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Contribution of Chemotherapy Treatment Factors to Cognitive Outcomes in Survivors of Childhood Leukemia

Long-term cognitive deficits are frequently observed in survivors of childhood acute lymphoblastic leukemia (ALL). Studies conducted in mice have identified chemotherapy agents methotrexate (MTX), dexamethasone (DEX), and prednisone (PRED) as having a significantly adverse impact on brain development. However, few studies have examined the relationship between variations in childhood exposure to these agents and cognitive abilities among ALL survivors. We hypothesized that survivors who had received higher doses of MTX would exhibit significantly greater cognitive impairments than survivors who received lower doses. Further, we hypothesized that survivors treated with both PRED and DEX would have greater cognitive deficits than those treated with DEX only. The sample included 59 ALL survivors (35 males, 24 females) between the ages of 8 and 18 years old. Compared to normed means, male ALL survivors exhibited significantly lower scores on working memory and processing speed, $t_{(34)}$*=-3.912, p<0.001 and t(34)=-5.077, p<0.001, respectively; female ALL survivors exhibited significantly lower scores on working memory,* $t_{(23)}$*=-3.035, p<0.01. Variations in exposure to MTX, DEX, and PRED were not correlated with variations in cognitive outcomes. Further research is needed to determine what factors explain different cognitive outcomes after chemotherapy treatment for childhood ALL.*

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1. BACKGROUND

Acute Lymphoblastic Leukemia (ALL) is a cancer of the white blood cells. It involves an overproduction of lymphocytes—immature white blood cells—in the bone marrow. The accumulation of these cancerous cells inhibits the production of normal cells in the bone marrow.

ALL is the most prevalent pediatric cancer, accounting for approximately 26% of all cases of childhood cancer (Essig et al., 2013; Jacola et al., 2016). Additionally, ALL most frequently occurs in childhood with 60% of ALL cases occurring before the age of 20 (Bassan & Hoelzer, 2011; Hunger et al., 2012; Pui at al., 2008). Childhood ALL is typically diagnosed between the ages of two and five years (Pui et al., 2008), coinciding with a period of major developmental changes in the brain.

1.1 Cranial Radiation Therapy, Chemotherapy, and Late Effects

The past few decades have seen a tremendous increase in the survival rates of childhood ALL patients. The five-year survival rate was approximately 5% in 1960 (Edelmann et al., 2013). Today, the survival rate exceeds 90% (Pépin et al., 2016).

Cranial Radiation Therapy (CRT) introduced in the 1960s, was accredited with early increases in survival by targeting central nervous system sites of relapse. However, CRT use in cancer treatment has been associated with a high incidence of neurotoxicity (Montour-Proulx et al., 2005) and therefore, is now used sparingly. As a result, treatment with chemotherapy alone, consisting of the administration of a cocktail of drugs over several treatment phases lasting as long as three years, is the preferred approach to treating ALL patients.

The term "late effects" is used broadly to describe observed deficits associated with cancer treatment. Late effects emerge months or even years after the completion of treatment and persist across the lifespan. Studies show that long-term survivors of ALL experience significant deficits—believed to be associated with their treatment—including premature mortality, neoplasms, congestive heart failure, stroke, obesity, osteonecrosis, and neurocognitive dysfunction (Kadan-Lottick et al., 2009; Mody et al., 2008). Neurocognitive dysfunction is particularly impactful on quality of life.

Despite the efforts to reduce the observed intellectual impairments and attention dysfunction, they continue to be reported in survivors (Buizer et al., 2005; Cheung & Krull, 2015; Montour-Proulx et al., 2005). Studies have shown that survivors are at an increased risk of neurocognitive deficits in attention, processing efficacy, and executive function (Cheung & Krull, 2015). Understanding how childhood ALL or its treatment leads to intellectual impairments is a high priority for research.

1.2 Chemotherapy Protocols

Chemotherapy treatment is administered according to predetermined protocols that outline which chemotherapy agents should be administered, in what amounts, and how often. At diagnosis, patients are stratified into standard-risk (SR) or high-risk (HR)

categories based on likelihood of relapse. Individuals stratified as HR receive a more intense chemotherapy treatment than those considered SR. It is important to note that the exact doses of chemotherapy agents delivered vary between individuals based on risk-stratification, protocol type, and adjustments made to accommodate individual tolerances.

1.3 Chemotherapy Agents and Late Effects

It is widely believed that chemotherapy agents might have adverse effects on cognitive function. The agents most commonly suspected to play a large role in the emergence of late effects include intravenous methotrexate and prednisone (Montour-Proulx et al., 2005). Many studies investigating the impact of chemotherapy treatment have been conducted and a broad range of chemotherapy agents and factors have been attributed to causing the observed deficits (Duffner et al., 2014; Edelmann et al., 2013; Kingma et al., 2001; Waber et al., 2013).

Past research has linked glucocorticoids (i.e. prednisone and dexamethasone) to the cognitive outcomes observed in survivors of childhood ALL. Prednisone was the preferred glucocorticoid administered in the past to cancer patients. However, due to its better penetration into the central nervous system (Labar et al., 2010), dexamethasone is now frequently used instead. High levels of dexamethasone have been reported to have both short-term and long-term adverse effects on declarative memory, possibly through impacts on the hippocampus (Kingma et al., 2001). Greater academic problems and memory deficits have been reported in survivors treated with dexamethasone compared to those treated with prednisone (Waber et al., 2013). Glucocorticoid receptors are actively involved in memory storage and consolidation, consistent with the observation that dexamethasone-treated survivors were found to perform significantly worse on tests of vocabulary, academic learning, and verbal memory in comparison to normed means, while survivors treated without dexamethasone performed at or above normed means (Edelmann et al., 2013).

Intravenous methotrexate has been speculated to have adverse cognitive effects. A study investigating the contribution of methotrexate exposure to cognitive deficits found that individuals treated with an intense central nervous system directed therapy scored below average on more outcome measures than individuals who received fewer central nervous system directed treatments (Duffner et al., 2014).

Long-term neuropsychological effects of central nervous system directed chemotherapy treatment remain largely unknown (Buizer et al., 2005). A younger age at diagnosis and female sex have been associated with increased risk of late effects (von der Weid et al., 2003). Further, it has been reported that high-risk individuals experience a greater overall decline than standard-risk individuals (Mulhern et al., 2005).

While a detailed understanding of the mechanisms involved is lacking, sufficient research has been conducted to implicate exposure to chemotherapy agents in the

adverse behavioral and cognitive outcomes observed in survivors of childhood ALL (e.g. Edelmann et al., 2013; Kingma et al., 2001; Waber et al., 2013). The severity of deficits varies considerably between survivors, as does the intensity of chemotherapy treatments delivered to patients (e.g., between risk-stratification categories and between different contemporary ALL treatment protocols). Differences in cognitive outcomes between standard-risk and high-risk groups suggest that cumulative doses of chemotherapy agents may contribute to the magnitude of the observed deficits. However, few studies have systematically and comprehensively evaluated the relationship between cumulative chemotherapy drug exposure and cognitive outcomes in survivors (e.g. Essig et al., 2013).

1.4 Present Study

The present study seeks to characterize the cognitive deficits experienced by survivors of childhood ALL and determine whether there is a relationship between chemotherapy exposure and observed deficits. We hypothesized that survivors who had received higher doses of MTX and VCR would exhibit significantly greater cognitive impairments than survivors who received lower doses. Further, we hypothesized that survivors treated with both PRED and DEX would have greater cognitive deficits than those treated with DEX only.

2. METHODOLOGY

2.1 Participants

Study participants were survivors of childhood ALL, treated on contemporary chemotherapy-only protocols. The participant sample (n=59) was composed of 35 males and 24 females between the ages of eight years and 18 years at testing. Inclusion criteria for participation required participants to be at least two years post-treatment with no history of relapse, to have received chemotherapy-only treatment, and to be fluent in English. Participants were excluded if central nervous system involvement—presence of leukemia cells in the cerebrospinal fluid—was noted at diagnosis, if treatment included cranial radiation therapy or bone marrow transplant, or if a prior diagnosis of Down syndrome or brain injury was noted.

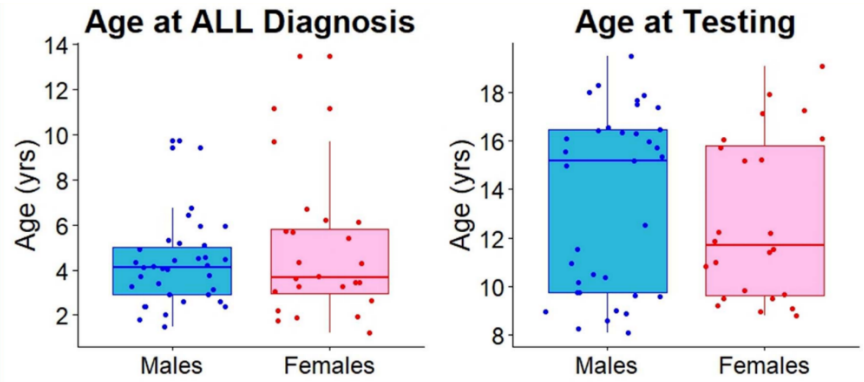
2.2 Materials & Measures

Survivors had previously been recruited as part of a multidisciplinary research program in childhood ALL; pre-existing data on cognitive outcomes was used for this study. To evaluate cognitive abilities, survivors completed the Wechsler Intelligence Scale for Children-IV (WISC-IV) and were assessed on four indices: verbal comprehension, perceptual reasoning, working memory, and processing speed.

Data on exposure to MTX (via intrathecal, intravenous, and oral delivery), PRED, and DEX was collected through retrospective review of medical files in the oncology clinic at SickKids Hospital. Information recorded in the chemotherapy protocol

charts was entered into an electronic database and matched with outcome measures using participant IDs assigned to patients at testing.

Figure 1. Box-and-Whisker Plots Displaying Age at Diagnosis and Age at Testing of ALL Survivor Sample (35 Males, 24 Females)

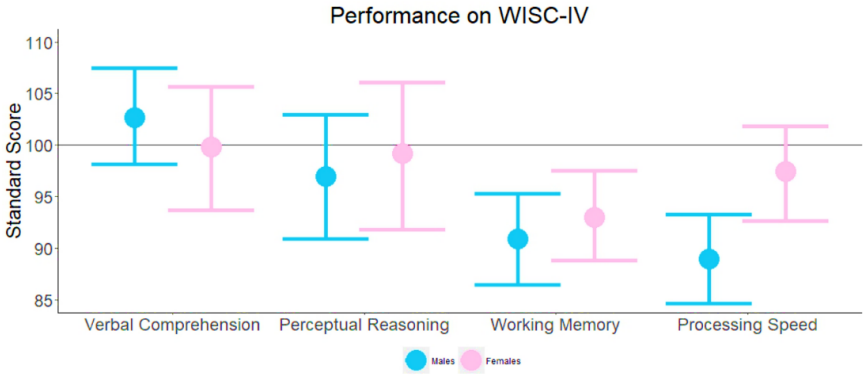


3. RESULTS

3.1 Analysis of Cognitive Outcome in ALL Survivors

Four independent-measure, one-tailed t-tests were conducted to compare ALL survivor scores on each of the four indices with normed means (Mean=100, SD=15). The scores were age and sex adjusted in accordance with WISC-IV. Survivor performance on all four indices (verbal comprehension, perceptual reasoning, working memory, and processing speed) is shown in figure 2. Lower scores indicate impairment.

Figure 2. Survivors Performance on All Four Indices of the WISC-IV



Note. Survivors performance on all four indices of the WISC-IV in comparison to the normed mean of 100, represented by the horizontal black line. Male and female average score with 95% confidence intervals are shown separately.

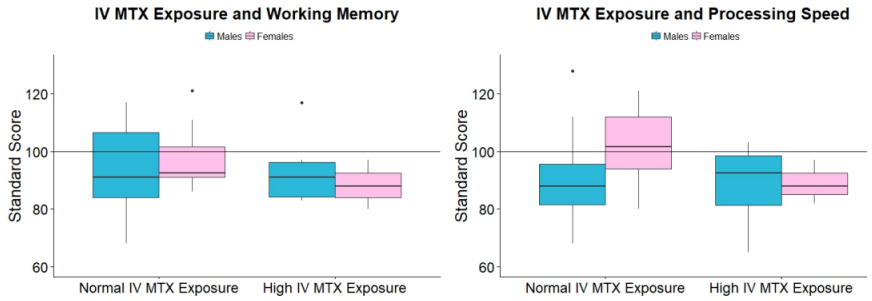
Compared to the general population (represented via normed means), male survivors exhibited significantly lower scores on working memory and processing speed, $t_{(34)}$=-3.912, p<0.001 and $t_{(34)}$=-5.077, p<0.001, respectively. Female survivors exhibited significantly lower scores on working memory, $t_{(23)}$=-3.035, p<0.01, than the general population.

No statistically significant differences were observed in verbal comprehension and perceptual reasoning between survivors and normed means. Female survivors did not differ significantly on processing speed compared to the general population.

3.2 Impacts of Chemotherapy Exposure on Cognitive Deficits in ALL Survivors

The cumulative amounts of MTX, PRED, and DEX were calculated and compared with the above observed cognitive deficits in working memory and processing speed. Once again, male and female survivors were studied separately. Analysis revealed no statistically significant correlation between the total amount of chemotherapy agent administered and the magnitude of cognitive impairment observed. Other factors, including age at diagnosis, years since diagnosis, and sex, were not associated with cognitive abilities.

Figure 3. Box-and-Whisker Plots of the Impact of Normal vs High MTX (Administered Intravenously) Exposure

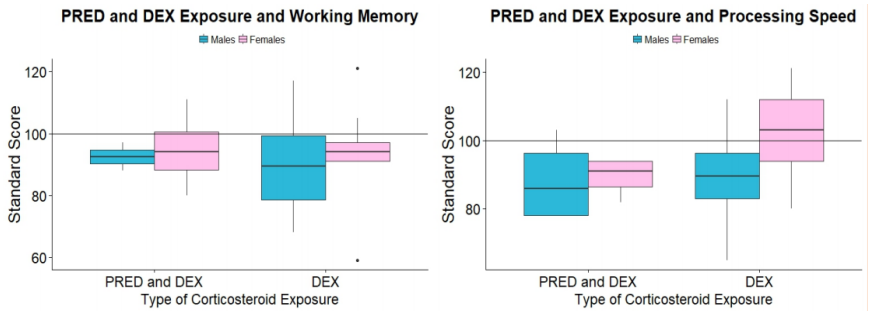


Note. Box-and-whisker plots of the impact of normal vs high MTX (administered intravenously) exposure on working memory and processing speed in male and female survivors. No statistically significant differences between performance outcomes and exposure level.

4. DISCUSSION

The investigation of cognitive performance of survivors compared to normed means revealed that male and female survivors performed significantly worse on working memory, and male survivors performed significantly worse on processing speed, in comparison to the general population. These results corroborate the conclusions of previous studies which found statistically significant cognitive deficits in survivors compared to controls or population norms.

Figure 4. Box-and-Whisker Plots of the Impact of PRED and DEX vs DEX-Only Exposure



Note. Box-and-whisker plots of the impact of PRED and DEX vs DEX-only exposure on working memory and processing speed in male and female survivors. No statistically significant differences between performance outcomes and exposure type were obtained.

The above findings do not support our hypothesis that survivors who received a higher cumulative dose of MTX would exhibit greater cognitive impairments than survivors who received a lower MTX dose. Nor do the findings support our hypothesis that survivors who received both PRED and DEX would have greater cognitive deficits than those treated with DEX only. The severity of the cognitive deficits observed appear to not be directly correlated with the cumulative amount of exposure to MTX, PRED, and DEX.

4.1 Future Directions and Limitations

There were several challenges during the study that should be considered in interpreting the results. Firstly, the sample size was relatively small. Having few participants lowers the likelihood of obtaining truly representative results. Secondly, participant cognitive performance was collected only post-chemotherapy treatment. Therefore, it is impossible to know what the true changes in working memory and processing speed of the survivors are. Thirdly, conducting retrospective reviews of patient charts to calculate cumulative chemotherapy doses is a very tedious process. It is made difficult by a lack of notational consistency across different patient files, possibly impacting the accuracy of the reported cumulative doses. Further, the case-by-case nature of chemotherapy treatment could lead to discrepancies making it difficult to accurately collect and cumulate the data. Fourthly, because chemotherapy treatment is administered as a cocktail of numerous agents it is impossible to determine with certainty which drug is responsible for the adverse effects observed in survivors. Since the cumulative administered dose of different chemotherapy agents is frequently related—so that individuals receiving elevated levels of MTX similarly receive elevated amounts of VCR, for instance—it is impossible to determine explicitly whether it is a single drug, the combined effect of

two or more of the drugs, or an interaction between the drugs that contribute most significantly to the cognitive impairments exhibited by survivors. It is unethical and thus impossible to treat children with a single chemotherapy agent to determine the contribution of each chemotherapy agent separately. This is where laboratory experimentation in small animal models is very valuable: mice treated with a single chemotherapy agent can be studied to better understand the structural and functional brain abnormalities that result from the administration of a single drug.

4.2 Significance

With high treatment success rates, long-term quality of life for ALL survivors is a key concern during and after treatment. The characterization of cognitive outcomes in survivors is key to understanding the types and magnitude of impairments experienced. Identification of the factors that determine cognitive outcomes is critical for developing better screening tools for early detection of late effects in survivors and for creating effective therapy programs for individuals facing these impairments. The findings of this study reveal that there is not a simple and direct contribution of chemotherapy exposure to cognitive outcomes in survivors. It is possible that individual responses to drugs may be dependent on other factors such as nutrition, genetics, and/or ethnicity. This introduces considerable variability, so that uncovering the influence of chemotherapy intensity (if present) will require stratification based on these additional variables. Further research should investigate these factors—genetic and environmental—in relation to chemotherapy exposure to elucidate the causes of variability in survivor cognitive outcomes.

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