing speed, cognitive flexibility, and declarative memory; neuroimaging also revealed increased prefrontal activation (Kesler, Lacayo, & Jo, 2011; Olson & Sands, 2016).

In a particularly innovative study, Hardy et al. (2013) utilized *Cogmed RM*, an at-home, computerized training program to improve visual-spatial and auditory working memory in pediatric cancer survivors. The program consisted of 25 training sessions with phone-based coaching. The participants were divided into an experimental group and a control group. The experimental group completed a success-adapted version of the program that was graded for difficulty in congruence with accurate performance. The control group completed a non-adaptive version with exercises of the same difficulty level throughout the study. A baseline assessment of working memory was taken at three points: before the trial, following the intervention, and then three months post-intervention. The results showed significantly improved visual-spatial working

memory in the intervention group compared to the control, and this effect was sustained at the follow-up assessment three months later (Hardy et al., 2013; Olson & Sands, 2016).

Conklin et al. (2016) further investigated the efficacy of *Cogmed RM* and analyzed the neural mechanisms for the cognitive changes seen. Much like Hardy's original study, participants were randomly divided into an intervention and a control group, and assessments were taken before testing, postintervention, and six months later. For the neuroimaging component of the study, the participants were asked to complete a working memory task during an fMRI scan. Following intervention, the fMRI showed decreased activation in the prefrontal and parietal regions, which could indicate increased neuroplasticity and efficiency for networks involved in working memory. Additionally, processing speed, spatial and working memory, and attention were improved in the treatment group with sustained effects six months later. Furthermore, it was concluded from this study that *Cogmed RM* shows comparable efficacy and participation in comparison to therapy-based interventions (Conklin et al., 2015).

Although the computerized cognitive remediation programs have been promising, they are still inadequate to fully remedy the cognitive deficits suffered by cancer survivors. One of the major issues of this form of intervention is the burden that it places on the therapist, individual, and family; it is more self-directed in comparison to more regimented therapeutic interventions. That factor causes compliance to these programs to be an issue; most of the studies reviewed above only showed a 60-80% completion rate, with some as low as 30% (Olson & Sands, 2016). The ideal model in the future would include family and school-based interventions alongside these programs in order to achieve stronger results (Butler et al., 2008).

Conclusion

Although the field of pediatric cancer research has made tremendous strides in the past few decades, there is still much more to be done in the lives of these survivors. Now that the cognitive risks are well-established, researchers and practitioners alike are responsible for proactively working to counteract these cognitive effects before they take place, if at all possible. Ideally, this would mean identifying each individual's risk before the onset of treatment and taking necessary steps to either avoid perpetuation of these risk factors or to ameliorate the deficits at the earliest possible point. The ideal holistic approach for a child's cancer treatment should consider and work toward four components: 1) low morbidity due to the cancer and/or treatment; 2) lowest possible treatment-related neurotoxicity; 3) high efficacy of treatment and interventions following treatment; and 4) a high quality of life (QoL) following treatment termination. In an effort to achieve this, research in this field should continue to investigate various risk factors contributing to the late effects and pursue the implementation of efficacious and accessible interventions for the remediation of said effects in a time-sensitive manner.

References

ACS. (2019, February 12, 2019). Treatment of children with acute lymphocytic leukemia (ALL). Retrieved from https://www.cancer.org/cancer/leukemia-in-children/treating/children-with-all.html#written_by

Ahles, T. A., Saykin, A. J., Noll, W. W., Furstenberg, C. T., Guerin, S., Cole, B., & Mott, L. A. (2003). The relationship of APOE genotype to neuropsychological performance in long-term cancer survivors treated with standard dose chemotherapy. *Psychooncology, 12*(6), 612-619. doi:10.1002/pon.742

Alhowail, A. H., Bloemer, J., Majrashi, M., Pinky, P. D., Bhattacharya, S., Yongli, Z., . . . Suppiramaniam, V. (2019). Doxorubicin-induced neurotoxicity is associated with acute alterations in synaptic plasticity, apoptosis, and lipid peroxidation. *Toxicology Mechanisms and Methods, 29*(6), 457-466. doi:10.1080/15376516.2019.1600086

Anderson, F. S., & Kunin-Batson, A. S. (2009). Neurocognitive late effects of chemotherapy in children: The past 10 years of research on brain structure and function. *Pediatric Blood & Cancer, 52*(2), 159-164. doi:10.1002/pbc.21700

Benzing, V., Eggenberger, N., Spitzhüttl, J., Siegwart, V., Pastore-Wapp, M., Kiefer, C., . . . Leibundgut, K. (2018). The Brainfit study: Efficacy of cognitive training and exergaming in pediatric cancer survivors–a randomized controlled trial. *BMC Cancer, 18*(1), 18. doi:10.1186/s12885-017-3933-x

Blom, H. J., & Smulders, Y. (2011). Overview of homocysteine and folate metabolism. With special references to cardiovascular disease and neural tube defects. *Journal of Inherited Metabolic Disease, 34*(1), 75-81. doi:10.1007/s10545-010-9177-4

Buizer, A. I., de Sonneville, L. M., van den Heuvel-Eibrink, M. M., Njiokiktjien, C., & Veerman, A. J. (2005). Visuomotor control in survivors of childhood acute lymphoblastic leukemia treated with chemotherapy only. *Journal of International Neuropsychological Society, 11*(5), 554-565. doi:10.1017/s1355617705050666

Buizer, A. I., de Sonneville, L. M. J., & Veerman, A. J. P. (2009). Effects of chemotherapy on neurocognitive function in children with acute lymphoblastic leukemia: A critical review of the literature. *Pediatric Blood & Cancer, 52*(4), 447-454. doi:10.1002/pbc.21869

Butler, R. W., & Copeland, D. R. (2002). Attentional processes and their remediation in children treated for cancer: A literature review and the development of a therapeutic approach. *Journal of the International Neuropsychological Society, 8*(1), 115-124.

Butler, R. W., Copeland, D. R., Fairclough, D. L., Mulhern, R. K., Katz, E. R., Kazak, A. E., . . . Sahler, O. J. Z. (2008). A multicenter, randomized clinical trial of a cognitive remediation program for childhood survivors of a pediatric malignancy. *Journal of Consulting and Clinical Psychology, 76*(3), 367-378. doi:10.1037/0022-006X.76.3.367

Butler, R. W., & Mulhern, R. K. (2005). Neurocognitive interventions for children and adolescents surviving cancer. *Journal of Pediatric Psychology, 30*(1), 65-78. doi:10.1093/jpepsy/jsi017

Castellino, S. M., Ullrich, N. J., Whelen, M. J., & Lange, B. J. (2014). Developing interventions for cancer-related cognitive dysfunction in childhood cancer survivors. *Journal of the National Cancer Institute, 106*(8), dju186-dju186. doi:10.1093/jnci/dju186

Chaudhari, K., Reynolds, C. D., & Yang, S.-H. (2020). Metformin and cognition from the perspectives of sex, age, and disease. *GeroScience*. doi:10.1007/s11357-019-00146-3

Cheung, Y. T., & Krull, K. R. (2015). Neurocognitive outcomes in long-term survivors of childhood acute lymphoblastic leukemia treated on contemporary treatment protocols: A systematic review. *Neuroscience & Biobehavioral Reviews, 53*, 108-120. doi:https://doi.org/10.1016/j.neubiorev.2015.03.016

Cheung, Y. T., Sabin, N. D., Reddick, W. E., Bhojwani, D., Liu, W., Brinkman, T. M., . . . Krull, K. R. (2016). Leukoencephalopathy and long-term neurobehavioural, neurocognitive, and brain imaging outcomes in survivors of childhood acute lymphoblastic leukaemia treated with chemotherapy: A longitudinal analysis. *Lancet Haematology, 3*(10), e456-e466. doi:10.1016/s2352-3026(16)30110-7

Choi, K., Zhuang, H., Crain, B., & Doré, S. (2008). Expression and localization of prostaglandin transporter in Alzheimer disease brains and age-matched controls. *Journal of Neuroimmunology, 195*(1-2), 81-87. doi:10.1016/j.jneuroim.2008.01.014

Cole, P. D., Finkelstein, Y., Stevenson, K. E., Blonquist, T. M., Vijayanathan, V., Silverman, L. B., . . . Waber, D. P. (2015). Polymorphisms in genes related to oxidative stress are associated with inferior cognitive function after therapy for childhood acute lymphoblastic leukemia. *Journal of Clinical Oncology, 33*(19), 2205-2211. doi:10.1200/jco.2014.59.0273

Conklin, H. M., Ashford, J. M., Clark, K. N., Martin-Elbahesh, K., Hardy, K. K., Merchant, T. E., . . . Zhang, H. (2016). Long-term efficacy of computerized cognitive training among survivors of childhood cancer: A single-blind randomized controlled trial. *Journal of Pediatric Psychology, 42*(2), 220-231.

Conklin, H. M., Khan, R. B., Reddick, W. E., Helton, S., Brown, R., Howard, S. C., . . . Mulhern, R. K. (2007). Acute neurocognitive response to methylphenidate among survivors of childhood cancer: A randomized, double-blind, cross-over trial. *Journal of Pediatric Psychology, 32*(9), 1127-1139. doi:10.1093/jpepsy/jsm045

Conklin, H. M., Ogg, R. J., Ashford, J. M., Scoggins, M. A., Zou, P., Clark, K. N., . . . Zhang, H. (2015). Computerized cognitive training for amelioration of cognitive late effects among childhood cancer survivors: A randomized controlled trial. *Journal of Clinical Oncology, 33*(33), 3894-3902. doi:10.1200/jco.2015.61.6672

Correa, D. D., Kryza-Lacombe, M., Baser, R. E., Beal, K., & DeAngelis, L. M. (2016). Cognitive effects of donepezil therapy in patients with brain tumors: A pilot study. *Journal of Neuro-oncology, 127*(2), 313-319. doi:10.1007/s11060-015-2035-3

Davis, J., Ahlberg, F. M., Berk, M., Ashley, D. M., & Khasraw, M. (2013). Emerging pharmacotherapy for cancer patients with cognitive dysfunction. *BMC Neurology, 13*, 153-153. doi:10.1186/1471-2377-13-153

Farrell, S. M., Tunbridge, E. M., Braeutigam, S., & Harrison, P. J. (2012). COMT Val(158)Met genotype determines the direction of cognitive effects produced by catechol-O-methyltransferase inhibition. *Biological Psychiatry, 71*(6), 538-544. doi:10.1016/j.biopsych.2011.12.023

Federico, A., Morgillo, F., Tuccillo, C., Ciardiello, F., & Loguercio, C. (2007). Chronic inflammation and oxidative stress in human carcinogenesis. *International Journal of Cancer, 121*(11), 2381-2386. doi:10.1002/ijc.23192

Ferlazzo, N., Gorgone, G., Caccamo, D., Currò, M., Condello, S., Pisani, F., . . . Ientile, R. (2011). The 894G > T (Glu298Asp) variant in the endothelial NOS gene and MTHFR polymorphisms influence homocysteine levels in patients with cognitive decline. *NeuroMolecular Medicine, 13*(3), 167. doi:10.1007/s12017-011-8148-8

Frodl, T., Schaub, A., Banac, S., Charypar, M., Jäger, M., Kümmler, P., . . . Meisenzahl, E. M. (2006). Reduced hippocampal volume correlates with executive dysfunctioning in major depression. *Journal of Psychiatry & Neuroscience, 31*(5), 316-323.

Gaman, A. M., Uzoni, A., Popa-Wagner, A., Andrei, A., & Petcu, E.-B. (2016). The role of oxidative stress in etiopathogenesis of chemotherapy induced cognitive impairment (CICI)-"Chemobrain". *Aging and Disease, 7*(3), 307-317. doi:10.14336/AD.2015.1022

Goulden, N., Khusnulina, A., Davis, N. J., Bracewell, R. M., Bokde, A. L., McNulty, J. P., & Mullins, P. G. (2014). The salience network is responsible for switching between the default mode network and the central executive network: Replication from DCM. *NeuroImage, 99*, 180-190. doi:https://doi.org/10.1016/j.neuroimage.2014.05.052

Hardy, K. K., Willard, V. W., Allen, T. M., & Bonner, M. J. (2013). Working memory training in survivors of pediatric cancer: A randomized pilot study. *Psychooncology, 22*(8), 1856-1865. doi:10.1002/pon.3222

Ikonomidou, C. (2018). Chemotherapy and the pediatric brain. *Molecular and Cellular Pediatrics, 5*(1), 8-8. doi:10.1186/s40348-018-0087-0

Inaba, H., & Pui, C.-H. (2010). Glucocorticoid use in acute lymphoblastic leukaemia. *The Lancet. Oncology, 11*(11), 1096-1106. doi:10.1016/S1470-2045(10)70114-5

Jones, R. M., & Pattwell, S. S. (2019). Future considerations for pediatric cancer survivorship: Translational perspectives from developmental neuroscience. *Developmental Cognitive Neuroscience, 38,* 100657-100657. doi:10.1016/j.dcn.2019.100657

Kamdar, K. Y., Krull, K. R., El-Zein, R. A., Brouwers, P., Potter, B. S., Harris, L. L., . . . Okcu, M. F. (2011). Folate pathway polymorphisms predict deficits in attention and processing speed after childhood leukemia therapy. *Pediatric Blood & Cancer, 57*(3), 454-460. doi:10.1002/pbc.23162

Kesler, S. R., Lacayo, N. J., & Jo, B. (2011). A pilot study of an online cognitive rehabilitation program for executive function skills in children with cancer-related brain injury. *Brain Injury, 25*(1), 101-112. doi:10.3109/02699052.2010.536194

King, S., & Green, H. J. (2015). Psychological intervention for improving cognitive function in cancer survivors: A literature review and randomized controlled trial. *Frontiers in Oncology, 5*, 72-72. doi:10.3389/fonc.2015.00072

Krajinovic, M., Robaey, P., Chiasson, S., Lemieux-Blanchard, E., Rouillard, M., Primeau, M., . . . Moghrabi, A. (2005). Polymorphisms of genes controlling homocysteine levels and IQ score following the treatment for childhood ALL. *Pharmacogenomics, 6*(3), 293-302. doi:10.1517/14622416.6.3.293

Krull, K. R., Brinkman, T. M., Li, C., Armstrong, G. T., Ness, K. K., Srivastava, D. K., . . . Hudson, M. M. (2013). Neurocognitive outcomes decades after treatment for childhood acute lymphoblastic leukemia: A report from the St Jude lifetime cohort study. *Journal of Clinical Oncology, 31*(35), 4407-4415. doi:10.1200/JCO.2012.48.2315

Krull, K. R., Hardy, K. K., Kahalley, L. S., Schuitema, I., & Kesler, S. R. (2018). Neurocognitive outcomes and interventions in long-term survivors of childhood cancer. *Journal of Clinical Oncology, 36*(21), 2181-2189. doi:10.1200/JCO.2017.76.4696

Kuśmierek, M., Jasionowska, J., Maruszewska, P., Kalinka-Warzocha, E., Gałecki, P., Mikołajczyk, I., & Talarowska, M. (2020). The impact of cancer treatment on cognitive efficiency: Chemobrain–does it exist? *The European Journal of Psychiatry, 34*(1), 20-26. doi:https://doi.org/10.1016/j.ejpsy.2019.10.002

Lim, I., Joung, H.-Y., Yu, A. R., Shim, I., & Kim, J. S. (2016). PET evidence of the effect of donepezil on cognitive performance in an animal model of chemobrain. *BioMed Research International, 2016*, 6945415-6945415. doi:10.1155/2016/6945415

Mao-Ying, Q.-L., Kavelaars, A., Krukowski, K., Huo, X.-J., Zhou, W., Price, T. J., . . . Heijnen, C. J. (2014). The anti-diabetic drug metformin protects against chemotherapy-induced peripheral neuropathy in a mouse model. *PLoS One, 9*(6), e100701. doi:10.1371/journal.pone.0100701

Marinangeli, C., Didier, S., Ahmed, T., Caillerez, R., Domise, M., Laloux, C., . . . Vingtdeux, V. (2018). AMP-activated protein kinase is essential for the maintenance of energy levels during synaptic activation. *iScience, 9*, 1-13. doi:10.1016/j.isci.2018.10.006

Marusak, H. A., Iadipaolo, A. S., Harper, F. W., Elrahal, F., Taub, J. W., Goldberg, E., & Rabinak, C. A. (2018). Neurodevelopmental consequences of pediatric cancer and its treatment: Applying an early adversity framework to understanding cognitive, behavioral, and emotional outcomes. *Neuropsychology Review, 28*(2), 123-175. doi:10.1007/s11065-017-9365-1

McAllister, T. W., Ahles, T. A., Saykin, A. J., Ferguson, R. J., McDonald, B. C., Lewis, L. D., . . . Rhodes, C. H. (2004). Cognitive effects of cytotoxic cancer chemotherapy: Predisposing risk factors and potential treatments. *Current Psychiatry Reports, 6*(5), 364-371. doi:10.1007/s11920-004-0023-y

Mirko, S., Katja, J., Fabienne, E., Claudia, M. R., & Achim, C. (2015). Cognitively engaging chronic physical activity, but not aerobic exercise, affects executive functions in primary school children: A group-randomized controlled trial. *Journal of Sport and Exercise Psychology, 37*(6), 575-591. doi:10.1123/jsep.2015-0069

Moore, B. D., III. (2005). Neurocognitive outcomes in survivors of childhood cancer. *Journal of Pediatric Psychology, 30*(1), 51-63. doi:10.1093/jpepsy/jsi016

Moudi, M., Go, R., Yien, C. Y. S., & Nazre, M. (2013). Vinca alkaloids. *International Journal of Preventive Medicine, 4*(11), 1231-1235.

Mulhern, R. K., Khan, R. B., Kaplan, S., Helton, S., Christensen, R., Bonner, M., . . . Reddick, W. E. (2004). Short-term efficacy of methylphenidate: A randomized, double-blind, placebo-controlled trial among survivors of childhood cancer. *Journal of Clinical Oncology, 22*(23), 4795-4803. doi:10.1200/jco.2004.04.128

Olsen, N. J., Spurlock, C. F., 3rd, & Aune, T. M. (2014). Methotrexate induces production of IL-1 and IL-6 in the monocytic cell line U937. *Arthritis Research & Therapy, 16*(1), R17-R17. doi:10.1186/ar4444

Olson, K., & Sands, S. A. (2016). Cognitive training programs for childhood cancer patients and survivors: A critical review and future directions. *Child Neuropsychology, 22*(5), 509-536. doi:10.1080/09297049.2015.1049941

Österlundh, G., Kjellmer, I., Lannering, B., Rosengren, L., Nilsson, U. A., & Márky, I. (2008). Neurochemical markers of brain damage in cerebrospinal fluid during induction treatment of acute lymphoblastic leukemia in children. *Pediatric Blood & Cancer, 50*(4), 793-798. doi:10.1002/pbc.21378

Reddick, W. E., Shan, Z. Y., Glass, J. O., Helton, S., Xiong, X., Wu, S., . . . Mulhern, R. K. (2006). Smaller white-matter volumes are associated with larger deficits in attention and learning among long-term survivors of acute lymphoblastic leukemia. *Cancer, 106*(4), 941-949. doi:10.1002/cncr.21679

Röth, E., Marczin, N., Balatonyi, B., Ghosh, S., Kovács, V., Alotti, N., . . . Gasz, B. (2011). Effect of a glutathione S-transferase inhibitor on oxidative stress and ischemia-reperfusion-induced apoptotic signalling of cultured cardiomyocytes. *Experimental and Clinical Cardiology, 16*(3), 92-96.

Schmithorst, V. J., Holland, S. K., & Dardzinski, B. J. (2008). Developmental differences in white matter architecture between boys and girls. *Human Brain Mapping, 29*(6), 696-710. doi:10.1002/hbm.20431

Seigers, R., & Fardell, J. E. (2011). Neurobiological basis of chemotherapy-induced cognitive impairment: A review of rodent research. *Neuroscience & Biobehavioral Reviews, 35*(3), 729-741. doi:https://doi.org/10.1016/j.neubiorev.2010.09.006

Seigers, R., Timmermans, J., Horn, H., de Vries, E., Dierckx, R., Visser, L., . . . Buwalda, B. (2009). Methotrexate reduces hippocampal blood vessel density and activates microglia in rats but does not elevate central cytokine release. *Behavioural Brain Research, 207*, 265-272. doi:10.1016/j.bbr.2009.10.009

Shuper, A., Stark, B., Kornreich, L., Cohen, I. J., Avrahami, G., & Yaniv, I. (2002). Methotrexate-related neurotoxicity in the treatment of childhood acute lymphoblastic leukemia. *The Israel Medical Association Journal, 4*(11), 1050-1053.

Simó, M., Rifà-Ros, X., Rodriguez-Fornells, A., & Bruna, J. (2013). Chemobrain: A systematic review of structural and functional neuroimaging studies. *Neuroscience & Biobehavioral Reviews, 37*(8), 1311-1321. doi:https://doi.org/10.1016/j.neubiorev.2013.04.015

Small, B. J., Rosnick, C. B., Fratiglioni, L., & Bäckman, L. (2004). Apolipoprotein e and cognitive performance: A meta-analysis. *Psychology and Aging, 19*(4), 592-600. doi:10.1037/0882-7974.19.4.592

Thomason, M. E., Yoo, D. J., Glover, G. H., & Gotlib, I. H. (2009). BDNF genotype modulates resting functional connectivity in children. *Frontiers in Human Neuroscience, 3*, 55-55. doi:10.3389/neuro.09.055.2009

Thompson, A. L., Christiansen, H. L., Elam, M., Hoag, J., Irwin, M. K., Pao, M., . . . Kelly, K. P. (2015). Academic continuity and school reentry support as a standard of care in pediatric oncology. *Pediatric Blood & Cancer, 62*(S5), S805-S817. doi:10.1002/pbc.25760

Thorn, C. F., Oshiro, C., Marsh, S., Hernandez-Boussard, T., McLeod, H., Klein, T. E., & Altman, R. B. (2011). Doxorubicin pathways: Pharmacodynamics and adverse effects. *Pharmacogenetics and Genomics, 21*(7), 440-446. doi:10.1097/FPC.0b013e32833ffb56

van Assema, D. M. E., Lubberink, M., Rizzu, P., van Swieten, J. C., Schuit, R. C., Eriksson, J., . . . van Berckel, B. N. M. (2012). Blood–brain barrier P-glycoprotein function in healthy subjects and Alzheimer's disease patients: Effect of polymorphisms in the ABCB1 gene. *European Journal of Nuclear Medicine and Molecular Imaging Research, 2*(1), 57. doi:10.1186/2191-219X-2-57

Wang, L., Jhee, K.-H., Hua, X., DiBello, P. M., Jacobsen, D. W., & Kruger, W. D. (2004). Modulation of cystathionine β-synthase level regulates total serum homocysteine in mice. *Circulation Research, 94*(10), 1318-1324. doi:doi:10.1161/01.RES.0000129182.46440.4a

Wardill, H. R., Mander, K. A., Van Sebille, Y. Z. A., Gibson, R. J., Logan, R. M., Bowen, J. M., & Sonis, S. T. (2016). Cytokine-mediated blood brain barrier disruption as a conduit for cancer/chemotherapy-associated neurotoxicity and cognitive dysfunction. *International Journal of Cancer, 139*(12), 2635-2645. doi:10.1002/ijc.30252

Welfare, M., Adeokun, A.M., Bassendine, M.F., & Daly, A.K. (1999). Polymorphisms in GSTP1, GSTM1, and GSTT1 and susceptibility to colorectal cancer. *Cancer Epidemiology, Biomarkers & Prevention 8*(4), 289-292.

Winocur, G., Binns, M. A., & Tannock, I. (2011). Donepezil reduces cognitive impairment associated with anti-cancer drugs in a mouse model. *Neuropharmacology, 61*(8), 1222-1228. doi:https://doi.org/10.1016/j.neuropharm.2011.07.013

Yanar, K., Çakatay, U., Aydın, S., Verim, A., Atukeren, P., Özkan, N. E., . . . Yaylım, İ. (2016). Relation between endothelial nitric oxide synthase genotypes and oxidative stress markers in larynx cancer. *Oxidative Medicine and Cellular Longevity, 2016*, 4985063-4985063. doi:10.1155/2016/4985063

Yang, M., Kim, J.-S., Song, M.-S., Kim, S.-H., Kang, S. S., Bae, C.-S., . . . Moon, C. (2010). Cyclophosphamide impairs hippocampus-dependent learning and memory in adult mice: Possible involvement of hippocampal neurogenesis in chemotherapy-induced memory deficits. *Neurobiology of Learning and Memory, 93*(4), 487-494. doi:https://doi.org/10.1016/j.nlm.2010.01.006

Zeller, B., Tamnes, C. K., Kanellopoulos, A., Amlien, I. K., Andersson, S., Due-Tønnessen, P., . . . Ruud, E. (2013). Reduced neuroanatomic volumes in long-term survivors of childhood acute lymphoblastic leukemia. *Journal of Clinical Oncology, 31*(17), 2078-2085. doi:10.1200/jco.2012.47.4031

Zhou, W., Kavelaars, A., & Heijnen, C. J. (2016). Metformin prevents cisplatin-induced cognitive impairment and brain damage in mice. *PLoS One, 11*(3), e0151890-e0151890. doi:10.1371/journal.pone.0151890