Cognitive and Academic Sequele in Bangladeshi Children with Acute Lymphoblastic Leukemia Treated With Long-Term Chemotherapeutic Agents

Md Golam Hafiz[1,*], Chowdhury Yakub Jamal[2]

[1]Associate Professor, [2]Professor & Chairman, Department of Pediatric Hematology and Oncology, Bangabandhu Sheikh Mujib Medical University, Bangaladesh

***Corresponding Author:**
Email: golamhafiz59@yahoo.com

ABSTRACT

The survival rate of childhood acute lymphoblastic leukemia (ALL) is about 90 percent; new research is emerging of its late effects. Literature reviewed investigating the relationship of treatment protocol of ALL too specific late effects, underlying mechanisms and possible remedy.

2,750 diagnosed children of ALL with age of 1-15 years were included in this retrospective study. Literature was surveyed the occurrence and topography of late effects (cognitive and intellectual). The patients had completed the child symptom inventory (CSI) to rate their child's academic performance on a 4-point Likert scale (1=falling, 2=below average, 3=average, 4=above average). Literature was reviewed to find out the underlying mechanisms of these deficits and possible remedy. Here, mice were used as models to answer these questions for assessment of treatment of children with ALL.

Male female ratio was 1.4:1. Based on CSI, 31.81% had below average, 45.27% average and 22.90% above average behavioral and academic performance. Early chemotherapy induced academic and learning deficit was found 34.43%, late 43.48% and no sequelae 22.07%. Early radiation induced cognitive impairment was 23.08% and late 35.52% and had no deficits 41.38%. Neuropsychological impairment was found 24.42% in early phase and 34.9% in late and 40.72% found without any impairment. Chemotherapy induced cognitive impairment at early phase were 38.65%, late 20.39% and 40.94% had no deficits. Male preponderance of these deficits were found both early and late phase of treatment. Childhood leukemia exhibit cognitive and academic deficits and should be placed in a special education program. Behavioral evidence has highlighted impairments in areas of attention, working memory and processing speed leading to decrease in intelligent quotient (IQ). Neurophysiological evidence in ALL has impact abnormalities on white matter and acquired brain damage resulting from chemotherapy.

The exact role of chemotherapeutic agents causing cognitive and academic sequelae is still unknown. The deficits are more pronounced in male at early phase of treatment may be due to increased acceptance of chemotherapeutic agents. Female are affected less may be due to their genetic factors. Cognitive and academic impairment are common following chemotherapy. Radiation also causes cognitive deficits in children with ALL. Neuropsychological impairment was also a feature following chemotherapy in ALL. Improved mice model of cognitive and learning deficits are recommended in survivors of childhood ALL with suggestions for future directions in this field in hopes that ensuing treatment regimens will further reduce or eliminate these deficits in future.

Key words: *Cognitive and academic sequelae; Acute lymphoblastic leukemia; Chemotherapeutic agents*
Abbreviations: *ALL=acute lymphoblastic leukemia; CSI=child symptom inventory; IQ=intelligent quotient*

INTRODUCTION

It is evidenced that cancer chemotherapy results in cognitive changes during treatment, immediately post-treatment and years following therapy[1-6]. Cognitive deficits are diverse and vary in severity; however, problems with memory function and executive process are the most common. These impairments can have negative impacts on the quality of life and possess a significant challenge for cancer in children[7].

Among the survivors of all types of pediatric cancer, the incidence of neuropsychological and neurologic abnormalities is variable, depending on tumors type, location, timing and methods of CNS therapy. The children with brain tumor[8-13], acute leukemia[14-19]; neuropsychological and neurologic deficits demands special education or even institutionalization in 8%-50%. It is reported that 36 children of various intracranial tumors survived 5 years after treatment, 45% had IQs< 90 and 17% had IQ < 70[8]. The children who had other tumors required specific CNS treatment appear to be at similar risk.

Radiotherapy is the most problematic for growth and development of children with cancer. Learning difficulties among childhood cancer survivors primarily have been attributed to cranial irradiation and are related to their cumulative dose, size of individual fraction and age at time of treatment[8-11,20-22]. Impairment may be subtle or devastating but normally is not advance after first 3 to 5 years of radiotherapy[15,21]. The children having brain tumors who are younger than 36 months at diagnosis and those who treated as older brain tumor patients (3,500 to 5,500 cGy) are at increased risk for development serious cognitive impairment and neurologic (blindness and visual impairment)[9-10,20].

21 of 28 children who were diagnosed before the age of 36 months were evaluated 8 years after treatment. Significant impairment in neuropsychological and developmental outcome was found in 7 patients who were treated with cranial irradiation (IQ,80) and 14 patients who had received only surgery or chemotherapy (IQ,97)[11]. Delaying radiotherapy until affected patients are older has been achieved in few patients with good outcome[23-24]. Lower doses of radiation can be used safely because of antitumor effect of chemotherapy[25], neurologic morbidity is expected to be significantly less than before. The earlier results support this prediction[26].

CNS directed therapy with cranial irradiation (18 to 24 cGy) which had diminished intelligence IQ, poor academic performance, subsequent development of cancers and endocrinopathies[27-29]. Methotrexate and 5-fluorouracil commonly used cancer chemotherapeutic agents, caused deficits in spatial as well as non-spatial memory. These are consistent with the present findings, and it employed the same drug regimen (once per week for 3 weeks) and recovery period[30]. Reiriz et al.[31], reported, cyclophosphamide impaired memory in an inhibitory avoidance task in mice. This is a hippocampal dependent task and involves aversive conditioning. Memory was impaired when a single dose of cyclophosphamide was administered 1 day before but not 1 week before therapy.

Cyclophosphamide or 5-fluorouracil was administered to female rats, which were subsequently tested for spatial learning ability in a Morris water maze task and a T maze active avoidance task[32]. Rats treated with either drug exhibited enhanced performance. Lee et al. showed, rats were trained 7–9 weeks or 29–42 weeks after chemotherapy which is much later than the 1 week recovery time in relation to our study. Lee et al. showed that different results might be expected when multiple drugs are administered simultaneously rather than individually. Cyclophosphamide and doxorubicin together were administered to most protocol based treatment regimens in various childhood malignancies. The different results may be the age of the patients as well as the female rats in Lee et al.[32] were not ovariectomized leading to possible influence and interaction of cycling hormones with chemotherapy. The same chemotherapeutic agents used have been shown to reduce estrogen levels[33] and lower estrogen has been associated with improved performance in spatial tasks[34]. Different components of the hippocampal system appear to be involved in the spatial tasks reported by Lee et al. and the contextual conditioning procedures used in our study[35, 36].

Neurologic hearing loss from therapy with cisplatin[37] or aminoglycosides or chronic otitis media, histiocytosis X (Langherhans' cell histiocytosis) and head and neck rhabdomyosarcoma[38-39]. At the extreme end spectrum of chronic neurotoxicity associated with CNS treatment is progressive necrotizing leukoencephalopathy. It is characterized clinically by dementia, dysarthria, dysphagia, ataxia, spasticity, seizures and coma and histopathologically by reactive astrocytes, gliosis and demyelinization[40].

Following extensive literature search we found no such related publication on cognitive and academic sequelae in Bangladeshi children with ALL treated with long term chemotherapeutic agents. So, to highlight, this retrospective review study was performed to disseminate our observation in perspective of Bangladeshi children.

MATERIALS AND METHODS

This retrospective study was carried out through searching the data in the Department of Pediatric Hematology and Oncology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh from January 2005 to December 2015 in two thousand seven hundred fifty diagnosed children with ALL. Patients were categorized as early phase (≤12 month) and late phase (>12month) based on the appearance of cognitive and academic sequelae receiving chemotherapy and or radiotherapy.* The clinical performance based measures were with Digital Span Test[41-42], Verbal Fluency Test[43], Grooved Pegboard Test[44] and Trail Making Test[45] (DIVERGT). Each patient was administered all measures in a fixed order. All raw scores were converted to age adjusted standard scores on population mean ± SD (100±15). In addition, caregivers completed the child symptoms inventory (CSI) to rate their child's academic performance on a 4- point Likert scale (1=falling, 2=below average, 3=average, 4=above average). The CSI is a standardized rating scale designed to screen for behavioral, emotional, academic and cognitive symptoms consistent with formal diagnostic criteria[46]. For this study, only the global ratings for academic and cognitive problems were analyzed.

1. Inclusion and Exclusion Criteria

To see the cognitive and academic sequelae treated with chemotherapeutic agents, 1-15 years of diagnosed children with ALL irrespective of gender who received long-term protocol based chemotherapy or radiotherapy were included. The patients with inadequate or poor interventions and any chemotherapy received outside this hospital prior to diagnosis were excluded.

2. Search Strategies

The literature were searched on cognitive and academic sequelae with ALL who were planned to receive protocol based chemotherapy and or radiotherapy using PubMed electronic data base on: 'pediatric cancer,' 'pediatric oncology,' 'hematopoietic stem cell transplantation,' 'bone marrow transplantation,' 'mucositis,' 'stomatitis,' 'chemotherapy,' 'radiotherapy,' and 'acute and long-term effects of chemotherapy,' The abstracts or full texts of original

articles, editorials and communications were also reviewed.

3. Selection of Subjects

Three different observers analyzed the findings of article to locate the potential eligibility of this retrospective study. Articles were selected initially according to the title, then abstracts were reviewed thoroughly and only those articles which were absolutely eligible for this study were selected. Based on the abstracts, full manuscript was acquired for final disposition. In disagreement in between the reviewers, a fourth reviewer had given power to made final decision on the eligibility of this manuscript.

RESULTS

The flow chart showed search process of articles on cognitive and academic sequelae with acute lymphoblastic leukemia with long term chemotherapy and or radiotherapy (Fig.1). In this review study only 18 articles were finally selected for analysis.

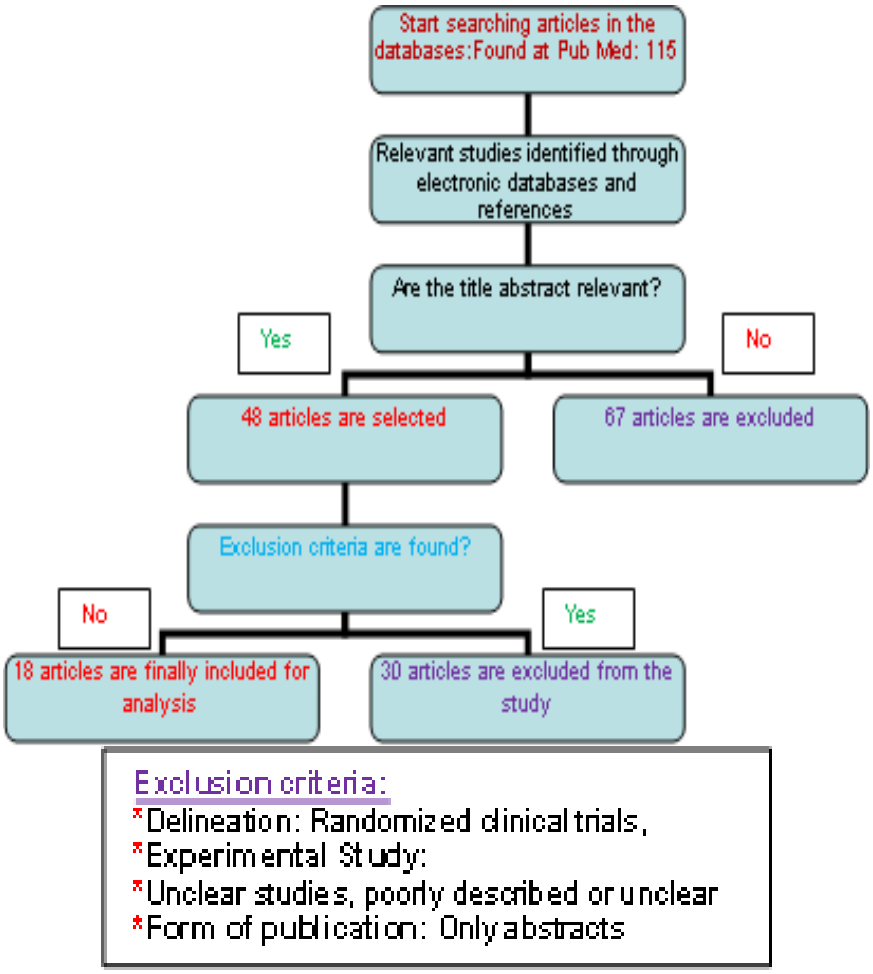

Fig.1: Flowchart of search process on cognitive and academic sequelae with acute lymphoblastic leukemia

The male female ratio of study population was 1.4:1. Mean ± SD of age 1-5 years, 5-10 years and 10-15 years were 3.5 ±1.3, 7.8 ± 2.3 and 11.5 ±3.6 years respectively (Table 1). The male preponderance of cognitive and academic sequelae was found in all age group of children. The behavioral and academic performance found 31.81% below average, 45.27% average and 22.90% above average based on CSI (Fig. 2). Chemotherapy induced academic and learning deficit had found 34.43% in early phase and 43.48% in late phase of treatment and had no deficit 22.07% with ALL children (Fig. 3). The radiation induced cognitive impairment was 23.08% in early and 35.52% in late phase of therapy but 41.38% had no sequelae (Fig. 4). No neuropsychological impairment found in 40.72% children but had 24.35% in early and 34.9% in late phase of treatment in children with ALL (Fig. 5). Out of 2,750, no chemotherapy induced cognitive impairment found in 40.94% patients but 38.65% in early phase and 20.39% in late phase of treatment (Fig. 6).

Table1: Age and sex distribution of the children with acute lymphoblastic leukemia (n=2,750)

Age (Year)	Male (%)	Female (%)	Mean ± SD
1-5	600(21.80)	450(16.36)	3.5 ± 1.3
5-10	675(24.54)	550(20.00)	7.8 ± 2.3
10-15	350(12.72)	125(4.54)	11.5 ± 3.6

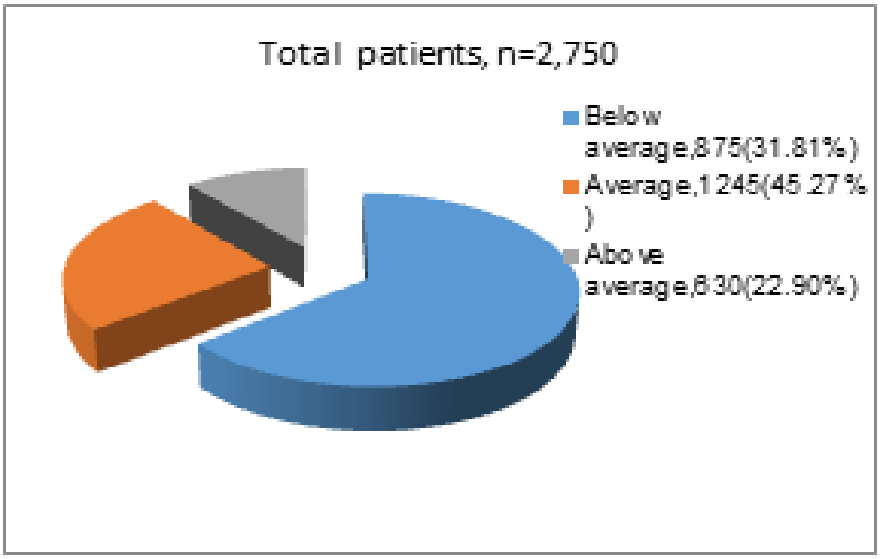

Fig. 2: Child symptom inventory based behavioral and academic performance (n=2,750)

DISCUSSION

1. Late Effects of Childhood Cancer

Out of 10 million cancer survivors alive in United States today, at least 270,000 patients were diagnosed when they were under the age of 21[47], though there are no national wide definite registration of cancer patients in our country, the value is definitely less, it is about 12,000 because of poor diagnostic facilities. With the advancement of cancer treatment over the past few decades, new research focuses on ‘’late effects’’, chronic and progressive conditions associated with completion of cancer therapy, now prevalent among long-term cancer survivors. It usually present three or more years of diagnosis with only one in three survivors free of long-term effects[48-49]. Late effects among cancer survivors are so pervasive that the Children’s Oncology Group (COG) has recommended regular evaluation to monitor the development after treatment which is difficult to follow-up due to time constrain and expensive assessments[50].

Cognitive late effects presumably resulting from chemotherapy administered to the central nervous system (CNS) during the time of rapid brain development[49,51]. Childhood cancer survivors compared to their counterpart are 10 times more likely to have severe cognitive deficits and significantly less likely to complete high school or to complete higher education after graduation[49,52]. Frequency of impairment of task efficiency, memory and emotional regulation is 50% higher among adulthood survivor of childhood cancer compared to siblings[53]. In this review study behavioral and academic performance found 31.81% below average, 45.27% average and 22.90% above average based on CSI scale (Fig. 2).

ALL is the most common disease among childhood cancer survivors[54]. With advanced treatment regimen, more 90% of children with ALL enter into long-term remission with highest survival rate[54]. Literature review on cognitive late effects associated with treatment ALL exist[55-56], whereas evaluation of cognitive late effects in preclinical models of young mice is still lacking. Objective of this current review is to highlight the benefits of using preclinical models to complement the research.

2. Acute Lymphoblastic Leukemia (ALL)

Leukemia represents about one-third of all childhood cancers, ALL accounting for 75% of pediatric leukemia, the most common form of cancer in children and adolescents[57]. Out of 4,000 cases diagnosed annually in the United States, two-thirds are in these age groups [58]. In our perspective, about 1,500 newly diagnosed ALL are admitted annually in our hospital. It is the malignant disorder of lymphoid cells when a surplus of stem cells develops into lymphocytes referred to as leukemic cells which are not able to fight against infection and leave less room for healthy cells and platelets[58]. These cells are found in bone marrow are transferred by the circulatory system including CNS. Despite possible environmental, genetic and viral influences the exact cause of ALL remains unknown[59]. While ALL is less prevalent in adults, mortality rate

among them is much higher than in adolescents and children. Treatment for the majority of ALL subtypes consists of four phases: induction, intensification (consolidation), high dose or CNS directed therapy and maintenance. Although two-thirds of childhood cases are curable with only 12 months of treatment, the vast majority of patients undergo therapy for two years or more [58]. In our center we treat the child more or less 36 month depending on the risk group. Chemotherapeutic agents used vary in type and doses, most common being used are methotrexate (MTX), cytosine arabinoside (cytarabine), anthracyclines (doxorubicin), asparaginase, mercaptopurine, vincristine, and corticosteroids[58]. Cranial irradiation therapy (CRT), once the most common form of CNS prophylaxis has largely been replaced by intrathecal (IT) and systemic chemotherapy. This change has been made to eliminate radiation induced CNS damage[60]. The alterations in long-term outcome are just beginning to unfold [61].

3. Academic and Learning Deficits

Childhood ALL and its treatment are associated with poor academic outcome with age at diagnosis is important education related risk factor. Infantile leukemia found to have 50% learning deficits more than five years after diagnosis and risk increased with younger age at the time of therapy[62]. Survivors of ALL have likelihood of being placed in a special education program and reach a lower educational level than their siblings[63-64]. ALL treatment during childhood is related to poor academic performance, clear learning deficits may not arise until four or five years after the initiation of therapy[65]. Poor academic performance is not correlated with frequent absent from school[66]. Past treatment for ALL commonly included CRT; the majority of studies on this topic have included radiation as part of treatment, but rarely without simultaneous use of chemotherapy[48]. General measures of intellectual functioning were used Wechsler Intelligence Scales[67]. The scores declined seven years following treatment with cranial irradiation[68]. The childhood cancer survivors display a decreased rate of learning new information and new skills, leading to a decline in IQ score[48,69]. Here, early chemotherapy induced academic and learning deficit was 34.43%, late 43.48% and no sequelae 22.07% of childhood cancer survivors (Fig. 3).

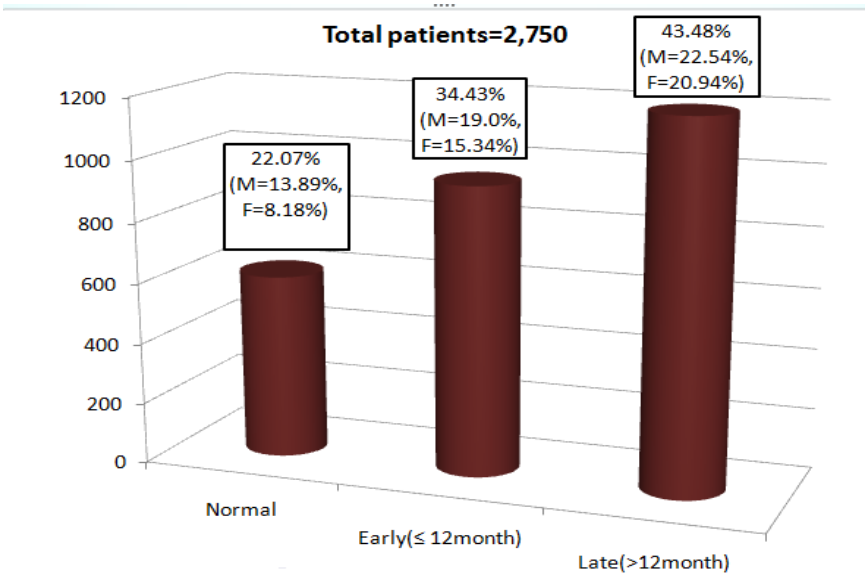

Fig. 3: Chemotherapy induced academic and learning deficit

Comparisons between CNS prophylaxes involving CRT or IT have yielded mixed results with no significant difference between the group. 12-point difference in mean IQ was found between ALL and controls irrespective of CNS prophylaxis[70]. The radiation and non-radiation groups demonstrated deficits may indicate synergistic effects between MTX and cytarabine, the latter increasing the neurotoxic effects of the former, the result are similar to CRT. No significant influence of treatment was found between children who received IT-MTX in addition to systemic MTX, a lower dose of CRT or a higher dose of CRT, although 22 to 30 percent of children found a significant decline in IQ [69]. In this review study radiation induced cognitive impairment was 23.08% in early and 35.52% in late phase of therapy but 41.38% had no sequelae (Fig. 4). Systemic MTX may potentiate the neurotoxic effects of IT-MTX affecting brain via indirect pathways[71]. High doses of IV-MTX may reduce vascularization of the brain, particularly hippocampal blood vessel density[72].

Loss of intellectual functioning is characterized by deficits in attention, working memory and processing speed[59]. Neurocognitive impairments in ALL survivors have focused on deficits in attention (approx. 25%) of survivors[73].

Deficits in the targeting, recalling and manipulating of information to guide goal-directed behavior have been noted seven years post-treatment[74-75]. ALL survivors found to have performance on visual attention which required the child to shift attention between the local and global level of stimuli[76]. Children diagnosed younger than 5 years exhibit difficulties in both fundamental and complex attention skills. Children diagnosed more than 5 years have difficulty with more complex skills only[77]. Deficits in more complex skills arise from reduced fluency. Age at diagnosis may impact attention functioning in children with intensified treatments results more extensive and widespread deficits[78].

Disruption in basic skills may not become apparent until difficulties with higher level several years later, when emergences of complex repertoires from component skills not found in normal progression. ALL survivors decrease in IQ level in cognitive skills of processing speed, working memory and intelligence with processing speed playing a significant role in the development of working memory[79]. Working memory underlies the development of higher-level reasoning and intelligence. Evidence for impaired working memory and slowed information processing has been found for ALL survivors received chemotherapy[80-83].

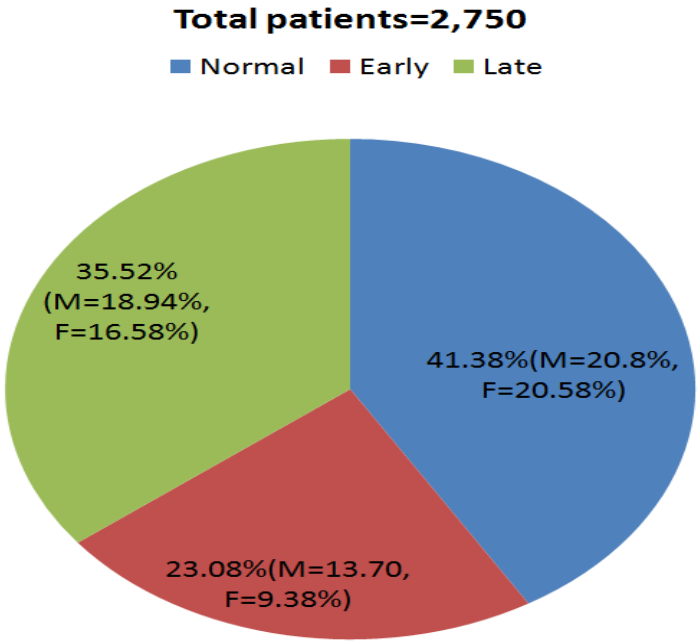

Fig. 4: Radiation induced cognitive impairment

The substitution of IT for cranial irradiation has possibly reduced the severity of the impairments outlined above[78-79], but evidence of long-term neurocognitive deficits in ALL still exists[55-56,82]. As compared to newly diagnosed children who had completed 3 years treatment had greater cognitive impairments and to have learning disabilities despite the fact that no learning difficulties had been found in these children prior to chemotherapy[65.] Triple IT therapy (MTX, cytarabine and hydrocortisone), no significant difference in the level of cognitive impairment was found between the groups, although the MTX group showed a slightly slower processing speed[86]. About 40 percent of childhood cancer survivors given chemotherapy may experience neurocognitive deficits years' later[50].

The impacts of chemotherapy for ALL are inconsistent possibly because of differences among methodological approaches and protocols. There are multiple methodological challenges in longitudinal cognitive assessment, such as selection of appropriate neurocognitive domains and control groups, differences in criteria for impairment and repeated testing[87]. The percentage of ALL survivors experiencing neurocognitive deficits may be raised up to 70 percent depending on the specific type of cognitive domain assessed in working memory[88]. ALL treatment protocols often vary leaving the question of which agents and doses affect neurocognitive outcome still uncertain[56-57]. Treatment is comprised of multiple phases with a unique combination of drugs even a single agent substitution within the complex protocol alters whether or not cognitive late effects appea[89].

4. Neurophysiological Evidence

Neurophysiological deficits are common among childhood ALL survivors have implicated white matter abnormalities results from a disruption of myelinization process during childhood[48]. Along with white matter hypodensity, MTX causes leukoencephalopathy,

multiple necrotic lesions in the periventricular white matter[59,90]. Behavioral symptoms develop gradually over a period of time with reduced attentiveness and intellectual deficits[91]. Impairment in attention accounted for a significant amount relating to decreased volumes of normal white matter and IQ[92]. The cumulative dose of IT- MTX (12 to 30) correlates positively with deficits in neuropsychological, attention and concentration[93]. Following MTX therapy identification of folate pathway in genetic polymorphisms predicts childhood cancer patients developing impairment in attention[73].

Myelinization causes the functional maturation across brain regions[94]. During early childhood frontal lobe undergoes a significant amount of myelinization[48]. Myelinization in this area typically occurs later in the development and mature frontal lobe characteristically has high volume of white matter, so, it is more vulnerable to damage early in brain development. The reduction in volume of dorsolateral prefrontal cortices, mammillary bodies and caudate nuclei in survivors who had received three years IT chemotherapy[95]. It is observed that no neuropsychological impairment found in 40.72% children but had 24.35% in early and 34.9% in late phase of treatment in children with ALL survivors (Fig. 5). No significant difference in volumetric brain size, but a reduction was found in both the mammillary bodies and dorsolateral prefrontal cortices. This pattern of abnormality corresponds to deficits of memory, processing speed, distractibility and attention. Advanced neuroimaging techniques that allow for more precise measurement of myelin integrity and degradation, which include diffusion tensor imaging, quantitative magnetization transfer imaging and quantitative multiple exponential T2 measurements[88].

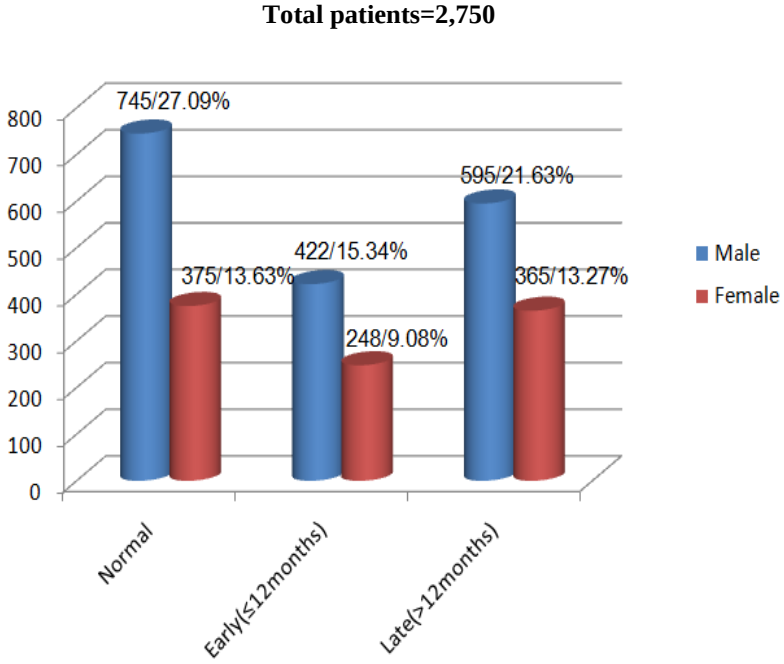

Fig. 5: Chemotherapy induced neuropsychological impairment

Primary, non-cancer cells are more vulnerable to the toxic effects of cytarabine, BCNU and cisplatin than cancer cells. At low-dose 60% oligodendrocytes are killed within 24 hours. Similarly, equivalent to the lower end of high-dose, nearly all oligodendrocytes are killed along with 50% glial-restricted precursor cells[96]. Once it is thought that a chemotherapeutic agent (doxorubicin) is unable to cross the blood-brain barrier reduces neural cell proliferation in dentate gyrus[97]. This is not evaluated from a developmental standpoint which is important to consider since blood-brain barrier of child is still undergoing development and is more susceptible to chemotherapy induced CNS damage.

Potential mechanisms of underlying chemotherapy induced cognitive deficits have been proposed specifically in relation to childhood cancer survivors. White matter damage and reduced cell proliferation may be increased oxidative stress, neuroinflammation, reduced blood flow, deregulation of the immune response and deficits in DNA-repair[98-99]. The effects of chemotherapeutic agents using neural cells, immature brains and mature brains may provide valuable insight into the mechanisms of cognitive late effects in ALL cancer survivors. In this review study, out of 2,750, no chemotherapy induced cognitive impairment found in 40.94% patients but 38.65% in early phase and 20.39% in late phase of treatment of childhood cancer survivors (Fig. 6).

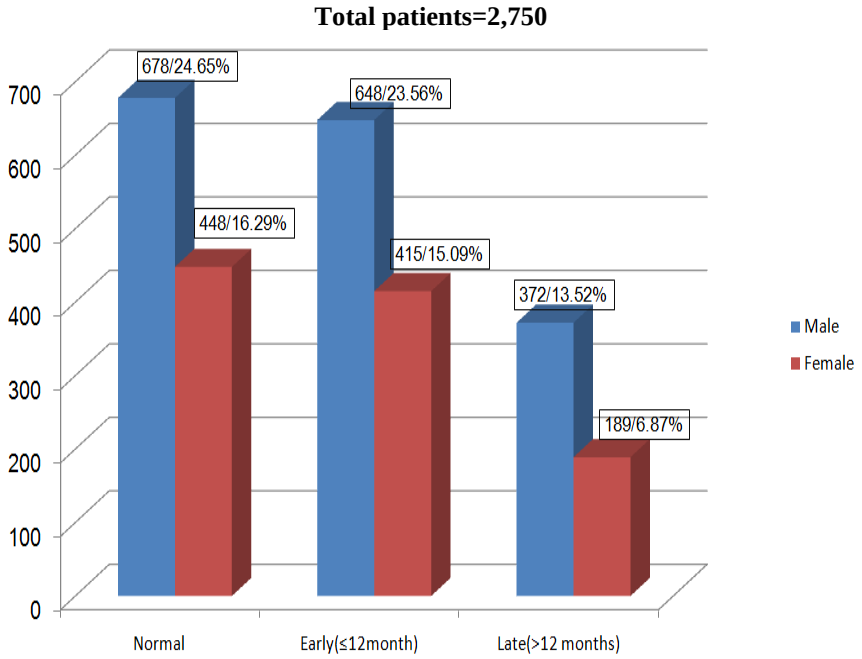

Fig. 6: Chemotherapy induced cognitive impairment

5. **Benefits of Preclinical Mice Models**

It is not possible to conduct a research in a patient which is needed to answer the interrelated questions which drugs combination or doses are at risk. Assessment of cognitive outcome would take longer time for cure of the children[100]. It is difficult to distinguish drug effects from other factors (physiological consequences or patient depression)[101]. The use of preclinical models is another way to find the deficits of learning processes by chemotherapy. This allows drug effects independently of other contributing factors and provides a rapid way to evaluate many drugs. Chemotherapeutic agents and mice models have involved drug application of a single agent[102-104], but mice model make it possible to study drug combinations. Mechanisms of chemotherapy induced neurotoxicity can be studied using preclinical models. Methylphenidate is used to treatment cognitive late effects in childhood cancer survivors[105-107]. Sex differences among drug effects can be studied in mice; it is reported that girls are more susceptible to the neurotoxic effects of these agents[108]. But in this study, male preponderance of these deficits were found both early and late phase of treatment (Fig. 3-6).

Mechanisms for chemotherapy induced neurotoxicity in clinical studies are little known, preclinical models in mice have reported that MTX and cytarabine cross blood-brain barrier in various routes. Cell death and disruption of cell division occurs in vivo after giving three i.v. dose of cytarabine in mice[96]. A single i.v. MTX (37.5-300 mg/kg) reduces hippocampal cell proliferation. The hippocampus is important for learning and memory; detrimental effects on cognitive performance results if neurogenesis is disturbed[109]. Intraventricular injections of MTX in mice for three alternative days resulted in lowered concentrations of hippocampal brain amines. These findings are consistent in which adult mice treated with MTX failed to learn to avoid an aversive stimulus relative to controls [110]. MTX (0.05 mg/kg or 0.1 mg/kg, i.p) administered during brain development in mice results in reduced density of synapses of the hippocampus[111]. Five repeated doses of intaventricular injection of MTX (1-2 mg/kg) produced neuropathological changes similar to the damage seen in human patients[112]. In this review study, it is found that the patients were given three high dose of MTX ($2.5gm/m^2$) during CNS directed therapy. So, there is definitely a detrimental effect on cognitive performance, which is consistent with the observation of authors.

Preclinical models have been useful to investigate chemotherapy induced deficits in learning and memory using adult models of breast cancer treatment of behavioral assays[113-116]. Mice have highlighted the possibility of drug combinations that have a greater effect than either drug alone. Chemotherapy induced cognitive deficits have been examined in mice with anti-depressants to block decreased cell proliferation treated with 5-fluorouracil[117]. Fluoxetine reverses depression of neurogenesis caused by MTX in mice[118]. These will guide the physicians about treatment options that decrease chemotherapy induced cognitive deficits and if require to treat these form of deficits in children with ALL[115]. Though Fluoxetine not yet started in our setting, very soon it will be added in ALL patients following high dose MTX therapy to prevent these unwanted deficits in future.

6. **Mice Models of Childhood Cancer Treatment**

Neonatal damage has been found to have more severe long-term deficits than damage in mature adult brain [119]. The first assessment of cancer treatment on developing brains used young rat pups at PND 17, an age selected because of developmental similarities to newborn infants. Treatment included CRT alone (1,000 R), MTX alone (5mg/kg, i.p), or a combination of CRT and MTX. Testing with a simultaneous discrimination task began when the rats were 12-14 weeks old. It is observed that mice receiving a combination therapy were significantly slower development compared to others[103].

Treatment protocols of ALL that include multiple phases of therapy of two years with single dose of radiation and /or MTX. This was done because of rats at this age develops at an exceedingly faster rate. This limitation is shared among the majority of studies using mice models to investigate childhood cancer treatment in young pups. 16-17 days old rat pups were treated with a single dose of MTX (0.005 mg/kg, i.p). At 12-14 weeks, they were tested on conditioned response and conditioned taste aversion tasks. Those treated with MTX developed delay conditioning at a slower rate. MTX-treated animals failed to display a taste aversion compared to controls, but were equal to controls by the next trial. Neonatal mice received MTX were slower to learn about environmental events [104] but no impairments were found in 17 day rat treated with MTX (0.005 mg/kg, i.p.). In contrast, no impairment was found on a more complex Pavlovian conditioning task focusing on negative discrimination[102].

Childhood cancer therapy consists of different drugs which was studied in mice with nine different treatment combinations of MTX (2 or 4 mg/kg, i.p.), prednisolone (18 or 36 mg/kg,i.p) and CRT (1000 cGy), treated at PND 17-18 [120]. Prednisolones are commonly included among the drugs used in ALL (double and triple IT) therapy and it is reported that glucocorticoid potentiate hippocampal damage by neurotoxins[121]. We had observed greater behavioral deficits in treatment group. Females showed altered behavior at lower doses than males[120]. The girls may be more susceptible to untoward effects of these drugs[108] but we found it more in male. While prednisolone antagonized MTX thereby, preventing behavioral alterations at low doses; it enhanced MTX and CRT related deficits at high doses[120].

Multidrug chemotherapeutic agents are used in ALL, but knowledge pertaining to individual agents to neurocognitive deficits is little known. The potential deficits of cytarabine, vincristine, doxorubicin and L-asparaginase cannot be dismissed to neurocognitive deficits. Preclinical models have provided evidence of cognitive disruption following administration of such agents. Cytarabine produced impairment in long-term spatial memory in mice after 30 days but not in the first day[122]. Vincristine causes disruption of sensory processing (neuropathies and mechanical sensitivity)[123], but impairment measured by the Morris water maze has found at high doses[124]. Only doxorubicin therapy led to impairment in inhibitory avoidance conditioning in mice but not on a passive avoidance task[125-126]. Combination therapy with cyclophosphamide and doxorubicin produced impairment in contextual fear conditioning and passive avoidance learning[127-128]. The correlation between L-asparaginase and cognition has not yet been observed, an important factor to consider for future research. The effects of corticosteroids commonly used in combination therapy are correlated with poor cognitive outcome. The children treated with dexamethasone may be at greater risk of late neurocognitive effects compared to children of ALL treated with prednisone[89].

CONCLUSION

The exact role of chemotherapeutic agents causing cognitive and academic sequelae is still under debate. The deficits are more pronounced in male at early phase of treatment may be due to increased acceptance of chemotherapeutic agents. Female are affected less may be due to their genetic factors. Cognitive and academic impairment are common following chemotherapy. Radiation also causes cognitive deficits in children with ALL. Neuropsychological impairment was also a feature following chemotherapy in ALL.

The survival rate for childhood cancer is gradually increasing; new researches are required what happens after remission. It is necessary for children and their parents to know the potential late effects of therapy[47]. They should be followed up for several years after treatment for emerging medical complications and academic problems. Further guidelines for childhood cancer survivors are outlined[47]. Assessment tools that can quickly identify the risk survivors are now under development[129]. Judgment of multimodal treatment protocols is necessary to evaluate specific drug effects that can leads to cognitive late effects. These will help the physicians about treatment options that reduce or eliminate chemotherapy induced neurocognitive deficits which have been supported by behavioral and neurophysiological evidence.

FURTHER SUGGESTION

Development of blood-brain barrier and lack of certain enzymes at early stages will impact how chemotherapeutic agents are metabolized by the body, as well as how the brain is affected. Dosage and route of administration also take these developmental aspects. This needs to be taken into consideration when choosing behavioral assays. Building a bridge between clinical and preclinical research would greatly improve the study of chemotherapy induced cognitive effects of childhood cancer treatment. Future preclinical research in this area should aim to provide a more accurate model of clinical treatment through alterations in drug

selection, treatment regimen and behavioral aspects. Since MTX and cytarabine are commonly administered during CNS prophylaxis, it would be valuable to investigate the effects of this specific combination of chemotherapeutic agents. Preclinical models are ideal for parsing apart the individual and combined effects on learning and memory where chemotherapeutic agents are used. Repeated administration of these agents can be examined by treating pre weanling pups on multiple consecutive days early in development rather than a single administration. Mice can be assessed during adolescence (PND 35) and adulthood (PND 60) for long-term effects of neurotoxicity. Appropriate behavioral assays need to be selected for neurocognitive deficits in ALL survivors. Since the exact mechanisms of chemotherapy induced cognitive impairment are not yet fully understood, a battery of preclinical assays of learning and memory should be studied, as sensitivity to chemotherapy induced cognitive deficits differs among tasks in models of adult chemotherapeutic treatment[99].

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CONFLICTS OF INTEREST

The author declares no conflicts of interest regarding the publication of this paper.

ETHICAL CONSIDERATION

The Institutional ethical committee and review board of BSMMU approved the protocols and signed informed consent was obtained from the patients, their parents or their guardians as appropriate.

LIMITATIONS OF THE STUDY

This was mostly based on single center which resulted in the limitations for conclusive massage, demanding the need for further multicenter study with large sample size on chemotherapy induced cognitive impairment in children with acute lymphoblastic leukemia.

DISCLOSURE

This paper has been read and approved by the author, has not been published totally or partly in any other journal and will not be published in any other periodicals.

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No funding had been taken from the department or from the parents.

AUTHOR CONTRIBUTION

This work was carried out in collaboration between the authors. Author MGH designed the study, wrote the protocol and interpreted the data. He also managed the literature searches and produced the initial draft. Author CYJ anchored the field study, gathered initial data and performed preliminary data analysis. He also managed the literature searches. Both the authors read and approved the final manuscript.

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