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RESEARCH ARTICLE

Neurocognitive Late Effects of Chemotherapy in Survivors of Acute Lymphoblastic Leukemia: Focus on Methotrexate

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Abstract

Childhood cancer survivors frequently experience long-lasting consequences of chemotherapy on health outcomes. Neurocognitive late effects of chemotherapy occur in 40 – 60% of acute lymphoblastic leukemia (ALL) survivors. These deficits affect mental health, school performance, job success, and are associated with poor quality of life, therefore presenting a clinical challenge for psychiatrists. However, not all cancer survivors are impacted by treatment in the same manner and emerging evidence suggests that genetic variation may modulate neurocognitive outcomes. Much like other complex psychopathologies, neurocognitive deficits in cancer survivors are the result of complex interactions between genetic and environmental variables. This review describes adverse neurocognitive outcomes observed in survivors of acute lymphoblastic leukemia (ALL) and discusses genetic variability in biochemical pathways targeted by chemotherapeutic agents as a possible mechanism contributing to psychopathology in ALL survivors.

Key Words: *acute lymphoblastic leukemia, chemotherapy, genetic variants, neurocognitive late effects, one-carbon metabolism*

Résumé

Les survivants d'un cancer pédiatrique éprouvent souvent des conséquences durables de la chimiothérapie sur leurs résultats de santé. Les effets tardifs neurocognitifs de la chimiothérapie surviennent chez 40% à 60% des survivants de la leucémie lymphoblastique aiguë (LLA). Ces déficits touchent la santé mentale, le rendement scolaire, la réussite professionnelle et sont associés à une piètre qualité de vie, et présentent donc un défi clinique pour les psychiatres. Cependant, les survivants du cancer ne sont pas tous affectés de la même manière par le traitement et de nouvelles données probantes suggèrent que la variation génétique puisse moduler les résultats neurocognitifs. À l'instar d'autres psychopathologies complexes, les déficits neurocognitifs chez les survivants du cancer sont le résultat d'interactions complexes entre les variables génétiques et environnementales. Cette revue décrit les résultats neurocognitifs indésirables observés chez les survivants de la leucémie lymphoblastique aiguë (LLA) et discute de la variabilité génétique des trajectoires biochimiques ciblées par les agents chimiothérapeutiques comme mécanisme possible contribuant à la psychopathologie chez les survivants de la LLA.

Mots clés: *leucémie lymphoblastique aiguë, chimiothérapie, variants génétiques, effets tardifs neurocognitifs, métabolisme des monocarbones*

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Introduction

Cancer survivors, late effects, and the field of psychiatry

Prior to the 1960s, treatment effects beyond survival was of little concern due to the high mortality rate of children with childhood cancer (Moleski, 2000). There are about 10,000 children living with cancer in Canada today (Childhood Cancer Canada, 2011). Fortunately, close to 80% of these children will survive five years or more (Childhood Cancer Canada, 2011), meaning that there are more childhood cancer survivors today than ever before. It has become clear that many of these survivors experience long-term health consequences that negatively impact school performance, employment potential, and overall mental health (Kirchhoff et al., 2010; Kunin-Batson, Kadan-Lottick, & Neglia, 2014; Oeffinger et al., 2006). These adverse effects were initially attributed to the psychological trauma of the disease and treatment, arising from factors such as facing a life-threatening disease, long-term hospitalization or arduous out-patient treatment, and treatment-related separation from family and friends (Kellerman, 1980; Koocher & O'Malley, 1981). Although these factors likely play a role, cancer therapies themselves are now known to have significant, long-term consequences (Brouwers, 2005). Besides health problems such as cardiac impairments, deficits in executive function are common in childhood cancer survivors (Nathan et al., 2007; Peterson et al., 2008). These cognitive deficits have a negative impact on the quality of life of cancer survivors (Kunin-Batson et al., 2014).

Cancer is but one example of medical conditions in which advances in treatment have resulted in improved survival, but also increased mental illness and treatment-related morbidity, presenting the field of psychiatry with new challenges (Cleeland et al., 2012). Other examples include survivors of traumatic brain injury (Fann, Katon, Uomoto, & Esselman, 1995; Max et al., 2011), or individuals who were born very prematurely (Burnett et al., 2013). In addition to its clinical significance, cancer treatment is unique in the way that it is a well-documented intervention that can be manipulated, and has a predictable impact on biological systems. Examining neurocognitive outcomes in cancer survivors provides a window that could inform the field of psychiatry about gene by environmental interactions that contribute to complex psychopathology. As such, research on treatment-related late effects opens up new opportunities for collaborative care and research.

We will illustrate this with acute lymphoblastic leukemia (ALL), which accounts for nearly 25% of all childhood cancers diagnosed before the age of 15 (National Cancer Institute, 2014; Surveillance, Epimiology, and End Results (SEER) Program Research Data 1975 - 2005, 2014). The incidence of childhood ALL peaks among children between two to seven years of age (Canadian Cancer Statistics, 2014; National Cancer Institute, 2014; Statistics for childhood leukemia, 2013; Surveillance, Epimiology, and End Results (SEER) Program Research Data 1975 - 2005, 2014), a time of major changes in the developing brain (O'Muircheartaigh et al., 2014). Neurocognitive problems are common in ALL survivors (Peterson et al., 2008) and may be explained by treatment-related damage to normal brain tissue during early developmental stages.

Treatment of acute lymphoblastic leukemia

ALL develops as a clonal proliferation of lymphoid precursors in the bone marrow and eventually results in impairment of normal blood cell production and life-threatening organ infiltration by leukemic cells. Approximately 90% of ALL patients are successfully treated, which is the highest percentage amongst childhood cancers (Childhood Cancer Canada, 2011).

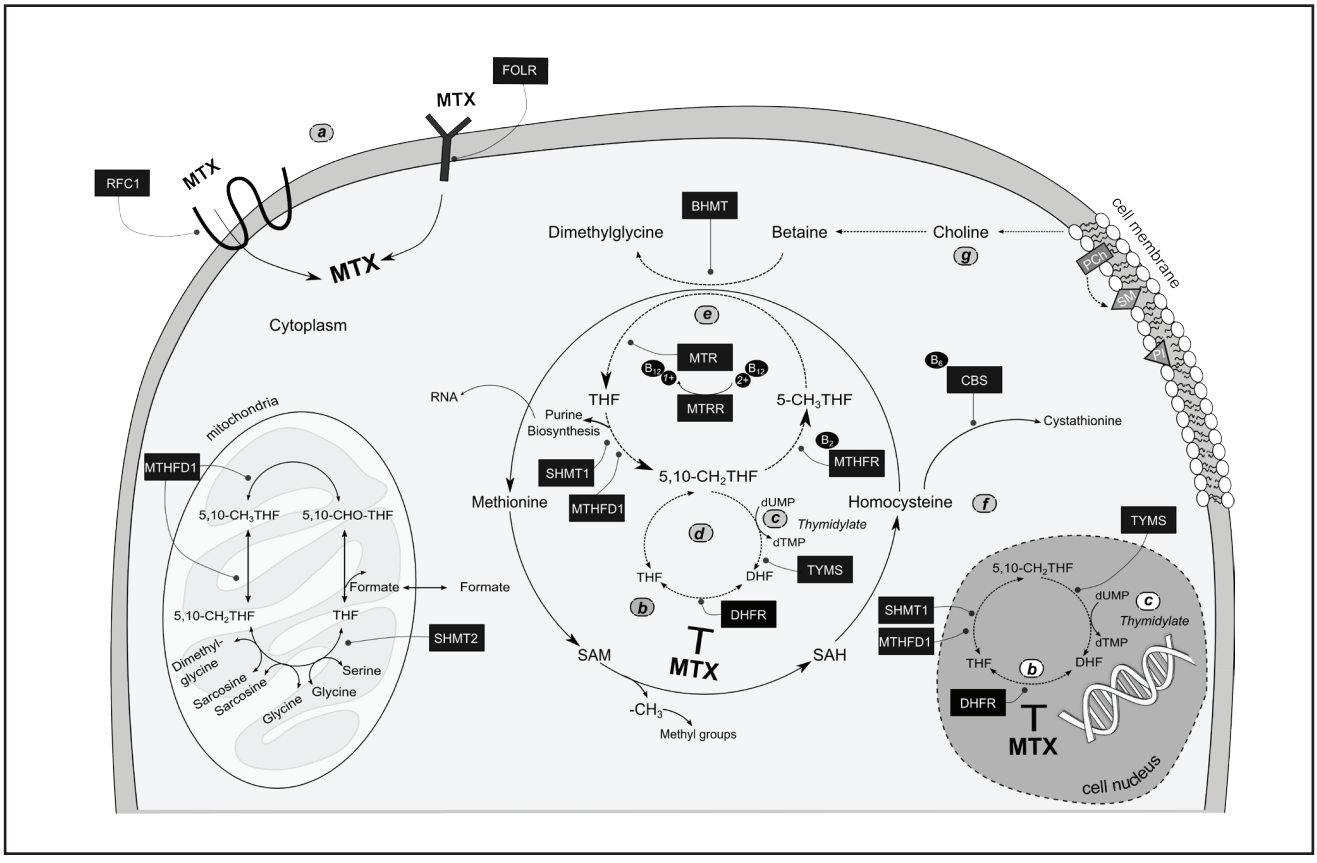
Contemporary treatment of ALL includes a cocktail of chemotherapy agents including glucocorticoids, vincristine, L-asparaginase, anthracyclines and methotrexate (MTX). While chemotherapy is considered less harmful than prophylactic cranial radiation which is still used in a small portion of ALL patients (Geenen et al., 2007; Pui et al., 2009; Spiegler et al., 2006), the impact is not benign (Moleski, 2000). Eradication of leukemic cells requires high doses of chemotherapy agents particularly during the initial treatment phases, including direct administration of MTX to the central nervous system (CNS) via intrathecal injection into the cerebrospinal fluid (CSF) space by lumbar puncture to target cells behind the blood brain barrier (Kwong, Yeung, & Chan, 2009; Pui, Robison, & Look, 2008). Treatment typically starts with an induction phase, the goal of which is to eradicate more than 99% of leukemic cells. The key agents are glucocorticoids, vincristine, and asparaginase and/or anthracycline. The induction phase is followed by consolidation therapy and treatment elements containing high doses of MTX to eradicate residual leukemic cells. The final and longest phase is the continuation or maintenance phase, during which patients mainly receive intrathecal and oral doses of MTX treatment as well as oral mercaptopurine for up to 2.5 years to three years.

Various components of modern multi-agent treatments such as glucocorticosteroids and MTX, may be associated with neurocognitive late effects (Waber et al., 2000). Much attention has focused on MTX, which remains a key agents of ALL treatment since its introduction in the 1950s (Chabner & Roberts, 2005; Simone, 2006). MTX is considered a major culprit in neurocognitive late effects, in part because ALL patients experience chronic exposure to MTX administered via various routes (oral, intravenous, intrathecal), and because of its impact on metabolic pathways that govern essential biochemical processes. Most of the work on the impact of genetic risk factors on neurocognitive impairments in ALL survivors has focused on variants that impact the pharmacodynamics of MTX (Kamdar et al., 2011; Krull

Figure 1. One-carbon metabolism and methotrexate

MTX enters the cell via the reduced folate carrier (RFC[1]) by using an endocytic pathway activated by a folate receptor (FOLR [α, γ]) (a) (Chabner & Roberts, 2005; Zhao, Matherly, & Goldman, 2009). MTX inhibits the enzyme dihydrofolate reductase (DHFR), blocking the the conversion of dihydrofolate (DHF) to tetrahydrofolate (THF), both in nuclear and cytoplasmic OCM (b). The resulting reduction of thymidylate synthesis leads to inhibited DNA synthesis and consequenty limits cancer cell proliferation (c). MTX-induced depletion of THF pools blocks the main pathway to remethylate homocysteine to methionine (e), which could result in an excess of homocysteine (f). To compensate for a loss in folate, a choline-dependent scavenger pathway (g) may be recruited to release the required methyl groups to regenerate SAM. Choline is usually anchored in the cell membrane in the form of phosphatidylcholine (PCh) and phosphatidynisitol (PI). The release of choline from the membrane to support methylation reactions may reduce the amount of phospholipids such as sphingomeylin (SM).

One-carbon metabolism requires a number of enzymes (black boxes), including dihydrofolate reductase (DHFR), serine hydroxymethyltransferase (SHMT1 and 2), methylenetetrahydrofolate dehydrogenase (MTHFD1), methylenetetrahydrofolate reductase (MTHFR), methionine synthase reductase (MTRR), methionine synthase (MTR), cystathionine beta synthase (CBS), thymidylate synthetase (TYMS), and betaine-homocysteine S-methyltransferase (BHMT). The black ovals labeled B2/6/12 refer to B vitamins. The reductive regeneration of B12 cofactor is essential for maintaining MTR in a functional state (GeneCards, 2014).



SAH =S-adenosylhomocysteine; CH2-THF = 5,10-Methylenetetrahydrofolate; 5-CH3-THF = 5-methyltetrahydrofolate (5-MTHF);
(Figure adapted from: Chabner & Roberts, 2005; Fox & Stover, 2008; Fredriksen et al., 2007; Steinfeld et al., 2009; Stover & Field, 2011).

et al., 2008), making this agent particularly relevant for the purposes of this review. We will limit our discussion to the direct impact of chemotherapy on brain development, but it should be noted that cognitive impairments could also be secondary to cerebrovascular changes induced by cardiotoxicity, which is a well-established adverse effect of chemotherapy as well (Ahles & Saykin, 2007).

Figure 1 depicts the impact of MTX on a cell's metabolic function. Essentially, MTX depletes folate pools thereby reducing thymidylate synthesis. Ultimately, DNA synthesis is inhibited with limits cancer cell proliferation (Chabner & Roberts, 2005). Cancer cells exhibit differential metabolic requirements compared to normal cells, making them a target for therapeutic agents like MTX. Unfortunately, collateral damage to normally proliferating cells appears as of yet unavoidable (Chabner & Roberts, 2005; Vander Heiden, 2011). To avoid acute MTX toxicity, folic acid analog leucovorin is administered after high-dose MTX administration (Pui et al., 2008).

Impaired executive functions in ALL survivors

It is estimated that between 40 and 60% of ALL survivors treated with chemotherapy experience some form of neurocognitive deficits (Moleski, 2000). Functional impairments in ALL survivors are predominantly found in executive

function (EF) (Montour-Proulx et al., 2005; Peterson et al., 2008; Reddick et al., 2014). A review by Diamond (2013) lists three core EFs, including: 1) inhibition, which involves resistance on acting on impulses or prematurely; 2) working memory, which pertains to actively holding and manipulating information in mind; and, 3) cognitive flexibility, which includes effectively switching between tasks (Anderson, 2002). Inhibition allows for selectively attending to the task at hand (Diamond, 2013), and is impaired across various neurodevelopmental disorders including attention/deficit hyperactivity disorder (ADHD) (Lipszyc & Schachar, 2010). Impairments in inhibitory control, sustained attention and display of behavioral symptoms of ADHD have been reported in ALL survivors treated with chemotherapy (Conklin et al., 2012; Krull et al., 2013; Peterson et al., 2008; Winick, 2011). ALL survivors also show deficits in working memory, particularly as evidenced by the backward digit span of the Wechsler intelligence scale (Ashford et al., 2010; Montour-Proulx et al., 2005; Peterson et al., 2008; Winick, 2011), and poor cognitive flexibility, as measured by paradigms that require an adaptation to a sudden change in response rules (Buizer, de Sonneville, van den Heuvel-Eibrink, & Veerman, 2005; Carey et al., 2008).

Deficits in EFs affect daily function and are associated with mental disorders like ADHD and obsessive compulsive disorder, poor physical health such as obesity, and lower school and job success (Anderson, 2002; Diamond, 2013), posing a risk for reduced quality of life in ALL survivors (Kunin-Batson et al., 2014).

Brain abnormalities in ALL survivors

Complex cognitive processes like EFs require coordinated neural activity (Deprez, Billiet, Sunaert, & Leemans, 2013). White matter (WM), which consists of glial cells and axon tracts insulated by myelin sheaths, enables speedy transfer and integration of information throughout the brain (O'Muircheartaigh et al., 2014). EFs are impaired in individuals with traumatic brain injury affecting WM, and in individuals with de-myelination disorders (Ghajar & Ivry, 2008; Wozniak & Lim, 2006). WM appears to be particularly vulnerable to the impact of chemotherapy agents (Cole & Kamen, 2006; Reddick et al., 2014).

Up to 80% of ALL patients treated with chemotherapy develop chronic or transient lesions in the deep WM identified on magnetic resonance imaging (MRI) as hyper-intensities (leukoencephalopathy) (Bhojwani et al., 2014; Reddick, Glass, Helton, Langston, Li, & Pui, 2005; Reddick, Glass, Helton, Langston, Xiong, et al., 2005; Vázquez et al., 2011). One neuroimaging study in a large cohort of childhood cancer survivors also found evidence of reduced WM volume in ALL survivors compared to healthy siblings, and these reductions in WM were significantly correlated with worse performance on measures of attention, intellect, and academic achievement (Reddick et al., 2014). Development of WM tracts have also found to be altered in ALL survivors (Aukema et al., 2009; Khong et al., 2006), and there is some evidence suggestive of de-myelination in ALL patients shortly after completing chemotherapy treatment (Yamamoto et al., 2006). In contrast, the evidence so far suggests that gray matter does not appear as sensitive to chemotherapy-induced damage (Reddick et al., 2014).

ALL survivors who were younger at the time of treatment suffer more serious cognitive impairment (Buizer, de Sonneville, & Veerman, 2009; Cole & Kamen, 2006). The same age-dependent relationship is apparent in children who sustained traumatic brain injury (Anderson, Catroppa, Morse, Haritou, & Rosenfeld, 2005). Likewise, regions in the brain that are more immature at time of treatment, e.g., the frontal lobes, may be more sensitive to chemotherapy-related damage than regions that are more mature (Carey et al., 2008; Ciesielski, Lesnik, Benzel, Hart, & Sanders, 1999; Deprez et al., 2013; Reddick & Conklin, 2010). Brain regions with protracted developmental trajectories often support complex cognive functions (Anderson, 2002; Casey, Tottenham, Liston, & Durston, 2005), which may explain findings of impairments in EFs in ALL survivors. Supporting this view, a functional neuroimaging study showed that ALL survivors recruited a greater, compensatory energy supply to regions in the frontal lobes while working on a complex cognitive task, compared to healthy peers (Robinson et al., 2010).

Why does MTX cause brain damage?

Brain abnormalities observed in ALL survivors are likely linked to the pharmacodynamics of chemotherapeutic agents (Krull et al., 2013). MTX depletes folate pools, thereby inhibiting a major constituent of one-carbon metabolism (OCM). OCM occurs in three cellular compartments, including the cytoplasm, mitochondria and nucleus (see Figure 1) (Fox & Stover, 2008; Stover & Field, 2011). Cytoplasmic OCM produces the cofactor and methyl group donor S-adenosylmethionine (SAM) (Fox & Stover, 2008). Methyl groups are essential for numerous methylation reactions such as the methylation of neurotransmitters, proteins (including histones), phospholipids, and cytosine bases in DNA (Chiang et al., 1996; Crider, Yang, Berry, & Bailey, 2012; Stover & Field, 2011). After releasing methyl groups, SAM is converted to S-adenosylhomocysteine (SAH). OCM processes are critically dependent on the production of tetrahydrofolate (THF), and associated 5,10-Methylenetetrahydrofolate (5, 10-CH2-THF) and 5-methyltetrahydrofolate (5-CH3-THF) (Fox & Stover, 2008; Stover & Field, 2011). Alterations in OCM are associated with a number of psychiatric disorders such as depression and schizophrenia and developmental anomalies such as orofacial clefts (Fox & Stover, 2008; Peter & Akbarian, 2011). Although the administration of leucovorin may ameloriate acute MTX neurotoxicity (Winick et al., 1992), its impact on the development of chronic neurocognitive deficits, if any, is poorly

understood (Cole & Kamen, 2006; Vijayanathan, Gulinello, Ali, & Cole, 2011).

OCM depends upon tightly controlled networks of interdependent biosynthetic pathways. Disruption of an essential cofactor such as folate not only alters methyl group availability, but may also trigger a cascade of disruptive events (Crider et al., 2012; Fox & Stover, 2008). For instance, depletion of folate could lead to an excess of homocysteine (hyperhomocysteinemia), which is toxic to cells and increases the risk for vascular abnormalities and stroke (see Figure 1) (Cole & Kamen, 2006; Krull et al., 2013; Li, Vijayanathan, Gulinello, & Cole, 2010a; 2010b). This could, at least in part, be responsible for the reported brain abnormalities in ALL survivors. Chemotherapy-induced damage may also be related to recruitment of alternative one-carbon sources such as choline and betaine to compensate for a loss in folate (see Figure 1). Choline supports phospholipids which constitute the major components of white matter and gray matter. Without them myelin formation and stability is disrupted (Laule et al., 2007; Scott & Weir, 1998; Steinfeld et al., 2009). Choline is particularly in high demand during early childhood to support dynamic changes in myelination (Steinfeld et al., 2009). Interruption of these coordinated processes is likely to be associated with lasting neurodevelopmental impairments (O'Muircheartaigh et al., 2014).

Why are ALL patients differentially affected by chemotherapy treatment?

A puzzling observation with regard to neurocognitive impairments in ALL survivors is that not all survivors are impacted by chemotherapy agents in the same manner, raising interest in the understanding of the potential sources of this variation. Differential outcomes may at least in part be caused by genetic variation that affects the metabolism or pharmacodynamics of MTX (Krull et al., 2008; 2013; Winick, 2011).

One example is 5, 10-methylenetetrahydrofolate reductase (MTHFR), which encodes the protein that catalyzes the conversion of methylenethetrahydrofolate to methytetrahydrofolate (see Figure 1) (Fox & Stover, 2008; GeneCards, 2014). Approximately 40% of individuals of European ancestry carry a C to T substitution at nucleotide 677 (rs1801133) on one allele, and approximately 10% carry this substitution on both alleles (Hessner et al., 1999; Schneider, Rees, Liu, & Clegg, 1998). Homozygous carriers are characterized by reductions in enzymatic activity resulting in mild hyperhomocysteinemia and decreased plasma and red cell folate levels (Fox & Stover, 2008). This may be innocuous under normal circumstances, but may result in increased sensitivity upon exposure to chemotherapeutic agents such as MTX. Krull and colleagues (2008) demonstrated that MTHFR variants (C677T and A1298C [rs1801131]) are associated with an increased likelihood of inattention problems following chemotherapy. Other polymorphisms of genes involved in OCM, such as methionine synthase (A2756G; rs1805087) and thymidylate synthase (1494del6; rs34489327) (see Figure 1), also increase the risk of functional impairments in ALL survivors (Kamdar et al., 2011; Krull et al., 2013). In other words, chemotherapeutic agents may have a differential impact on neurocognitive outcomes due to underlying genetic variation.

While OCM polymorphisms are a reasonable starting point to examine interactions between genes and environment contributing to neurocognitive outcomes, predispositions independent from chemotherapeutic agents may also play a role. To illustrate, Krull and colleagues (2013) found that variation in a gene encoding the lipid transport molecule (apoliopoprotein E) was associated with more attention problems in ALL survivors.

Summary and Future Directions

A growing number of cancer survivors experience serious long-term neurocognitive consequences from the treatment that saved their lives. The use of chemotherapy agents in standard care for ALL instead of cranial irradiation has proven to be beneficial in terms of long-term outcomes, although even contemporary treatments are not without consequences. This has obvious clinical significance for psychiatrists, as cancer survivors are at risk of developing an additional disorder that may require mental care. Complex psychopathology is often the result of many genes with relatively small effect, making it difficult to pinpoint the specific genetic susceptibility directly related to certain impairments (Manuck & McCaffery, 2014). Research in cancer-therapy induced neurocognitive impairments offers the opportunity of examining pathological phenomena caused by defined neurotoxic events (Cleeland et al., 2012). As such, cancer survivors provide a model for gene by environmental interactions that could inform the field of psychiatry about possible candidate risk genes or pathways contributing to relevant traits for psychiatric diseases.

We are only beginning understand the complexity of psychopathology in cancer survivors and this review highlighted some of the contributing factors only. We focused on the impact of MTX, which is a key agent used to treat ALL. However, other therapeutic agents such as glucocorticoids, likely also play a role in neurocognitive impairments. Interindividual variation that could increase the risk of neurocognitive impairments were highlighted, such as younger age at treatment and genetic variation that affect OCM, although it should be noted that other individual factors (e.g., diet or environment) may also be involved. Emerging research indicates that genetic variants may account for individual differences in neurocognitive outcomes in ALL survivors, which may indicate that treatment could be tailored to the genotype of patients to minimize or prevent long-term adverse effects. In order to optimize such individualized treatments we need to discern the impact of various factors that could contribute to psychopathology after

chemotherapy, including genetic variation, age, and dose of MTX for example. Animal models are ideally suited for this: not only do animal model allow for systematic evaluation and manipulation of possible risk factors, there are also a multitude of mouse models available with relevant genetic mutations that would allow for detailed investigation of the role of genetic variation. The use of neuroimaging provides a link between animal results and human clinical data (Gazdzinski et al., 2012). The ultimate aim of this work is to improve public health in Canada by pointing to modified cancer treatments that reduce the burden of long-term care, while simultaneously improving personal health outcomes of cancer survivors.

Acknowledgements/Conflicts of Interest

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