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Neurocognitive Outcomes in Long-term Survivors of Childhood Acute Lymphoblastic Leukemia Treated on Contemporary Treatment Protocols: A Systematic Review

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Abstract

The intensified administration of chemotherapeutic drugs has gradually replaced cranial radiation therapy (CRT) for the treatment of childhood acute lymphoblastic leukemia (ALL). While CRT is often implicated in neurocognitive impairment in ALL survivors, there is a paucity of literature that evaluates the persistence of neurocognitive deficits in long-term survivors of pediatric ALL who were treated with contemporary chemotherapy-only protocols. Results from this systematic review concurred to the probable cognitive-sparing effect of chemotherapy-based protocols over CRT in long-term survivors. However, coupled with multiple intrinsic and extrinsic factors, survivors who received chemotherapy treatment still suffered from apparent cognitive impairment, particularly in the attention and executive function domains. Notably, there is evidence to suggest that the late neurotoxic effect of methotrexate on survivors' neurocognitive performance may be dose-related. This review also recommends future pharmacokinetic, neuroimaging and genetic studies to illuminate the multifactorial nature of this subject matter and discusses the potential value of neurochemical, physiological, inflammatory and genetic markers for the prediction of susceptibility to neurocognitive impairment in long-term survivors of childhood ALL.

Keywords

Acute lymphoblastic leukemia; cancer survivorship; chemotherapy; neurocognitive; pediatric cancer

1. Introduction

Acute lymphoblastic leukemia (ALL) is the most prevalent cancer of childhood and accounts for 26.8% of cancer diagnoses among children worldwide.(Kaatsch,2010) The historical use of cranial radiation therapy (CRT), followed by intensive chemotherapy

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treatment of the central nervous system, has resulted in a 5-year-event-free survival rate of approximately 80% in standard-risk ALL.(Gaynon et al.,2010) However, it is widely reported that these ALL survivors often suffer from long-term neurocognitive deficits that have a negative impact on their health-related quality of life (HRQoL) and daily functioning. (Speechley et al.,2006; Huang et al.,2013)

There has been a paradigm shift in the treatment strategy for ALL over the past two decades. (Simone,2006) Although initial success was obtained with prophylactic CRT, this approach was gradually replaced by contemporary ALL therapeutic protocols, which consist of intensified intravenous and intrathecal administration of chemotherapeutic drugs for standard risk patients.(Pui et al.,2004; Simone,2006; Pui et al.,2009) A recent clinical trial reported that with the elimination of CRT, chemotherapy-only treatment protocols for ALL have resulted in an unprecedented overall survival rate of 93.5%.(Pui et al.,2009) Despite these promising results, patients who received contemporary treatments still experience a myriad of treatment-related adverse effects, such as osteonecrosis and cardiovascular and endocrine morbidity.(Pui et al.,2009; Essig et al.,2014)

This systematic review focuses on neurocognitive outcomes associated with contemporary ALL protocols. Notably, patients treated on chemotherapy-only protocols are reported to display lower performance on direct measures of attention and processing speed by the end of therapy.(Conklin et al.,2012) The frequency of these problems appear to be associated with age at diagnosis and gender of the child.(Krappmann et al.,2007) Thus, existing studies have established that even with the omission of CRT, ALL patients do suffer from mild but evident cognitive changes during active chemotherapy treatment.

Despite these reported problems, there is a paucity of studies that explore the long-term persistence of neurocognitive problems associated with contemporary ALL protocols. In this review, long-term survivors are defined as patients who have survived 5 or more years since the diagnosis of ALL, or more than 2 years from the cessation of treatment.(Landier et al., 2004; Feig et al.,2009) The majority of the survivorship research has focused on the delayed cognitive outcomes of CRT-based regimens, with robust studies of chemotherapy-only regimens clearly lacking. A recent study evaluated the late effects of chemotherapy in 556 CRT-naïve long-term ALL survivors who were treated more than 10 years prior to symptom assessment, selecting patients identified as low-risk on older therapeutic protocols.(Essig et al.,2014) ALL survivors reported poorer overall functional status, even though their perceived neurocognitive deficits and mental health status did not differ from a matched non-cancer population.(Essig et al.,2014) More clinical studies are needed to answer the question of whether contemporary protocols do preserve ALL survivors' neurocognitive function and are less likely to elicit adverse cognitive and behavioral late-effects.

In view of the limited literature on this subject, the objective of this systematic review is to gather current evidence on the persistence of neurocognitive late-effects of chemotherapy-only, contemporary treatment protocols on long-term survivors of childhood ALL. It is anticipated that the pooled results from existing studies will help consolidate the consistent evidence, identify controversial findings, and provide directions for future research.

2 . Methods

A literature search was conducted using PubMed, Scopus and PsycInfo databases in September 2014, with the following combination of keywords: “acute lymphoblastic leukemia”, “childhood”, “pediatric”, “behavioral”, “psychological”, “neuropsychiatry”, “anxiety”, “fatigue”, “depression”, “cognition”, “neurocognitive”, “memory”, “attention”, “learning”, “executive function”, “processing speed”, “sleep”, “stress” and “emotional”.

A set of inclusion/exclusion criteria was established to select studies that (1) were published between the years 2000 and 2014, (2) were written in English, (3) focused on long-term survivors of childhood ALL, defined as those who were diagnosed with precursor B-cell ALL before the age of 21 years old and were at least 5 years post-diagnosis at the time of assessment or at least 2.5 years post-cessation of treatment (based on the assumption that standard ALL treatment protocols are typically completed within 2.5 years from diagnosis), (4) involved a cohort of survivors who received chemotherapy-only treatment for standard-risk ALL and had no history of CRT or hematopoietic stem cell transplant, and (5) used quantitative methods to evaluate the neurocognitive endpoints.

Studies were excluded if they were meta-analyses, reviews, commentaries or qualitative in nature; if they only included a pure cohort of non-ALL survivors and/or ALL survivors who received CRT without presenting any stratified analysis for the neurocognitive outcomes in chemotherapy-only treated survivors; and/or if they did not describe the fundamental methods of the quantitative research, such as data collection methods, analytic and/or reporting strategies. This review is limited to precursor B-cell ALL as it is the more common presentation (80% to 85%) of acute pediatric ALL as compared to mature B-cell ALL and T-cell ALL, and also to ensure some degree of homogeneity in the types of treatment received by the study populations. Studies that were published before the year 2000 were excluded based on the historical development of ALL treatment protocols. The administration of intrathecal chemotherapy drugs gradually replaced prophylactic CRT in the 1990s for low-risk ALL patients.(Pui et al.,1995; Pui et al.,1998; COG.,2015) By late 1990s to early 2000s, clinicians from major international pediatric oncology groups started to adopt non-CRT chemotherapy-based protocols for standard- and high-risks patients as well.(Pui,2003; COG.,2015) Hence, this review included studies that were published in year 2000 or later to provide a current perspective on the contemporary treatment strategies for childhood ALL with a minimum of 5 years of follow-up.

The search was conducted at three sequential levels: (1) at the initial “title stage”, titles were screened to exclude studies that were clearly not related to main interests of this review; (2) at the “abstract stage”, abstracts of studies that passed the “title stage” were reviewed; and (3) at the final “full-text stage”, the manuscripts were examined to ensure that they fulfilled the inclusion/exclusion criteria. Data extraction and summary of study results were conducted by the investigators independently, and any disparities in the findings were reconciled.

Characteristics of the studies were systematically abstracted using a standard methodology. Specifically, information was abstracted on year of publication, study design, sample size, patient characteristics, neurocognitive domains assessed, and pertinent conclusions.

3. Results

The results of the literature search are depicted in Figure 1. The search provided 1501 studies from the three databases, of which 1272 were excluded at the “title stage”. A total of 229 abstracts were reviewed and 121 full-text manuscripts were subsequently appraised according to the inclusion and exclusion criteria. The systematic search resulted in 23 articles that were included in this review (Table 1).(Kingma et al.,2001; Von der Weid,2001; Langer et al.,2002; Hill et al.,2004; Spiegler et al.,2006; Mahone et al.,2007; Aukema et al., 2009; Harila et al.,2009; Kadan-Lottick et al.,2009; Kadan-Lottick et al.,2010; Robinson et al.,2010; Halsey et al.,2011; Daams et al.,2012; Krawczuk-Rybak et al.,2012; Lewis et al., 2012; Edelmann et al.,2013; Genschaft et al.,2013; Krull et al.,2013; Lewis et al.,2013; Ross et al.,2013; Schuitema et al.,2013; Edelmann et al.,2014; Elalfy et al.,2014)

3.1 Characteristics of studies

The vast majority of the studies had a cross-sectional design.(Von der Weid,2001; Langer et al.,2002; Hill et al.,2004; Spiegler et al.,2006; Mahone et al.,2007; Aukema et al.,2009; Kadan-Lottick et al.,2009; Kadan-Lottick et al.,2010; Robinson et al.,2010; Daams et al., 2012; Krawczuk-Rybak et al.,2012; Edelmann et al.,2013; Genschaft et al.,2013; Krull et al., 2013; Lewis et al.,2013; Ross et al.,2013; Schuitema et al.,2013; Edelmann et al.,2014; Elalfy et al.,2014) There were only 4 longitudinal studies that evaluated survivors’ neurocognitive changes from active treatment to post-treatment survivorship phase.(Kingma et al.,2001; Harila et al.,2009; Halsey et al.,2011; Lewis et al.,2013) Most studies focused on a pure sample of survivors who received chemotherapy-only treatment protocols while others included separate populations of ALL survivors who received CRT(Kingma et al., 2001; Von der Weid,2001; Langer et al.,2002; Spiegler et al.,2006; Harila et al.,2009; Kadan-Lottick et al.,2010; Halsey et al.,2011; Krull et al.,2011; Daams et al.,2012; Krull et al.,2013; Schuitema et al.,2013; Edelmann et al.,2014) or patients of other cancer types. (Aukema et al.,2009; Kadan-Lottick et al.,2010) The majority of the included studies had sample sizes between 10 to 50 subjects,(Kingma et al.,2001; Langer et al.,2002; Hill et al., 2004; Mahone et al.,2007; Aukema et al.,2009; Harila et al.,2009; Daams et al.,2012; Krawczuk-Rybak et al.,2012; Edelmann et al.,2013; Genschaft et al.,2013; Schuitema et al., 2013; Edelmann et al.,2014) with the exception of 4 studies with a larger cohort of more than 100 subjects(Von der Weid,2001; Kadan-Lottick et al.,2010; Halsey et al.,2011; Krull et al.,2013) and 3 studies with less than 10 subjects.(Lewis et al.,2012; Lewis et al.,2013; Ross et al.,2013) Most the studies reported survivors’ mean duration of time since diagnosis, which ranged between 5 and 22 years. Eighteen studies included a population of non-cancer controls or a normative healthy sample for comparative purposes.(Kingma et al.,2001; Hill et al.,2004; Spiegler et al.,2006; Mahone et al.,2007; Aukema et al.,2009; Harila et al.,2009; Kadan-Lottick et al.,2010; Robinson et al.,2010; Halsey et al.,2011; Daams et al.,2012; Lewis et al.,2012; Edelmann et al.,2013; Genschaft et al.,2013; Krull et al.,2013; Lewis et al.,2013; Schuitema et al.,2013; Edelmann et al.,2014; Elalfy et al.,2014) All patients in the

included studies received customized chemotherapy-only contemporary protocols (referred to as “contemporary protocols” thereafter) that originated from the Berlin-Frankfurt-Münster (BFM) Study Group, Children’s Oncology Group (COG), Dana-Farber Cancer Institute ALL Consortium, Dutch Childhood Leukemia Study Group (DCLSG) and St. Jude Children's Research Hospital (SJCRH). The most commonly administered drugs were vincristine, corticosteroid (hydrocortisone, dexamethasone or prednisone), L-asparaginase, and anthracycline (either doxorubicin or daunorubicin). Central nervous system (CNS) directed therapy in standard- to high- risks patients involved intrathecal methotrexate alone, triple intrathecal methotrexate, hydrocortisone and cytarabine (triple therapy) and/or high-dose intravenous methotrexate with leucovorin rescue.

Majority assessed the clinical presentation of executive function, attention/concentration, memory and motor function impairments in ALL survivors.(Kingma et al.,2001; Von der Weid,2001; Langer et al.,2002; Hill et al.,2004; Spiegler et al.,2006; Mahone et al.,2007; Aukema et al.,2009; Harila et al.,2009; Kadan-Lottick et al.,2009; Kadan-Lottick et al.,2010; Robinson et al.,2010; Halsey et al.,2011; Daams et al.,2012; Krawczuk-Rybak et al.,2012; Lewis et al.,2012; Edelmann et al.,2013; Genschaft et al.,2013; Krull et al.,2013; Lewis et al.,2013; Ross et al.,2013; Schuitema et al.,2013; Edelmann et al.,2014; Elalfy et al.,2014) Commonly utilized neurocognitive batteries were the Amsterdam Neuropsychological Test(De Sonneville,1999), an adult or child version of the Wechsler Intelligence Scale(Wechsler,1997), Delis–Kaplan Executive Function System(Delis et al.,2001) and Woodcock Johnson Tests of Achievement(Woodcock et al.,2001).

Eleven studies utilized structural neuroimaging (volumetric analysis, voxel-based morphometry [VBM], diffusion-tensor imaging [DTI]) and functional neuroimaging (functional magnetic resonance imaging [fMRI]) evaluation as a complement to the neurocognitive results.(Kingma et al.,2001; Hill et al.,2004; Aukema et al.,2009; Robinson et al.,2010; Halsey et al.,2011; Daams et al.,2012; Edelmann et al.,2013; Genschaft et al., 2013; Schuitema et al.,2013; Edelmann et al.,2014; Elalfy et al.,2014) *Tau* protein level in the cerebrospinal fluid (CSF) was quantified in one study as a biomarker of neurotoxicity. (Krawczuk-Rybak et al.,2012)

3.2 Neurocognitive outcomes

Consistent evidence from this review concurred that neurocognitive impairment in long-term survivors who received contemporary protocols was less apparent than impairment among those who were subjected to CRT.(Kingma et al.,2001; Von der Weid,2001; Langer et al.,2002; Spiegler et al.,2006; Harila et al.,2009; Daams et al.,2012; Krull et al.,2013; Schuitema et al.,2013) One included study conducted neuropsychological tests on 93 ALL survivors approximately 20 years after diagnosis. (Schuitema et al.,2013) Group differences were detected among CRT survivors, survivors who received contemporary protocols and healthy controls on visuomotor accuracy ($p=0.045$), sustained attention ($p=0.005$) and visuospatial sequencing ($p<0.001$); CRT survivors performed significantly worse than healthy controls on these domains but no differences were noted between the survivors who received chemotherapy and the healthy controls.(Schuitema et al.,2013) This study suggests that omitting CRT may help preserve survivors’ global cognitive abilities.

Results from included studies suggested that despite the elimination of CRT, survivors who were treated with contemporary protocols still suffered from minor but detectable cognitive impairment. While a handful of studies did not observe a statistically significant difference in levels of cognitive functioning between ALL survivors who received contemporary protocols and non-cancer controls or age-matched populations(Hill et al.,2004; Spiegler et al.,2006; Schuitema et al.,2013), eight included studies observed that survivors displayed poorer neurocognitive performances than the controls.(Kingma et al.,2001; Harila et al., 2009; Robinson et al.,2010; Daams et al.,2012; Genschaft et al.,2013; Krull et al.,2013; Edelmann et al.,2014; Elalfy et al.,2014) One included study reported that compared with the expected rate of 2% (predicted rate of healthy controls with two standard deviations below the age-based population mean), higher rates of severe impairment were noted in executive function (15.9%), attention (14.5%) and memory (13.1%) in survivors who received purely chemotherapy treatment.(Krull et al.,2013) Mild but apparent reduced levels of sustained attention, executive functioning (cognitive flexibility, verbal fluency and attentional flexibility), delayed memory and motor functioning were observed in chemotherapy-treated survivors.(Kingma et al.,2001; Harila et al.,2009; Robinson et al., 2010; Daams et al.,2012; Genschaft et al.,2013; Krull et al.,2013; Edelmann et al.,2014; Elalfy et al.,2014) Hence, there is mounting evidence to suggest that even in the absence of CRT, contemporary protocols might induce an accelerated rate of cognitive decline in survivors.

Amongst the studies that involved a pure cohort of chemotherapy-treated ALL survivors, there is adequate evidence to show that survivors who received high-dose intravenous methotrexate (defined in this review as a single-dose of more than 1 g/m^2 of methotrexate) had more neurocognitive problems than those given low-dose methotrexate, indicating that neurotoxicity related to methotrexate might be dose-related.(Aukema et al.,2009; Krawczuk-Rybak et al.,2012; Krull et al.,2013) A negative correlation was found of MTX doses with distractibility ($r=-0.452$, $p<0.05$).(Krawczuk-Rybak et al.,2012) It is worthwhile to mention that one study observed a direct impact of methotrexate on neurocognitive function, such that cumulative doses of intravenous methotrexate increased the risk for slowed processing speed by 3% for each 1 g/m^2.(Krull et al.,2013) However, there are limited studies in the literature that compared the neurotoxic intensity of triple intrathecal therapy (i.e. cytarabine, methotrexate, hydrocortisone) and intrathecal methotrexate monotherapy; one of the included studies reported no significant differences in cognitive outcomes between both groups.(Elalfy et al.,2014) Similarly, there was no consistent conclusion drawn regarding the difference in neurocognitive performance between ALL survivors who received dexamethasone and prednisolone.(Kadan-Lottick et al.,2009; Edelmann et al.,2013)

As for structural and functional neural outcomes, authors reported smaller white matter (WM) volume and lower fractional anisotropy in chemotherapy-treated survivors, despite the lack of evident correlation between WM volume and neurocognitive test scores.(Kingma et al.,2001; Hill et al.,2004; Aukema et al.,2009; Robinson et al.,2010; Halsey et al.,2011; Daams et al.,2012; Edelmann et al.,2013; Genschaft et al.,2013; Schuitema et al.,2013; Edelmann et al.,2014; Elalfy et al.,2014) One included study reported that although ALL survivors and non-cancer controls showed similar levels of activations at the dorsolateral prefrontal cortex during low levels of the working memory N-back task, survivors showed

greater activation than non-cancer controls as the working memory load of the N-back task increased.(Robinson et al.,2010) The same study also observed that at an increased level of cognitive demand, survivors recruited a greater amount of oxygenated blood compared to non-cancer controls. There is evidence to suggest that ALL survivors treated with chemotherapy alone demonstrated signi cant differences in long-term neurocognitive function and altered neuroanatomical integrity, in the form of having higher fractional anisotropy in fibre tracts within the right hemisphere.(Edelmann et al.,2014) Overall, subtle cognitive impairment in working memory, executive function and processing speed observed in the studies was in agreement with the reduction in survivors' brain volume and hyperactivation of the frontoparietal attentional network.

4. Discussion

Childhood ALL mortality rates have decreased significantly since the introduction of effective chemotherapy combinations. The challenge now is to further reduce the cancer- and treatment- related morbidity and improve the HRQoL of ALL survivors. This review focused on long-term survivors' neurocognitive functioning, which is an indispensable component of HRQoL.

Existing epidemiological and neuroimaging results from the included studies have highlighted that ALL survivors who received contemporary protocols are still at-risk for neurocognitive problems. Future studies should then advance from merely describing and quantifying the prevalence of these adverse outcomes, to detailing their underlying pathophysiological processes so that early detection and preventive measures may be evaluated. For this purpose, a prospective longitudinal design with designated clinically important follow-up time-points is more appropriate to account for the trajectory of cognitive changes from diagnosis to the survivorship phase.

The abundant knowledge on the toxic effects of CRT-based ALL treatments is built upon decades of research. This review has identified differing conclusions among studies in relation to the severity of neurocognitive problems experienced by survivors who did not receive CRT. The discrepancy in the findings might be highly dependent on the assessment approach (intelligence or academics versus attention and executive function), specific treatment (the types, dose intensities, routes of administration and rates of infusion of chemotherapy regimens) and the risk stratification of the sampled cohort in each study. Moreover, cancer treatment is often administered as a cocktail of multiple drugs instead of as a single agent. Most anti-cancer agents possess complex pharmacokinetic profiles, such that toxicities may be more accurately reflected by the drug concentration in the blood, rather than just the administered doses. Coupled with the physiologic changes in children with cancer, it is plausible that the drugs might exert additive toxic effects on the brain when they are administered concomitantly. Two included studies of this review effectively demonstrated that different chemotherapy regimens could illicit varying degrees of cognitive impairment on survivors.(Edelmann et al.,2013; Elalfy et al.,2014) This review proposes that pharmacokinetic studies in children will allow clinicians to examine the correlation between delayed presentations of neurotoxicities and cumulative concentration of the drugs or total drug exposures during active treatment. Pharmacological studies may also unveil the

neurotoxic mechanisms behind these drug-drug and drug-physiologic interactions in contemporary regimens. Whilst the place in therapy for CRT fades and is now largely replaced by chemotherapy as the principal modality of prophylactic ALL treatment, efforts should be taken to evaluate the toxic effects of contemporary anti-cancer drugs on survivors' cognitive function. Table 2 summarizes the common drugs used in contemporary ALL treatment protocols. To highlight, the neurotoxic nature of dose-intensified methotrexate cannot be underestimated. One included study found that there was no statistically significant difference in intelligence quotients observed between survivors who were treated with a combination of high-dose methotrexate and intrathecal methotrexate, and survivors who received intrathecal methotrexate and CRT, suggesting that high-dose methotrexate may be as detrimental to survivors' cognitive function as CRT.(Halsey et al.,2011)

Having established the neurotoxic effects of chemotherapy, it is worthwhile to identify markers of brain injury that predict the presentation of these toxicities in long-term survivors. Ideally, a predictive marker should be easily measured, specific and able to capture neurotoxic processes early before the onset of adverse neurocognitive outcomes. This section discusses some potential early biomarkers of brain injury that might aid clinicians in identifying subgroups of ALL survivors who are at-risk for neurotoxicity.

- *Neurochemical markers in the CSF:* The most evident advantage of analyzing neurochemical biomarkers in the CSF is that they have direct contact with the brain, as compared to blood-based biomarkers that are separated by the blood-brain barrier. CSF samples are also readily available when ALL patients receive intrathecal administration or lumbar punctures. One included study evaluated *Tau* protein level in CSF as a biomarker of neuronal loss and white matter injury during active treatment for ALL.(Krawczuk-Rybak et al.,2012) It was found that the elevation of *Tau* protein concentration indicated the possibility of degenerative changes within neurons and *Tau* protein level measured at the end phase of reinduction was negatively correlated with neuropsychological test scores for visuomotor function, processing speed and attentional functions in survivors. (Krawczuk-Rybak et al.,2012) Other potential neurochemical markers include CSF neuron-speci c enolase (NSE), glial brillary acidic protein (GFAP) and the neuro lament protein light sub-unit (NFP).(Österlundh et al.,2008)
- *Physiological markers:* Indicators of pathophysiological states or physiological responses to the exposure of anti-cancer drugs might potentially serve as useful predictors for brain injury. For example, it is known that folate deficiency following methotrexate administration leads to increased serum homocysteine levels.(Refsum et al.,1991; Rühs et al.,2012) Notably, post-high-dose methotrexate plasma homocysteine level was reported to be marginally higher in ALL children who presented with seizures, as compared to those who did not.(Rühs et al.,2012) One recently published study also found that serum homocysteine level might predict neurotoxicity in chemotherapy-receiving ALL survivors; higher cumulative methotrexate level at 42 hours (relative to leucovorin rescue) and higher homocysteine concentration were associated with increased risk of

leukoencephalopathy, which might be implicated in delayed neurocognitive effects in cancer survivors.(Bhojwani et al.,2014)

Cognitive, emotional and behavioral regulation is governed by the neuroendocrine system which plays an important role in cortisol variation.(Firoozi et al.,2013) High-dose corticosteroids may suppress the hypothalamic-pituitary-adrenal axis and lead to the dysregulation of cortisol levels in cancer patients.(Pound et al.,2012; Drozdowicz and Bostwick,2014) One study evaluated perceived stress and salivary cortisol levels in response to the Trier Social Stress Test for Children in chemotherapy-only treated ALL patients and healthy controls. The authors reported higher salivary cortisol levels and increased cortisol suppression in ALL patients following oral dexamethasone, and an elevated level of cortisol was associated with more fatigue and poorer HRQoL.(Gordijn et al.,2012) Corticosteroid is an important component in contemporary protocols. Future studies should evaluate the delicate interrelations among high-dose corticosteroid exposure during the active treatment phase, changes in cortisol levels in response to stress and their effects on neurocognitive and behaviorial outcomes in long-term ALL survivors.

- *Markers of oxidative stress:* Although chemotherapeutic agents are mostly unable to cross the blood-brain-barrier due to its molecular size, it can cause toxicity to the brain indirectly via the pro-inflammatory cytokine pathways by active transport and through circumventricular regions in the brain.(Wilson et al.,2002) They bind to the endothelial receptors in the brain vasculature to stimulate the release of other inflammatory mediators, such as cell adhesion molecules, chemokines, nitric oxide and prostaglandins, that can cause structural injury to the brain and eventual clinical presentation of cognitive impairment and behavioral problems.(Wilson et al.,2002; Seruga et al.,2008; Caron et al.,2009; Stenzel et al.,2010) Oxidative stress from methotrexate treatment was reported to be associated with poorer executive functions in 88 ALL children at the end of chemotherapy, as indicated by elevated levels of oxidated phosphatidylcholine in the CSF.(Caron et al.,2009) Other potential markers of oxidative stress include tumor necrosis factor- (TNF-)α, interleukins and c-reactive protein.(Mazur et al.,2004; Protas et al.,2011) Longitudinal studies are needed to determine whether the acute and chronic dysregulation of inflammatory biomarkers can predict long-term effects on ALL survivors' cognitive function.
- *Neuroimaging markers:* This review has identified key structural and functional brain abnormalities that are related to neurocognitive impairment in ALL survivors. The challenge now is to design a dynamic model that encompasses changes in neuroimaging markers from the early subclinical stage to the clinical presentation of neurocognitive impairment in survivors, and to evaluate the predictive value of multimodal neuroimaging. In ALL patients who received the chemotherapy-only treatment, 23.3% of the patients developed leukoencephalopathy, of whom 69% had persistent abnormal ndings on MRI at the end of therapy.(Bhojwani et al.,2014) Although these structural changes in brain white matter may be transient, they might hinder normal brain maturation and development, leading to long-term cognitive deficits. Currently, there is minimal literature that explores the relation between brain injury during active treatment and delayed neurocognitive changes

in ALL survivors, partly because prospective studies that involve neuroimaging are resource intensive and expensive to conduct. It is proposed that neuroimaging studies among larger populations of survivors might provide a more representative and comprehensive view on the mechanisms behind brain injury and neurocognitive outcomes.

Differences in the severity and presentation of neurocognitive problems between survivors might imply that there is individual variability of the adverse outcome. This review proposes the existence of genome-disease, genome-drug and genome-environment interactions as a potential explanation to such variability:

- *Genome-disease interaction*: Numerous clinically relevant genes have been identified in neurological conditions such as ADHD, Alzheimer's and Parkinson diseases. It is plausible that inert genetic polymorphisms within ALL survivors might determine susceptibility to developing neurocognitive problems. One study has identified increased prevalence of severe attention deficits among ALL survivors with polymorphism in monoamine oxidase A (MAOA), which is also a candidate gene implicated in neurological and psychiatric disorders.(Krull et al., 2013) Screening of polymorphisms in candidate genes that drive neurological and psychiatry disorders may provide insights on the vulnerability of survivors to cognitive problems.
- *Genome-drug interaction*: Polymorphisms in genes have profound influence over the pharmacokinetics and pharmacodynamics of drugs in individuals. Mounting evidence has highlighted the important role of pharmacogenetics in the metabolism of chemotherapeutic drugs such as methotrexate and corticosteroids.(Kishi et al., 2003; Fleury et al.,2004; Castaldo et al.,2011; Egbelakin et al.,2011; Yang et al., 2012) For example, the most commonly known enzyme cytochrome P450 is responsible for the metabolism of corticosteroids and vincristine. Multiple studies have established the relationship between methylenetetrahydrofolate reductase (MTHFR) polymorphism and variations in methotrexate-induced toxicities in ALL patients.(Yang et al.,2012) Mounting evidence has shown that even in non-cancer populations, variation in folate metabolism due to the genetic polymorphism of MTHFR is related to neuropsychiatric and behavioral diseases such as schizophrenia and ADHD.(Gilbody et al.,2007; Gokcen et al.,2011; Saha et al., 2014) Other than MTHFR, methionine synthase (MTR), cystathionine β-synthase (CBS) and endothelial nitric acid synthase (eNOS, NOS3) have been identified as essential to maintaining post-methotrexate homocysteine levels.(Krajinovic et al., 2005; Marcoux et al.,2013) Consequently, the different functional forms of these important proteins may modulate methotrexate exposure and homocysteine levels, thereby influencing the presentations of methotrexate-associated neurotoxicity.
- *Genome-environment interaction*: Longstanding behavioral research has revealed that liabilities to cognitive and behavioral disorders share genetic and environmental variance.(Manuck and McCaffery,2014) Cognitive function and behavioral outcomes in growing children are associated with the external influence from parental education, family cohesion, socio-economic factors and adaptive

coping strategies.(Pike et al.,2006; Banerjee et al.,2007; Hicks et al.,2009) This may illustrate the importance of early cognitive interventions (cognitive rehabilitation, psycho-education etc.) in high-risk groups that have such genetic polymorphisms.

Survivors of ALL may also experience relative differences in etiology of neurocognitive problems based on time since diagnosis and non-CNS treatment factors. Long-term survivors of childhood cancer are at increased risk for fatigue and sleep disturbance(Meeske et al.,2005; Mulrooney et al.,2008), which are associated with increased risk for neurocognitive problems.(Clanton et al.,2011) Long-term survivors treated with anthracyclines are at increased risk for cardiac morbidity as they age.(Hudson et al.,2013) These cardiac problems have been associated with neurocognitive impairment in long-term survivors of childhood Hodgkin lymphoma.(Krull et al.,2012) Future studies should examine the contribution from these, as well as other, health behaviors and chronic health conditions in long-term survivors of childhood ALL.

Other than neurocognitive outcomes, post-treatment behavioral and emotional effects are important aspects of cancer survivorship that are often under-investigated in long-term survivors. One study has shown that although a higher frequency of ADHD symptoms were observed in patients with CRT, survivors who received chemotherapy alone also experienced symptoms of inattention and hyperactive/impulsive behavior.(Krull et al.,2011). Depression has been reported to remain persistent in 21.7% of childhood ALL patients throughout the first year of chemotherapy treatment,(Myers et al.,2014) but even at more than 5 years post-diagnosis, a marginally higher rate of impairment in emotional regulation was observed in ALL survivors who were treated with chemotherapy compared to their non-cancer siblings (19.2% vs. 14.4%, respectively).(Kadan-Lottick et al.,2010) The persistence of behavioral and emotional problems might have a negative impact on survivors' neurocognitive abilities, and also influence their functional and psychosocial outcomes, such as educational attainment, employment, relationships and parenthood.(Massimo et al.,2006; Lund et al.,2011) Future survivorship studies should include these elements so that the research findings can be translated into evidence-based clinical algorithms to address survivors' lifelong functional aspects holistically.

To summarize, neurocognitive outcomes in ALL survivors are multifactorial in nature (Figure 2). There are a variety of factors that were not evaluated in this review, such as the influence of health status and lifestyle (metabolic syndromes, chronic conditions, nutritional status, symptoms management, physical activity and psychological well-being)(Badr et al., 2013; Brinkman et al.,2013; Hartman et al.,2013; Huang et al.,2013; Tonorezos et al.,2013), environmental factors (coping strategies, education and psychological status of family members)(Norberg and Boman,2008; Trask et al.,2009; Tremolada et al.,2013; Long et al., 2014; Williams et al.,2014; Williams and McCarthy,2014) and the interaction between chemotherapy and other supportive care drugs that may exert additive neurotoxic effects (antibiotics, antifungals and neuropsychiatric drugs)(Haidar and Jeha,2011; van Schie et al., 2011; Barrett et al.,2013; Ruggiero et al.,2013). A multidisciplinary approach is needed to ascertain the impact of contemporary ALL treatments on these adverse outcomes. Moving on, we propose a viable research approach by developing a robust infrastructure that allows

for coordinated data collection at pre-diagnosis, active treatment, post-treatment and survivorship phases. Researchers will need to process information from genetic, biochemical, physiological and neuroimaging perspectives in order to unveil the science behind this persistent presentation of neurotoxicity in ALL survivors. It is anticipated that this may pave the way for the eventual implementation of pharmacological, non-pharmacological and lifestyle interventions that may address the neurocognitive problems in survivors, and facilitate evaluation of the impact of these interventions.

5. Conclusion

Even with the omission of CRT, long-term ALL survivors who are treated with contemporary chemotherapy protocols are at-risk of experiencing neurocognitive deficits. A multifactorial and targeted approach is needed to identify treatment and preventive strategies to halt the development of these abnormalities. The world of oncology is currently in the age of personalized medicine, of which “customization” forms the concept behind the diagnosis of cancer, choice of therapy and risk assessment of acute drug-related toxicities during the active treatment of cancer. However, true customization of survivorship care is less practiced. There is much potential in harnessing current medical technology to assemble a patient’s genetic profile, neuroimaging data, biomarkers and physiological indicators during different phases of cancer treatment, and utilize this objective information to predict susceptibility to neurocognitive impairment. The eventual goal is to develop an evidence-based model that enables clinicians to utilize different sources of clinical data to identify and modify risk factors at an early stage. As we adopt this holistic approach for research and clinical practice, tailoring a customized long-term care plan for each ALL survivor will be possible.

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HIGHIGHTS

- Radiation-naïve survivors of childhood ALL suffer from neurocognitive deficits.
- Late neurocognitive problems in survivors may be dependent on drug exposures.
- Neurochemical, inflammatory and genetic markers may be predictors of brain function.

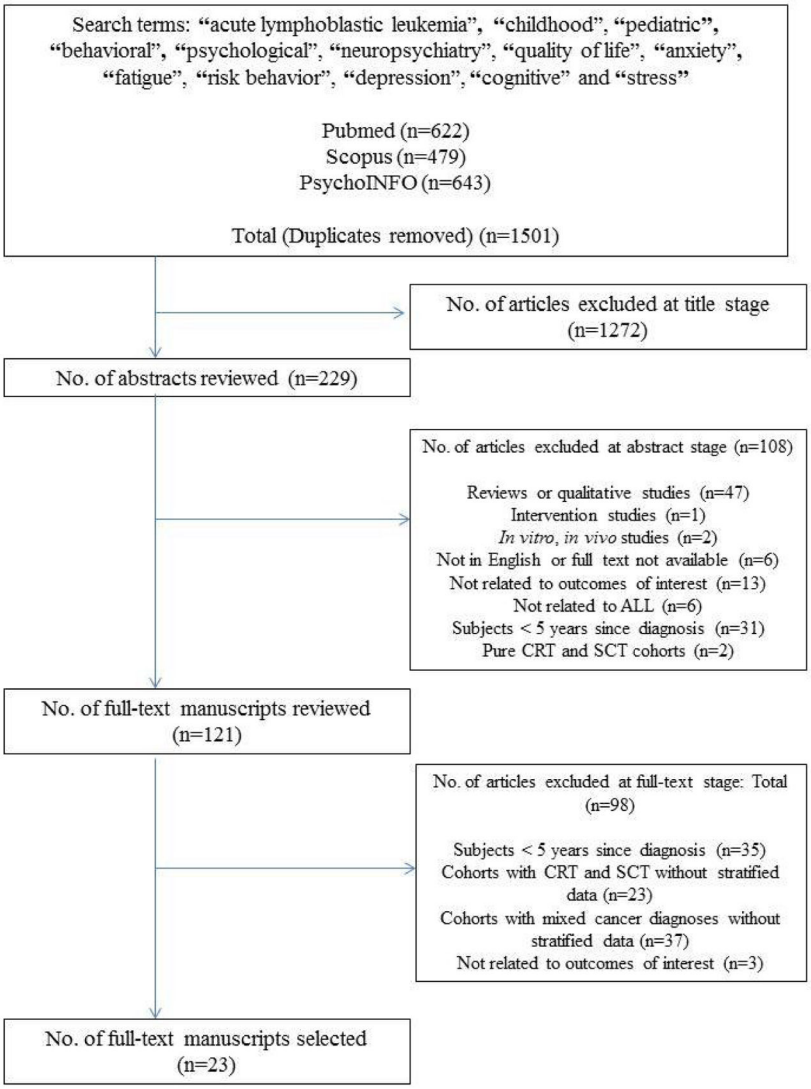

Figure 1.

Results of literature search

CRT: Cranial radiation therapy; SCT: Stem-cell transplant

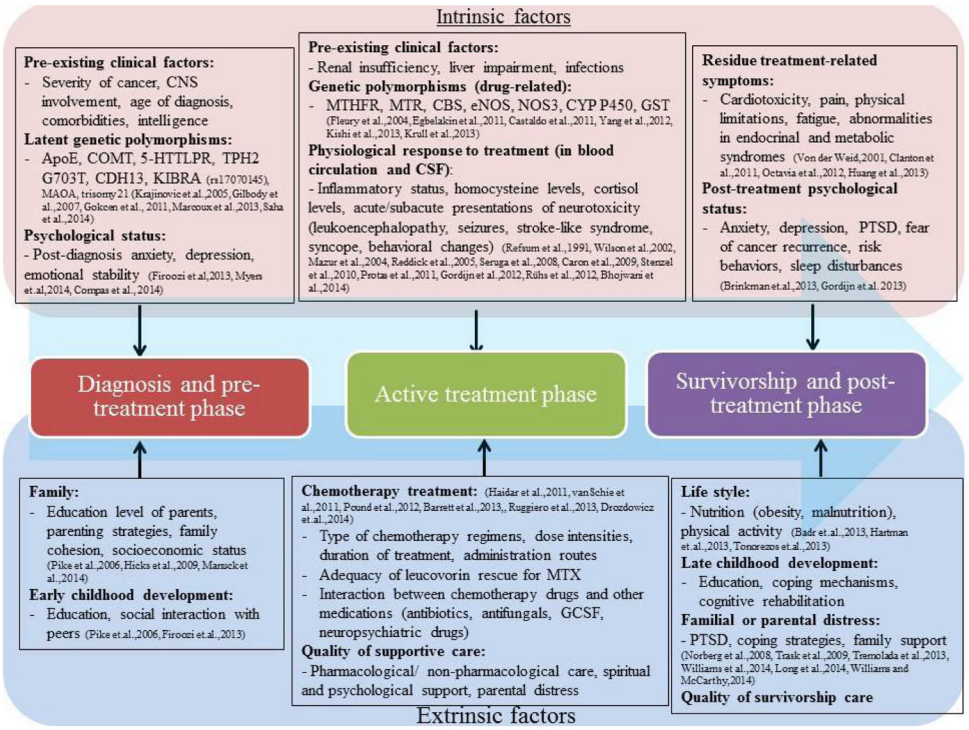

Figure 2.

Intrinsic and extrinsic factors that contribute to neurocognitive outcomes in childhood acute lymphoblastic leukemia survivors

ApoE: apolipoprotein E; CBS: cystathionine-β-synthase; CDH13: cadherin 13; COMT: catechol-O-methyltransferase; CNS: central nervous system; CSF: cerebrospinal fluid; GCSF: granulocyte-colony stimulating factor; GST: glutathione S-transferase; KIBRA: kidney and brain expressed protein; MAOA: monoamine oxidase A; MTHFR: methylenetetrahydrofolate reductase; MTR: methionine synthase reductase; MTX: methotrexate; NOS: nitric oxide synthase; PTSD: Post-traumatic stress disorder; TPH2: tryptophan hydroxylase-2; 5-HTLPR: serotonin-transporter-linked polymorphic region

Table 1

Characteristics of studies

Study	Design	Chemotherapy-only group(s) Sample size (participation rate)	Years from diagnosis Mean (SD) [range]	Comparative groups	Domains assessed	Assessment tools	Pertinent findings on outcomes of interest
1 (Edelmann et al.,2014)	Cross-sectional	36 (72%)	14.97 (1.74)	39 CRT ALL survivors Population norms	IQ, academics achievement, attention, memory, processing speed, executive function	WASI, WJ, TMT-A, TMT-B, CPT, CVLT, WAIS, GPT, Test of Memory and Learning	• Chemo survivors showed statistically significant poorer performances than norms, on reading, math, attention variability, verbal selective reminding and motor processing speed. • Chemo survivors showed statistically significant better performances than CRT survivors, in verbal selective reminding, memory and visual-motor processing speed.
2 (Elalfy et al.,2014)	Cross-sectional	62 (NR)	[a] Post-tx: 2.72 (0.61) 4.19 (1.44) 7.96 (1.98)	60 non-cancer	IQ, visual perception, visual memory, mental flexibility and executive function	WISC, BVRT, TMT-A, TMT-B	• Cognitive impairment is related to the type of chemo protocols. • No relationship between cognitive tests and number of IT MTX, ITT and HDMTX.
3 (Edelmann et al.,2013)	Cross-sectional	Dex: 18 (91.7%) Pred: 20 (85.7%)	Dex: median 15.9 [range: 14.8 – 17.9] Pred: median 13.3 [range: 12.0 – 15.1]	Population norms	IQ, academic achievement, memory	WAIS, WJ, Test of Memory and Learning	• Dex survivors showed statistically significant poorer performances than norms, on vocabulary, reading and math. • Dex survivors showed statistically significant poorer performance than Pred survivors, in

Study	Design	Chemotherapy-only group(s) Sample size (participation rate)	Years from diagnosis Mean (SD) [range]	Comparative groups	Domains assessed	Assessment tools	Pertinent findings on outcomes of interest
							vocabulary, reading, math, immediate and vocabulary, reading, math, immediate and vocabulary, reading, math, immediate and vocabulary, reading, math, immediate and vocabulary, reading, math, immediate and vocabulary, reading, math, immediate and
4 (Genschaft et al.,2013)	Cross-sectional	27 (NR)	12.4 (6.1 – 18.5) since remission	27 non-cancer	Memory, executive function, IQ, attention	LGT-3, CPT, CFT 20R	• Chemo survivors showed statistically significant poorer performances than controls, on total memory, non-verbal memory and IQ.
5 (Krull et al.,2013)	Cross-sectional	214 (66.0%)	20.9 (5.5)	353 CRT ALL survivors Population norms	IQ, attention, memory, processing speed, executive function, academic achievement	WASI, CPT, CVLT, BRIEF, WJ	• Significant rates of impairment for cognitive domains and behavior ratings in chemo survivors (5.7% to 14.5%). • Dexamethasone exposure associated with impaired attention and executive function. • IV MTX exposure associated with impaired processing speed by, after controlling for CRT.
6 (Lewis et al.,2013)	Longitudinal (case-series)	5 (NA)	*b* Varied	5 non-cancer	Language	PPVT, CELF, TLC-E, TOPS series	• Overall, no significant change in language performance, with the exception of some individual subjects with declining language scores.

Study	Design	Chemotherapy-only group(s) Sample size (participation rate)	Years from diagnosis Mean (SD) [range]	Comparative groups	Domains assessed	Assessment tools	Pertinent findings on outcomes of interest
7 (Ross et al.,2013)	Cross-sectional (case-series)	4 (44.4%)	5.0 – 10.0	NA.	IQ, executive function, motor function, behavior (both proxy- and self-rated)	WASI, EOWPVT, ROCF, Grooved Pegboard, CVLT, DKEFS, BRIEF, BASC	• Chemo survivors had normal or above-average levels of cognitive function, except for one patient with severe motor functioning and significant anxiety and emotional problems.
8 (Schuitema et al.,2013)	Cross-sectional	49 (36.0%)	21.4 (2.9)	49 non-cancer 44 CRT ALL survivors	IQ, attention, working memory, visuomotor function	ANT, WAIS	• No significant differences between chemo survivors and controls. • Chemo survivors showed better performances than CRT survivors in almost all cognitive measures.
9 (Daams et al.,2012)	Cross-sectional	18 (78.3)	20.0 (2.0)	14 CRT ALL survivors35 non-cancer	Attention, working memory, visuomotor function	ANT	• Chemo survivors had similar levels of cognitive function as controls, except for working memory and accuracy of inhibition.
10 (Krawczuk-Rybak et al., 2012)	Cross-sectional	31 (NR)	6.3	NA.	IQ, memory, attention, visuomotor function	WISC, WASI	• Chemo survivors had normal performance for total IQ. • A higher dose of MTX was correlated with poorer performance on distractibility.
11 (Lewis et al.,2012)	Cross-sectional (case-study report)	1 (NA)	11.25	1 non-cancer (sibling)	Language	PPVT, CELF, TLC-E, TOPS series	• No significant differences in language skills

Study	Design	Chemotherapy-only group(s) Sample size (participation rate)	Years from diagnosis Mean (SD) [range]	Comparative groups	Domains assessed	Assessment tools	Pertinent findings on outcomes of interest
							between survivor and sibling-control. between survivor and sibling-control.
12 (Halsey et al.,2011)	[c] Longitudinal	HDMTX: 116 ITMTX: 104 HDMTX +ITMTX: 35 (39.0%)	5 years post-initiation of tx	34 IT MTX+CRT ALL survivors 132 non-cancer	IQ	WPPSI, WAIS, WISC	• No statistically significant difference in IQ between HDMTX +ITMTX and ITMTX+CRT survivors. • No statistically significant difference in IQ between HDMTX +ITMTX and ITMTX survivors.
13 (Kadan-Lottick et al.,2010)	Cross-sectional	624 (87%)	23.7 (4.5) [range: 16.0 – 34.3] (at least 5 years post-diagnosis)	1168 CRT ALL survivors 382 non-cancer (siblings) 3998 other cancers	Self-reported processing speed, memory, academic functioning, task efficiency, emotional regulation, organization, psychological distress	BRIEF, CCSS-NCQ, BFI	• Although the rates of impairments in chemo survivors were higher than siblings in self-reported cognitive functioning and emotional regulation, these differences did not reach statistical significance. • Rates of self-reported impairment in cognitive domains and emotional regulation in chemo survivors are 11.1% to 19.2%.
14 (Robinson et al.,2010)	Cross-sectional	8 (NR)	Post-tx: 6.46	7 non-cancer	IQ, executive function, processing speed	WISC, DKEFS, N-back	• Chemo survivors showed statistically significant poorer performances than controls, on working memory, processing speed, IQ and in subtests

Study	Design	Chemotherapy-only group(s) Sample size (participation rate)	Years from diagnosis Mean (SD) [range]	Comparative groups	Domains assessed	Assessment tools	Pertinent findings on outcomes of interest
							for executive function. for executive function.
15 (Aukema et al.,2009)	Cross-sectional	11 (55.0%)	Post-HDMTX: 11.5 (1.2) [range: 10.6 – 13.6] Post-LDMTX: 5.9 (2.4) [3.4 – 9.9]	17 non-cancer 6 medulloblastoma Population norms	IQ, processing speed, motor function	WISC, Purdue Pegboard	• Compared with the norm population, HDMTX and LDMTX survivors performed worse on processing speed and motor speed. • HDMTX survivors had statistically significant poorer processing speed than LDMTX survivors. • No significant differences in motor speed between groups.
16 (Harila et al.,2009)	Cross-sectional [d] Longitudinal	20 (74%)	17 [range: 11 – 22]	44 CRT ALL survivors 45 non-cancer	IQ, memory, orientation and attention, motor function	WAIS, WMS, BVRT, TMT-A, TMT-B, Purdue Pegboard, Finger-Tapping Test, Reaction Time Test, Stroop Color-Word Test	• Chemo survivors had poorer overall IQ than controls, and in certain tests for memory, attention and motor function. • Chemo survivors showed better performances than CRT survivors, on IQ, memory and attention. • Chemo survivors who were tested previously at the end of therapy showed significant decline in verbal IQ, but not in performance IQ.
17 (Kadan-Lottick et al.,2009)	Cross-sectional	92 (42.0%)	Dex: 9.8 (0.5) Pred: 9.8 (0.6)	NA.	IQ, sustained attention, memory,	WISC, WIAT, Beery Test of VMI, CPT, CMS	• No significant differences in overall cognitive

Study	Design	Chemotherapy-only group(s) Sample size (participation rate)	Years from diagnosis Mean (SD) [range]	Comparative groups	Domains assessed	Assessment tools	Pertinent findings on outcomes of interest
					VMI, academic achievement VMI, academic achievement		and academic performances between survivors who received Dex and Pred.
18 (Mahone et al.,2007)	Cross-sectional	22 (NR)	Post-tx: 6.2 [range: 3 – 11]	22 non-cancer	Motor function (motor timing, judgment of time duration, frequency perception)	Finger-tapping test, judgment of short interval and pitch task	• Chemo survivors had statistically significant poorer performances than controls, on judgment of long duration and motor timing, but not judgment of pitch.
19 (Spiegler et al.,2006)	Cross-sectional	HDMTX: 32 VHDMTX: 22 (66.0%)	HDMTX: 9.0 (1.9) [range: 5.1 – 13.5 – 13.5] VHDMTX: 11.8 (3.2) [range: 5.5 – 20.6]]	25 CRT ALL survivors Population norms	IQ, academic achievement, attention, memory	WISC, WAIS, WRAT, WRMT, GDS, CMS, WMS	• No significant differences in all measures between HDMTX and VHDMTX survivors. • Overall, no significant differences between chemo (HDMTX and VHDMTX) survivors and norms, except for impulsivity. • Chemo survivors showed statistically significant better performances than CRT survivors, on IQ, memory, attention and reading comprehension.
20 (Hill et al.,2004)	Cross-sectional	10 (64.7%)	Post-tx: at least 3 years	10 non-cancer	Verbal and visual delayed memory	WRAML, ROCL	• No significant differences between chemo survivors and controls, on verbal and visual delayed memory.

Study	Design	Chemotherapy-only group(s) Sample size (participation rate)	Years from diagnosis Mean (SD) [range]	Comparative groups	Domains assessed	Assessment tools	Pertinent findings on outcomes of interest
21 (Langer et al.,2002)	Cross-sectional	38 (NR)	Post-tx: 7.0 (1.7) at least 4.5 years	83 CRT ALL survivors	IQ, memory, learning, attention	HAWIK, RFT, Test d2 by Brickenkamp	• CRT survivors had statistically significant poorer IQ than chemo survivors. • CRT survivors had poorer attention and memory scores than chemo survivors (not statistically significant). • No significant association between cognitive tests and IT MTX doses.
22 (Kingma et al.,2001)	Longitudinal	17 (26.6%)	8.6 (6.6 – 11.9)	28 CRT ALL survivors 225 non-cancer (Dutch norms)	IQ, verbal-auditory learning, memory, attention, motor function, VMI	WISC, WPPSI, RAVLT, Beery test of VMI, Purdue Pegboard	• Chemo survivors had statistically significant poorer performances than the norm group, on delayed recall, attention and motor function. • CRT survivors had statistically significant poorer performances than chemo survivors in almost all cognitive measures.
23 (Von der Weid,2001)	Cross-sectional	106 (93.3%)	Median 10.0 [range: 5.0 – 21.5]	35 CRT ALL survivors	IQ	WISC	• CRT survivors had statistically significant poorer IQ than chemo survivors, specifically in the areas of arithmetic, verbal memory, processing speed and visuomotor coordination.

ALL: Acute lymphoblastic leukemia; ANT: Amsterdam Neuropsychological Tasks; BASC: Behavior Assessment System for Children; BRIEF: Behavior Rating Inventory of Executive Function; BSI: Brief Symptom Inventory; BVRT: Benton Visual Retention, chemo: Chemotherapy; CCSS-NCQ: Childhood Cancer Survivor Study – Neurocognitive Questionnaire; CELF: Clinical Evaluation of

Language Fundamentals; CFT: Culture Fair Intelligence Test; CMS: Children's Memory Scale; CPT: Conners Continuous Performance Test; CRT: Cranial radiation therapy; CTRS: Conners' Teacher Rating Scale; CVLT: California Verbal Learning Test; DKEFS: Delis–Kaplan Executive Function System; Dex: Dexamethasone; EOWPVT: Expressive One Word Picture Vocabulary Test; GDS: Gordon Diagnostic System; HAWIK: Hamburg-Wechsler Intelligence Scale for Children; HDMTX: High-dose methotrexate; IQ: Intelligence quotient; IT: Intrathecal; ITT: Intrathecal triple therapy; LGT-3: Lern- und Gedachtnistest; LDMTX: Low-dose methotrexate; NA: Not applicable; NR: Not reported; MTX: Methotrexate; Post-tx: Post-treatment; PPVT: Peabody Picture Vocabulary Test; QoL: Quality of life; Pred: Prednisolone; RAVLT: Rey Auditory Verbal Learning Test; RFT: Recurring Figures Test; ROCF: Rey-Osterrieth Complex Figure Test; TLC-E: Test of Language Competence-Expanded; TMT-A: Trail-making test A; TMT-B: Trail-making test B; TOPS: Test of Problem Solving; VHDMTX : Very high-dose methotrexate; VMI: Visual motor integration; VLT: Verbal Learning Task; WASI: Wechsler Abbreviated Scale of Intelligence; WPPSI: Wechsler Preschool and Primary Scale of Intelligence; WISC: Wechsler Intelligence Scale for Children; WMS: Wechsler Memory Scale; WRAML: Wide Range Assessment of Memory and Learning; WRAT: Wide Range Achievement Test; WRMT: Woodcock Reading Mastery Test; WJ: Woodcock Johnson III -Test of Achievement

[a]The reported time from treatment is based on the different types of protocols.

[b]The stratified data of the 5 subjects who fulfilled the inclusion criteria of having 5 or more years from diagnosis.

[c]There are multiple time points of assessment; results of the time point that corresponds to 5th year post-initiation of treatment is reported here.

[d]More than one time point of assessment was available for a subset of subjects.

Table 2

Commonly used anti-cancer agents in contemporary treatment protocols for childhood acute lymphoblastic leukemia and their effects on neurological outcomes

Drug	Evidence of neurotoxicity	Potential areas of research
Methotrexate	• Methotrexate crosses the blood-brain-barrier. Due to its pharmacological properties, it is not surprisingly that methotrexate is identified as one of the neurotoxic candidate drugs. • To note, methotrexate can be administered in multiple dosage forms, routes and doseintensities: – Intravenously in low/standard doses (less than 1g/m^2) – Intravenously in high doses (more than 1g/m^2) – Intrathecal (as measured by the number of intrathecal doses) – Orally – Intramuscularly – Intraosseously • Impairment in intelligence quotient was comparable between survivors who were treated with a combination of high-dose methotrexate and intrathecal methotrexate and survivors who received intrathecal methotrexate and CRT.(Halsey et al.,2011) • The prevalence of methotrexate-associated leukoencephalopathy ranged widely from 9% to 60% in ALL patients treated with IT and IV methotrexate, depending on the time of evaluation.(Reddick et al.,2005) • Increasing the exposure to methotrexate corresponded to more severe presentations of leukoencephalopathy.(Bhojwani et al.,2014) • Methotrexate-induced folate deficiency was associated with neurotoxic symptoms. Elevated levels of homocysteine and its excitatory amino acid neurotransmitter metabolites (homocysteic acid and cysteine sulfinic acid) contributed to neurotoxicity.(Quinn et al.,1997)	• As CRT is gradually replaced by intrathecal and high-dose intravenous methotrexate in high-risk ALL patients, does the latter indeed better preserve the neurocognitive function in survivors? • As methotrexate can be administered in different routes and forms, are the plasma levels of the drug more reflective of the neurotoxic outcomes, as compared to just reported/administered doses? • Can pharmacokinetics studies draw a clearer association between cumulative exposure to methotrexate during active treatment and long-term neurotoxicity in survivors? • Is methotrexate-induced leukoencephalopathy reversible in long-term survivors? • Can homocysteine levels and markers of oxidative stress induced by methotrexate during active treatment predict neurocognitive outcomes in survivors? • Do genetic polymorphisms in the enzymes responsible for themetabolism of methotrexate contribute to the difference in severity of cognitive impairment in survivors?
Leucovorin	• Leucovorin is commonly known as a chemoprotectant that counteracts the anti-proliferative activity of methotrexate. Leucovorin crosses the blood-brain-barrier more readily than folic acid itself and has a greater bioavailability to neurons. • It is typically administered 48 to72 hours after high-dose methotrexate to minimize the acute presentation of methotrexate-related toxicities. • Higher methotrexate level at (relative to leucovorin rescue) was associated with increased risk of leukoencephalopathy.(Bhojwani et al., 2014)	• Can *in vivo* and *in vitro* studies demonstrate the potential neuroprotective property of leucovorin on neurons? With the concomitant administration of high-dose methotrexate, is leucovorin effective in minimizing or halting the damage induced to the neurons? • In striking a balance between maximizing the efficacy of methotrexate and minimizing its neurotoxic nature to the brain, do the adequacy and appropriate iming of leucovorin rescue play a role in minimizing neurocognitive deficits in patients?

Drug	Evidence of neurotoxicity	Potential areas of research
	• There is limited evidence in the literature that evaluates the effect of leucovorin on neurons and its impact on the long-term presentation of neurotoxicity in ALL survivors.	
Anthracycline	• Anthracyclines do not cross the blood-brain-barrier. • Studies suggest that IV anthracyclines might elicit an inflammatory response and dysregulation in cytokine levels, of which circulating pro-inflammatory cytokines have also been implicated in anthracycline cardiotoxicity.(Octavia et al.,2012) Although the drug molecule cannot cross the blood-brain-barrier, cytokines can do so and damage neurons through oxidative stress mechanisms. • Results from in vitro studies have suggested that patients who received anthracycline might experience cancer-related fatigue due to its calcium responses of myotubes or skeletal muscles.(Van Norren et al.,2009)	• Can the inflammatory response elicited by anthracyclines during active treatment play a role in mediating “serum sickness behaviors”, such as fatigue, mood disorders and cognitive impairment in survivors? • Can cardiotoxic markers be related to neurotoxic outcomes?
Asparaginase	• L-asparaginase does not cross the blood–brain barrier. • Depletion in asparagine levels are found in the CSF. Accumulation of aspartate (aspartic acid) is found to result in enhanced excitability and neuronal damage in individuals with intellectual disabilities.(Ruzzo et al., 2013) • Acute neurologic complications, such as cerebral venous sinus thrombosis and stroke-like syndrome, have been reported in some cases of asparaginase toxicity in ALL patients.(Ross et al.,2013)	• What is the effect of acute/subacute asparaginase neurotoxicity during active treatment on survivors’ delayed neurocognitive outcomes?
Vincristine	• Vincristine does not cross the blood-brain-barrier. • CNS toxicity from vincristine is rare but it is commonly associated with peripheral neuropathy. Its association with peripheral neuropathy might be implicated in motor impairments in cancer survivors.(Buizer et al., 2005)	• Are patients who experience clinically significant neuropathy with vincristine more vulnerable to having fine motor impairment?
Cytarabine	• Cytarabine does not cross the blood-brain-barrier at standard dose. • IT liposomal cytarabine, when given concomitantly with other systemic chemotherapy such as methotrexate, can result in significant neurotoxicity.(Jabbour et al.,2007)	• Does the IT administration of triple therapy: cytarabine, methotrexate and hydrocortisone, cause more cognitive impairment in survivors than IT methotrexate alone? • Do the cumulative doses of IT drugs and the IT injection counts contribute to the severity of cognitive impairment?
Corticosteroid	• Corticosteroid crosses the blood-brain-barrier. • Psychiatric effects of corticosteroids have been well established in both adult and pediatric populations. Substantial behavioral and psychiatric changes are observed in children during the active treatment of corticosteroid.(Pound et al.,2012; Drozdowicz and Bostwick,2014; Warris et al.,2014)	• Are the neuropsychiatric and behavioral symptoms of corticosteroid administration still persistent in survivors? • When administered in combinations with other cytotoxic drugs, do dexamethasone, prednisolone and hydrocortisone differ in their neuropsychiatric effects?

ALL: acute lymphoblastic leukemia; CNS: central nervous system; CRT: cranial radiation therapy; IT: intrathecal; IV: intravenous