Review article

Journal of Human, Health and Halal Metrics; 2021, 2(1): 63-74
https://doi.org/10.30502/jhhhm.2021.283539.1031

Methotrexate-induced neurocognitive late effects in treatment of pediatric acute lymphoblastic leukemia: a review

Mahdi Taherian[1], Zohreh Tajabadi[2], Arash Azhideh[2], Reza Taherian[3*]

1- General Directorate of Natural, Traditional and Complementary Products, Iran Food and Drug Administration, Ministry of Health and Medical Education, Tehran, Iran.
2- School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran.
3- School of Medicine, Hamadan University of Medical Sciences, Hamdan, Iran.

Submission: 29 April 2021 ***Revision***: 8 June 2021 ***Acceptance***: 2 October 2021

Abstract

Background and objective: Childhood cancer survivors frequently experience long-lasting consequences of chemotherapy. Acute lymphoblastic leukemia is one of the most common malignancies that occur during childhood. By the help of new protocols, 5-year survival is about 80%. Despite all improvement in treatment and increasing surveillance, morbidities of these treatments are lifetime. The aim of this study was to review the recent updates on chronic neurologic deficits occurred by treatment of acute lymphoblastic leukemia, risk factors of these neurologic deficits, and prevention of their side-effects. Also, this review discusses the genetic variability in biochemical pathways targeted by chemotherapeutic agents as a possible mechanism contributed to psychopathology in acute lymphoblastic leukemia survivors.

Results and conclusion: The most important drug used for treatment of acute lymphoblastic leukemia is methotrexate. It is also the main drug for central nervous system prophylaxis. Most of chemotherapies drugs cannot pass blood brain barrier but methotrexate is an exception. Methotrexate is a double-edge sword, because it can pass blood brain barrier and can be used for central nervous system prophylaxis to decrease the relapses. On the other hand, it can cause chronic neurologic deficits as a result of its passage from blood brain barrier in the developing brain. In conclusion, prophylactic interventions during treatment (e.g., administration of leucovorin) and after treatment (e.g., cognitive training and maintenance of academic growth) are effective routes in prevention of late effects in survivors of acute lymphoblastic leukemia.

Keywords: Acute lymphoblastic leukemia, central nervous system, childhood cancer, Methotrexate

Abbreviations

ALL: acute lymphoblastic leukemia; MTX: methotrexate; CNS: central nervous system; CRT: cranial radiation therapy; CT: computed tomography; MRI: magnetic resonance imaging; MTHFR; 5,10-methylenetetrahydro-folate reductase

* Correspondence to: Reza Taherian; E-mail: Taherian.reza72@gmail.com

1. Introduction

By decreasing the mortality rate in children suffered from childhood cancer, more attention is paid to treatment routes beyond survival. Most of these survivors experience long-term health consequences that negatively impact on their executive function and quality of life [1,2]. Although, the advances in treatment of childhood cancers have resulted in improved survival, the increased morbidity associated with the examined treatments has evolved the field of neurology with new challenges [3]. Other examples include survivors of traumatic brain injury [4] or premature neonates [5]. Other than its high prevalence, cancer treatment is a well-documented intervention giving an opportunity to reduce the complications. Examining neurocognitive outcomes in childhood cancer survivors provides information for development of chemotherapy protocols to reduce treatment-related complications. Therefore, research on treatment-related neurocognitive late effects offers new opportunities for collaborative care and research.

As the most prevalent malignancy of childhood, acute lymphoblastic leukemia (ALL) is accounted as one-quarter of all childhood cancers [6]. Childhood ALL is prevalent among children aged 2-7 years [6], a critical period of brain development. Survival rate of childhood ALL up to 5-year has increased to 80% in recent years. Therefore, monitoring of long-term toxicity and functional efficiency in survivors of childhood leukemia has become important [7]. Chronic neurotoxicity is emerging as a worrying late effect in survivors of childhood ALL and 40–60% of patients experience neurocognitive difficulties [8,9]. Contemporary treatment of ALL includes a mixture of chemotherapy agents of vincristine, anthracyclines, glucocorticoids, L-asparaginase, and methotrexate (MTX). Various components of multi-agent treatment of ALL may be associated with neurocognitive late effects. Recently, MTX has been interested as the most suspected agent. MTX is considered as major culprit in neurocognitive late effects because ALL patients are exposed to MTX chronically via intravenous, intrathecal, and oral routes. Thereby, it passes blood-brain barrier which results in targeting of remained leukemic cells in the brain, known as CNS prophylaxis [9]. In this review, we discuss about recent findings with respect to neurocognitive late-effects in survivors of childhood ALL with a focus on MTX. Electronic search in MEDLINE/PubMed (since 1966 to 1 September 2021) was done by using the disease-specific terms and the outcome-specific terms. Out search algorithm was included to (acute lymphocytic leukemia OR acute lymphoblastic leukemia OR childhood leukemia OR pediatric leukemia OR ALL OR leukemia) AND (neuropsychological OR neurocognitive OR cognitive OR memory OR intelligence OR attention OR processing speed OR IQ OR intelligence quotient OR achievement OR math OR reading OR motor functioning) AND methotroxate. There was no language limitation.

2- CNS prophylaxis

Infiltrated leukemic cells remain in CNS after systemic therapy of ALL because blood-brain barrier inhibits the drugs' entrance. Without CNS prophylaxis, relapsing or metastasis [10] may occur in more than 80% of ALL survivors through which rate of morbidity and mortality increases in the patients [11]. To prevent relapse of leukemia in childhood ALL, CNS prophylactic therapy was introduced in the 1970s. By this therapeutic method, childhood ALL was no longer an untreatable disease [12-14]. At first, CNS prophylaxis was included to cranial radiation therapy (CRT) at 18-24 Gy, which was associated with neurocognitive and behavioral problems leading to reduced intelligence quotient, poor academic functioning and increased aging of the brain, early onset of dementia, secondary cancers, and endocrine disorders. Over the years, it was found that chemotherapy could be a good alternative for CRT in

childhood ALL treatment, because it can reduce possibility of CNS relapse without any complications occurred by CRT [8,15-24]. Chemotherapy decreases the incidence of delayed neurotoxicity and reduced neurocognitive impairments compared to CRT [13,18]. Current CNS chemotherapies are systemic and intrathecal therapy. Systemic therapy includes high-dose intravenous MTX and corticosteroids injection. Intrathecal therapy consists of intrathecal injection of MTX and triple intrathecal therapy includes separate injection of MTX, cytarabine (a nucleoside analog), and hydrocortisone or injection of their combination. Method of chemotherapy depends on therapeutic protocol, cooperative group, and treatment centers [11-13,16,25].

3- Neurotoxic effects of chemotherapy

Adverse effects of pediatric cancers' treatment are classified to acute and chronic symptoms. Acute effects are those observed within a limited time such as temporary cognitive changes induced by cancer therapy [19]. In comparison, progressive late effects such as impairments in functioning after successful completion of cancer therapy, which occurred about two years or more after diagnosis are considered as chronic [19, 26]. Late effects occur in about two-third of survivors of childhood cancer [27]. These late effects can damage several organs especially nervous system. Since CNS prophylaxis is toxic to a developing brain, survivors of pediatrics ALL are especially at risk of long-term and progressive cognitive impairment [27,28]. Academic, intellectual, and neuropsychological impairments caused by CNS prophylactic treatment are known as "neurocognitive late effects" [29,30].

Currently, chemotherapy is considered as standard method of CNS prophylaxis for majority of children and adolescents with ALL. Thus, neurocognitive late effects of this treatment is under investigation [31,32]. In this regard, majority of survivors show evidence of deficits in at least one area of functioning including attention, intellectual functioning, and executive functioning [33].

3-1- Attention

Ability to focus on a stimulus selectively, sustaining that focus, and changing it optionally is defined as attention. Attention is commonly impaired in pediatric ALL survivors, so that approximately one-fourth of them show impaired attention [34,35]. Domain of attention consists of some subdomains including sustained attention, selective attention, shifting attention, and divided attention [36]. Several studies have reported impairment in sustained [37], selective [38,39], shifting [40], and divided [41] attention. Deficits in subdomains of attention in the patients affect their ability to concentrate and lead to their distraction followed by decreased academic achievement and quality of life [42].

3-2- Intellectual functioning

It refers to general mental capacity such as learning, reasoning, and problem solving. Contradict results have been reported with respect to intellectual functioning. For example, some studies observed evidences of declines in intellectual functioning in ALL survivors just treated by chemotherapy [39,43,44], while the others found no difference between ALL survivors and control group [38,45]. Given the inconsistent findings about effect of chemotherapy on intellectual functioning in ALL survivors, some comprehensive reviews have been investigated. Moleski et al. reported that about two-third of previous studies observed impairment in at least one area of intellectual functioning. Most of studies that did not report any deficit in intellectual functioning among ALL survivors had significant methodological weaknesses especially in their control group [33]. Peterson et al. conducted a meta-analysis in 2008 and showed that survivors of pediatric ALL just treated by chemotherapy experience impairment in various areas of intellectual

functioning including full scale IQ, verbal IQ, performance IQ, working memory, and processing speed [46]. Another meta-analysis conducted by Iyer et al. in 2015 confirmed the results of earlier reviews. The authors indicated the impairments of full scale IQ, verbal IQ, and performance IQ in survivors of pediatric ALL compared to healthy peers [25].

3-3- Executive functioning

Executive functioning refers to a cognitive process consisting of individual's ability to organize thoughts and activities, prioritize tasks, and manage time. Although, some aspects of executive functioning cover the other areas of neurocognitive functioning such as memory and attention [47], the abilities arisen from a normal executive functioning are critical in normal academic, adaptive, and social functioning [48]. Thus, investigation of its impairment in survivors of pediatric ALL is of concern [49]. Studies have found that survivors of pediatric ALL just treated by chemotherapy suffer from inability in information processing [25,50], attentional control/inhibition [39], and cognitive flexibility [25,38,41]. In these patients, exposure to dexamethasone was not associated with poor executive function or other cognitive measures, while high plasma concentration of MTX was positively associated with a poor executive function [51]. These deficits negatively affect behavior and school performance [31] resulting in long-term occupational, social functioning and, quality of life impairments [48,52].

4- Potential pathophysiology of MTX-induced neurotoxicity

Antifolates, nucleoside analogs, and corticosteroids are of chemotherapeutic agents administered in ALL treatment and exert their antineoplastic effects by different mechanisms [13]. MTX is the most important drug administered as antifolate therapy in patients with ALL. It interferes with different metabolic pathways which control vital biochemical processes [9].

MTX inhibits dihydrofolate reductase enzyme which converts dihydrofolate to tetrahydrofolate that is necessary for DNA synthesis. MTX decreases purines and thymidylate synthesis by folate depletion leading to inhibition of DNA synthesis and blockade of cancer cells' proliferation [14,15]. Folate is necessary for neuronal development and normal function of nervous system [53] and its depletion leads to S-adenosylmethionine (SAM) reduction. SAM is a methyl group donor which facilitates methylation of proteins (such as myelin) [13], phospholipids, and neurotransmitters. Reduced SAM is compensated by a choline-dependent pathway. Choline is mostly found in cell membranes in form of phosphatidylcholine and phosphatidylinositol. Phospholipids are the most important components of white and gray matter and play a critical role in myelination. Therefore, release of choline from phospholipids such as sphingomyelin disturbs their integrity and impairs myelin development [15]. It has been suggested that white matter damage is of important factors contributed to neurocognitive outcomes [53]. After methylation, SAM is converted to S-adenosylhomocysteine (SAH) which inhibits SAM-mediated methylation processes and further myelination [13].

Reduced tetrahydrofolate also inhibits homocysteine conversion to methionine which then converts to SAM by methionine synthase (an enzyme that needs vitamin B_{12} and zinc as cofactors) [15]. Therefore, homocysteine accumulates in the blood and CSF [13]. Homocysteine induces endothelial toxicity and leads to inflammation, vascular damage, microangiopathy, and stroke [12,13,17,19]. Homocysteine is also converted to homocysteic acid and homocysteine sulfinic acid which stimulate N-methyl-D-aspartate (NMDA) receptor and exert excitotoxicity in neurons leading to neuronal death [15,20]. In addition, increased concentration of adenosine by MTX metabolism can react with homocysteine and form SAH [13].

MTX may have direct toxic effect on neurons and induce oxidative stress in cell membranes. For example, MTX stimulates β-oxidation of fatty acids in CSF. Concurrent folate depletion and homocysteine accumulation lead to neurons' exposure to oxidative damage [13,54].

Nucleoside analogs exert their antineoplastic effects by inhibition of DNA and RNA synthesis. Adenosine analogs are presynaptic depressants and induce apoptosis in neurons. Glucocorticoids cause excitotoxicity in neurons via NMDA receptors. Intake of glucose by neurons and glia cells is blocked by glucocorticoids leading to excessive accumulation of synaptic glutamate which further induces neuronal death via apoptosis [13].

5- Radiographic findings

Computed tomography (CT) scan and magnetic resonance imaging (MRI) are useful modalities for detection of acute or chronic consequences induced by treatments. Brain CT scans often reveal intracerebral calcification and cortical or subcortical atrophy but MRI is useful for detection of anatomic alteration of CNS white matter [55-58]. No significant correlation was observed between gender and brain calcification and cerebral atrophy. Most of studies have not shown any correlation between radiologic findings and neurologic deficits and cognitive sequelae but a correlation between subtle cognitive deficits and CT scan abnormalities have been found which improved neuropsychological sectorial abilities [59,60].

One of the most common acute consequences of chemotherapy is leukoencephalopathy. Bhojwani et al. evaluated the incidence of leukoencephalopathy in patients treated by chemotherapy alone (group 1) and in those treated by chemotherapy together with cranial radiation therapy (group 2). They found that 23.3% of chemotherapy-treated patients (group 1) developed leukoencephalopathy, of whom 69% showed persistent abnormalities in MRI until the end of treatment. Long term follow-up showed that abnormalities are in white matter and in the frontal striatal tract. These abnormalities disturb normal maturation and development of the brain which lead to long term cognitive deficits [61].

6- Predisposing factors

Chemotherapy affects ALL survivors differently. Neurocognitive consequences of childhood ALL and its treatment are related to both mediators and moderators. Mediators include biological factors of patient cognitive reserve and immune and/or inflammation status, disease-related factors of disease status, graft versus host disease, and tumor characteristics, and treatment-related factors. Moderators consist of gender, genetic variations, age at diagnosis and treatment, race, educational level, stress, socioeconomic condition, health behaviors, and family status [18,19,21,53,62]. The most important variables are discussed here.

6-1- Genetic variation

Different responses in patients may be due to specific patterns of genes' expression and polymorphisms correlated to folate metabolism pathways which affect metabolism and pharmacodynamics of MTX [9,13]. For example, there are variations in the gene encodes 5,10-methylenetetrahydrofolate reductase that converts methylenetetrahydrofolate to 5-ethyltetrahydrofolate. Approximately, 10% of Europeans carry a C to T substitution at nucleotide 677 (rs1801133) on both alleles, which causes reduced enzymatic activity followed by reduced level of folate in their plasma and red blood cells and increased blood homocysteine level. Homozygous carriers usually do not experience any health problem under normal condition but they may be susceptible to MTX or other chemotherapeutic agents. Some MTHFR polymorphisms such as C677T and A1298C (rs1801131) are responsible for homocysteine's fluctuation in the serum and may develop inattention problems upon chemotherapy, particularly when folate intake is

low [13,21]. Additionally, some variations in methionine synthase (A2756G; rs1805087) which are involved in elevation of homocysteine may have significant role in functional disabilities of ALL survivors. Homocysteinemia induces vascular injury and inflammation and negatively affects normal brain development [9,13,17,21]. Other polymorphisms are listed in Table 1.

Table 1- Main gene polymorphisms involved in MTX-induced neurotoxicity

Gene polymorphism	
5,10-methylenetetrahydrofolate reductase	C677T A1298C
Aminoimidazole carboxamide ribonucleotide transformylase	ATICC347G
Reduced folate carrier	RFC G80A
Y-glutamyl hydrolase	GGH C452T
Methionine synthase	MTR A2756G
Methionine synthase reductase	MTRR A66G
Methylenetetrahydrofolate dehydrogenase	MTHFD G1958A
Serine hydroxymethyltransferase	SHMT C1420T
Thymidylate synthase	TS 28-bp variable number of tandem repeat in the promoter region 1494del6; rs34489327

Other than one-carbon metabolism polymerphism, other variations play a role in neurocognitive outcomes. For example, a variation of the gene encoding apolipoprotein E4 is associated with increased attention problems in ALL survivors [9,19]. Furthermore, polymorphism in the genes encoding monoamine oxidase A, glutathione S-transferases of GSTT1 and GSTP1, endothelial nitric oxide synthase (eNOS), catechol-O-methyltransferase (COMT) and solute carrier organic anion transporter family member 2A1 (SLCO2A1) (related to oxidative stress and neuro-inflammation) is linked to severe neurocognitive problems. Furthermore, variation in the genes involved in regulation of brain white matter microstructural changes, neuronal plasticity, and axonal growth may contribute to different and a wide range of neurocognitive outcome in survivors; although further investigations are needed [18,19,21,54]. Therefore, it is important to use specific treatment strategies for patients depending on their genotype to reduce long term adverse effects [9].

6-2- Age

Early age at diagnosis and initiation of treatment is associated with more serious neurocognitive problems. Brain maturation and myelination is continued after birth in childhood and the brain is highly sensitive to the adverse effects of chemotherapeutic agents in younger children [11,13,16,23,53]. Direct neuronal toxicity, white matter ischemic changes, and impaired methylation induced by MTX are of events leading to white matter damage and contribute to neurocognitive impairments [23,53]. Disrupted development of the brain may lead to reduced age-related synaptic pruning and disturbed integrity of white and gray matters. Decreased volume of white matter leads to higher neurocognitive disabilities [8,17-19,62]. Importantly, all regions of the brain are not similarly affected by chemotherapy. For example, the right frontal lobe is more sensitive to chemotherapy agents because of its less maturity [9,17,62].

6-3- Gender

It seems that females are at risk of more neurocognitive problems [11,14,16,18,23], possibly due to lower myelination in girls than boys in childhood [11]. However, there are a lot of controversies about age and sex association with neurocognitive issues [10,54,62].

6-4- Drug interactions

Drug interactions are important risk factor for MTX-related neurotoxicity. Simultaneous administration of other drugs and MTX may exacerbate methionine reduction and homocysteine elevation by two mechanisms; 1) Some drugs such as fluoroquinolone antibiotics, piperacillin, and proton pomp inhibitors interact with MTX directly, which results in increased MTX concentration in plasma and CSF, and 2) Drugs may interfere with MTX metabolic pathway. Such drugs mainly reduce vitamin B_{12}, which significantly affects MTX-related neurotoxicity. Vitamin B_{12} is necessary for normal function of methionine synthase. Thus, its inhibitory agents cause homocysteine elevation and further neurotoxicity. Moreover, decreased vitamin B_{12} is associated with increased MTX concentration in CSF that is a synergism for convergent metabolic pathways. Nitrous oxide is used with MTX for general anesthesia before administration of intrathecal MTX via lumbar puncture. Nitrous oxide causes irreversible oxidation of reduced cobalt (Co^{+}) to Co^{2+} and Co^{3+} and converts active vitamin B_{12} (which contains reduced cobalt) to inactive analogue. Nitrous oxide should not be used in patients who received MTX during treatment. Proton pump inhibitors are another example of this group, which may reduce bioavailability of vitamin B_{12}. Some antimetabolites (e.g., 6-mercaptopurine) decrease absorption of vitamin B_{12} due to enteropathy [15,21].

6-5- Protocols

Varied neurocognitive consequences may also be due to different therapeutic protocols used in chemotherapy of ALL patients. Adverse effects of MTX on CNS are reported in different ways of administration including high dose intravenous therapy (more than 500 mg/m2), repeated administration of intraventricular or intralumbar therapy, and low dose oral therapy [13,17,20]. Different chemotherapeutic agents used with MTX simultaneously (such as corticosteroids) in ALL therapy can aggravate neurotoxicity [21,25,54]. For example, survivors treated by clock controlled genes (CCGs) and modified BFM 90 protocols experienced worse neurocognitive problems likely due to higher cumulative doses of MTX and dexamethasone [62]. Although there is exception [16], most studies [10,11,21,23,53,62] reported that severity of neurocognitive outcomes is related to high dose of systemic MTX. Indeed, toxicity of high-dose MTX and its ability to cross blood-brain barrier is possibly the reason of its neurotoxicity [17]. Therefore, use of milder protocols by administration of lower doses of MTX might be helpful in alleviation of further neurotoxicity effects of MTX [11,13,16,18,20]. Although, other antifolate agents showing equal peripheral effects and less CNS penetration might be an appropriate alternative to MTX [13,16].

Neurotoxicity of MTX can be reduced by administration of folate supplement such as Leucovorin, but its high intake may cause psychiatric symptoms and increased possibility of CNS relapse [10,13,16,21]. Use of cranial radiation therapy by neurotoxic chemotherapy is associated with the most severe delayed neurocognitive outcomes such as delayed chronic leukoencephalopathy. It seems that increased permeability of blood-brain barrier due to radiation facilitates penetration of neurotoxic agents to CNS, which leads to increased agent-related neurotoxicity [13,19,53]. Survivors who experienced acute leukoencephalopathy in childhood are at increased risk of long-term functional, neurobehavioral, and neuroanatomical problems. Among ALL survivors treated by chemotherapy, such patients need early interventions to supply normal development of the brain [18].

7- Prevention of MTX neurotoxicity

Deleterious effects of chemotherapy on the developing brain are lifetime and prevention of consequences is critical in the patients. For more than 30 years, Leucovorin rescue was a base of high dose MTX (HDMTX) treatment [63].

Leucovorin is particularly effective in prevention of myelosuppression, gastrointestinal toxicity, and neurotoxicity during treatment with HDMTX [63, 64]. Leucovorin neutralizes the effects of MTX; therefore it should not be used in early phase because attenuates efficacy of anticancer effects [65]. Nonetheless, some patients show neurotoxicity of MTX. CNS toxicity may occur after HDMTX and concurrent intrathecal treatment, cranial irradiation, and infiltration of malignant cells. This situation increases the risks and complicates the etiology [66]. A potential mechanism of neurotoxicity is accumulation of adenosine after reduced synthesis of purine caused by MTX [67]. These findings have led to evaluation of 1-hour infusion of 2.5-mg/kg aminophylline in pediatric ALL patients [68]. Interestingly, four out of six patients had no symptoms of toxicity, while two patients showed long-lasting nausea. However, the result showed insignificant efficacy of aminophylline in curing or prevention of MTX-induced neurotoxicity. Studies have shown that some of MTX treatment protocols such as intrathecal MTX injection have more neurotoxic effects followed by HDMTX [69,70]. Use of radiation therapy or other chemotherapeutic agents have also aggravating effect [71]. Pediatric oncology groups recommend that observation of severe change in CT scan and MRI or new neurological deficit is sign of MTX discontinuation, even temporarily.

8- Conclusion

Survivors of childhood ALL are at high risk of neurological and neuropsychological late effects as a result of chemotherapy agents especially MTX. Thus, identification of high risk patients for cognitive decline should be considered in treatment of children with ALL. Long-term neurotoxicity in survivors of ALL is observed in those were at lower age at diagnosis and initiation of treatment, female patients, and if high doses of systemic or intrathecal MTX were administered. Prophylactic interventions during treatment (e.g., administration of leucovorin) and after treatment (e.g., cognitive training and maintenance of academic growth) are effective routes in prevention of late effects.

9- Acknowledgement

The authors gratefully wish to thank Dr. Tahereh Babai for her comments on this paper.

10- Conflict of interest

The authors declare that they have no conflict of interest.

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