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Pharmacokinetics of Chemotherapeutic Drugs in Pediatric Patients with Down Syndrome and Leukemia

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Abstract

Children with Down syndrome (DS) have a 10 – 30 fold increased risk of developing acute myeloid leukemia or acute lymphoblastic leukemia. Patients with DS and leukemia are treated with the same chemotherapeutic agents as patients without DS. Treatment regimens for pediatric leukemia comprise multiple cytotoxic drugs including methotrexate, doxorubicin, vincristine, cytarabine, and etoposide. There have been reports of increased toxicity, as well as altered therapeutic outcomes in pediatric patients with DS and leukemia. This review is focused on the pharmacokinetics of cytotoxic drugs in pediatric patients with leukemia and DS. The available literature suggests that methotrexate and thioguanine display altered pharmacokinetic parameters in pediatric patients with DS. It has been hypothesized that the variable pharmacokinetics of these drugs may contribute to the increased incidence of treatment-related toxicities seen in DS. Data from a small number of studies suggest that the pharmacokinetics of vincristine, etoposide, doxorubicin, and busulfan are similar between patients with and without DS. Definitive conclusions regarding the pharmacokinetics of cytotoxic drugs in pediatric patients with leukemia and DS are difficult to reach due to limitations in the available studies.

Keywords

Pharmacokinetics; Down syndrome; Leukemia; Chemotherapy; Pediatric

INTRODUCTION

Children with Down syndrome (DS) are at an elevated risk for developing leukemias in comparison to children without DS¹. Children with DS have a 10 – 30 fold increase in the risk of developing acute myeloid leukemia or acute lymphoblastic leukemia^{1,2}. Conversely, children with DS have a lower risk for developing solid tumors compared to children without DS¹. Pediatric patients with DS and leukemia are treated with the same chemotherapeutic drugs as patients without DS. Treatment regimens for pediatric leukemia are comprised of multiple cytotoxic agents that are generally administered in combination for varying durations depending on the type of leukemia being treated. Drugs such as

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methotrexate, doxorubicin, vincristine, cytarabine, and etoposide are utilized in various regimens to treat pediatric leukemias, while busulfan is used prior to a bone marrow transplant in certain leukemia patients. These drugs are effective in patients with and without DS; however, the prognosis for patients with DS and leukemia can differ depending on the form that is diagnosed. In general, patients with DS and acute myeloid leukemia (AML) have better outcomes than those who have acute lymphoblastic leukemia (ALL)³. One factor that may be associated with the poor clinical outcomes seen in patients with DS and ALL is the relative resistance to cytotoxic drugs of trisomic lymphoblasts. In comparison, myeloblasts from patients with DS and AML display increased susceptibility to cytotoxic drugs, which may contribute to higher cure rates in the clinic⁴. Pediatric patients with DS and leukemia often have altered drug toxicity profiles compared to pediatric patients without DS. Pediatric patients with DS and leukemia experience chemotherapy-related toxicities at a higher frequency and severity compared to those without DS. Toxicities that have been reported to occur at a higher frequency in patients with DS include cardiotoxicity, myelosuppression, infections, and mucositis^{5–9}. The reasons behind the increased rates of chemotherapy-related toxicities in patients with leukemia and DS are likely to be multifactorial¹⁰. It is known that pharmacokinetic variability can impact the toxicity of certain drugs during and/or after treatment¹¹. There may be a pharmacokinetic component to account for some of the increases in chemotherapy-related toxicity in pediatric patients with DS and leukemia.

Published reports have described altered pharmacokinetics of various non-cytotoxic agents in individuals with DS. In 1970, one of the first accounts of altered drug disposition in children with DS described altered metabolism and decreased protein binding of aspirin¹². The metabolism of acetaminophen to glutathione conjugates was found to be possibly increased in subjects with DS¹³. Stowe et al. suggested that theophylline clearance was lower in individuals with DS compared to individuals without DS¹⁴. Another report considered the pharmacokinetics of donepezil in patients with Down syndrome-related dementia. Patients showed reduced clearance of donepezil, and it was suggested that the elevated concentrations of the drug may contribute to the increased rates of donepezil-related adverse effects observed in patients with Down syndrome-related dementia^{15,16}.

The pharmacokinetics of antileukemic agents have been investigated in pediatric patients with DS to a limited extent. Most of the studies explored whether the altered pharmacokinetics of chemotherapeutic drugs correlate with the disproportionate rates of adverse effects among pediatric patients with DS with the goal of establishing more effective dosing regimens. The purpose of this succinct review is to present what is known about the pharmacokinetics of chemotherapeutic drugs in pediatric patients with leukemia and DS while highlighting the potential significance of the main findings.

LITERATURE ANALYSIS

Published reports on the pharmacokinetics of chemotherapeutic drugs in pediatric patients with leukemia and DS were considered for this review. Reports were identified from the PubMed and OVID online databases. Pediatric patients were defined as those less than 18 – 21 years of age. The following keywords were used during searches: “Down syndrome”,

“trisomy 21”, “pharmacokinetics”, “leukemia”, “disposition”, “pediatric”, and “chemotherapy”. Literature searches were done between February, 2015 and July, 2015. Searches resulted in 9 primary research articles on the pharmacokinetics of 6 drugs used for the treatment of leukemia in pediatric patients with DS. The search also revealed multiple primary research articles and reviews on altered drug metabolism in DS. The reports considered in this review date from 1970 to the 2010s.

ANTILEUKEMIC AGENTS THAT HAVE SHOWN ALTERED PHARMACOKINETICS IN DS

Methotrexate (MTX) is a folate antagonist that has a multitude of indications, including the treatment of ALL^{17,18}. The first report that considered the pharmacokinetics of MTX in DS was published in 1987 by Peeters and Poon. The authors reported that two patients with DS and leukemia that were being treated with MTX displayed “normal rapid clearance” of the drug. The patients with DS also exhibited severe MTX-related toxicity. The authors postulated that gene dosage effect due to the extra 21st chromosome alters the synthesis of purines which results in increased toxicity while the clearance of MTX appeared normal. The end result of this effect would be increased sensitivity to an antifolate agent such as MTX⁹. Later that same year, Garré et al. (1987) compared the pharmacokinetics and toxicity of MTX in children with and without DS being treated for ALL. The authors reported that the 5 patients with DS had higher median 42-hour plasma concentrations of MTX in comparison to control patients without DS (0.47 $\mu\text{mol/L}$ vs. 0.24 $\mu\text{mol/L}$ respectively, $p = 0.03$). The clearance of MTX was not found to be significantly different despite different plasma concentrations. This was an unexpected finding in light of the elevated MTX plasma concentrations in the patients with DS. The authors hypothesized that the unchanged clearance finding may result from difficulties to accurately estimate renal clearance in the patients with DS combined with the effect of limitations in sample size. When discussing toxicity and MTX plasma levels, the authors also suggested that altered metabolism of MTX in DS may result in the gradual release of MTX from body tissues, which would prolong elevated plasma levels and contribute to the increased toxicity. The incidence of grade 2 – 4 toxicity (Pediatric Oncology Group, standard grading criteria) was shown to be significantly higher in patients with DS following treatment with MTX ($p < 0.0001$). Folate deficiency in the DS setting and the resulting higher sensitivity to MTX were also noted as potential contributors to the increased incidence of MTX-induced toxicity. The authors concluded that altered MTX pharmacokinetics may contribute to the increased incidence of MTX-induced toxicity in patients with ALL and DS¹⁸.

In 2010, a report by Buitenkamp et al. also examined the pharmacokinetics of MTX and MTX-induced toxicity in pediatric patients with ALL and DS. This was a relatively large retrospective case-control study involving 44 patients with ALL and DS, and 87 patients with ALL and without DS. It was noted that patients with DS experienced more severe toxicities associated to MTX treatment, and that 20.5% of the total number of MTX doses given to the patients with DS had to be reduced during treatment. The authors utilized non-linear mixed effects modeling (NONMEM) to identify a 5% reduction in MTX clearance in patients with DS in comparison to the clearance in patients without DS ($p = 0.001$). No

significant differences in the plasma levels of MTX at 24 or 48 hours were detected. No correlation between MTX area under the concentration curve (AUC) and toxicity was found. The authors concluded that the small yet significant difference in MTX clearance between patients with and without DS was marginal and not likely to have a clinical impact. They proposed that the increased toxicity seen in patients with DS was a pharmacodynamically driven phenomenon¹⁹.

Thioguanine (6-TG) is an antimetabolite chemotherapy agent that requires intracellular transformation into active thioguanine nucleotides (TGN) for the inhibition of purine synthesis. 6-TG is generally utilized to treat AML and ALL²⁰. In 2009, Palle et al. investigated the pharmacokinetics of 6-TG in children with AML. This study included 4 children with DS. In patients treated with 6-TG during the induction phase of chemotherapy, the intracellular concentrations of TGN were considered a pharmacokinetic endpoint. It was reported that patients with DS had significantly higher TGN concentrations inside erythrocytes. Patients with DS had a median TGN concentration of 7.44 $\mu\text{mol}/\text{mmol}$ compared to 2.85 $\mu\text{mol}/\text{mmol}$ for the non-DS group > 2 years old and 2.97 $\mu\text{mol}/\text{mmol}$ in the non-DS group < 2 years old. The differences in concentration between the children with DS and without DS were found to be significant ($p = 0.04$). The patients with DS did receive reduced doses of 6-TG, so the reported TGN concentrations were dose-normalized. The authors concluded that these observations support the practice of dose reduction in pediatric patients with AML and DS²¹.

ANTILEUKEMIC AGENTS THAT HAVE NOT SHOWN ALTERED PHARMACOKINETICS IN DS

Vincristine is a vinca alkaloid derivative that is used to treat ALL, as well as other solid and hematological malignancies. It disrupts microtubule formation, which in turn disrupts the mitotic spindle, resulting in cellular arrest²². Vincristine is often a component in chemotherapy regimens used to treat patients with DS and ALL²³. In 2009, Lönnerholm et al. described the pharmacokinetics of vincristine in 6 children with ALL and DS versus 92 children with ALL and without DS. Using Bayesian analysis, the authors constructed a 2-compartment pharmacokinetic model that was fit to concentration-time data from the patients. They found no differences between the pharmacokinetic parameters of vincristine in children with DS versus children without DS. The authors noted that there was no pharmacokinetic justification for dose adjustments in patients with DS; however, they did indicate that differential drug sensitivity to vincristine is possible based on previous findings with other drugs²⁴.

Etoposide (VP-16) is a topoisomerase II inhibitor that prevents DNA uncoiling, arrests cell cycle progression, and triggers apoptosis in rapidly dividing cells. It is used for treating various malignancies, including ALL (an off-label indication in the United States)²⁵. The first study to report some data on the pharmacokinetics of VP-16 in pediatric patients with DS was published by Eksborg et al. in 2000. Two children with DS were shown to have AUC and half-life values that were consistent with the AUC values observed in children without DS. The authors also noted that the patients with DS did not experience increased

toxicity during treatment. The conclusion was that the pharmacokinetics of VP-16 is similar between patients with and without DS²⁶. In 2006, Palle et al. also published a study that included data on the pharmacokinetics of VP-16 in 5 patients with DS being treated for AML. It was reported that VP-16 clearance was 13.6 ml/min/m² for patients with DS, while patients without DS had clearances between 17.1 and 17.6. The 20% decrease in the clearance of VP-16 in patients with DS approached statistical significance ($p = 0.067$). The authors concluded that children with DS tended to have lower VP-16 clearance. They also acknowledged the limitations of their study and encouraged further confirmatory studies with larger sample sizes²⁷.

Doxorubicin is an anthracycline chemotherapeutic agent that can be used for AML and ALL treatment, as well as for various other malignancies. It has multiple mechanisms of action including DNA intercalation, topoisomerase II inhibition, and generation of damaging oxidative radicals²⁸. Anthracycline-related cardiotoxicity has been studied in patients with DS in the past; however, the pharmacokinetics of anthracyclines (including doxorubicin) in DS is seldom considered⁸. In the previously discussed study by Eksborg et al., the authors mentioned a single patient with DS treated with doxorubicin that displayed decreased clearance, but data were not shown²⁶. In 2006, Palle et al. analyzed the pharmacokinetics of doxorubicin in patients with and without DS. The 4 children with DS received reduced doses of doxorubicin, and displayed non-significant differences in clearance (538 ml/min/m² in non-DS versus 523 ml/min/m² in DS, $p = 0.48$) and in mean plasma concentrations (232 ng/ml in non-DS versus 151 ng/ml in DS, $p = 0.14$) in comparison to 37 children without DS. The authors concluded that there was little basis for adjusting doxorubicin doses based on pharmacokinetics, but also stated that reduced doses may be justified due to the increased sensitivity to anthracyclines in children with DS and AML⁷.

Busulfan is an alkylating agent that is indicated for treating chronic myelogenous leukemia. It can also be used for patients with AML prior to receiving bone marrow transplantation. Busulfan's cytotoxicity is the result of its ability to alkylate DNA²⁹. Patients with DS have been shown to tolerate busulfan while experiencing toxicity similar to that of patients without DS, although there is some evidence that suggests that patients with DS tend to have a higher risk of pulmonary complications during the post-transplant period³⁰. The pharmacokinetics of daily, high-dose busulfan dosing was considered by Shaw et al. in 1994. Of the 22 children studied, 19 had AML and 3 had ALL. Two patients with leukemia and DS were included in the study. However, one of the patients with DS exhibited a much different pharmacokinetic profile and data from this patient were excluded from the analysis. The authors noted that the second patient with DS had a pharmacokinetic profile that was consistent with the profiles observed in children without DS. Thus, the authors concluded that DS status was not likely to be the cause for the abnormal pharmacokinetic profile of busulfan in the first patient with DS³¹.

DISCUSSION

Based on the literature considered (table I), it appears that the pharmacokinetics of antileukemic drugs in subjects with DS may be altered in select instances. In this context, the very limited evidence on the pharmacokinetics of 6-TG suggests that patients with DS

showed relatively high intracellular concentrations of TGN metabolites²¹. MTX was shown to have increased toxicity and altered pharmacokinetics in patients with DS. Data from separate studies have shown increased MTX plasma concentrations and decreased clearance in patients with DS^{18,19}. However, the clinical significance of these pharmacokinetic differences is not concrete. Buitenkamp et al. concluded that the 5% reduction in MTX clearance was not likely clinically relevant despite being statistically significant. It has been suggested that factors such as reduced folate levels along with enhanced MTX transport into cells via the reduced folate carrier (RFC) are more likely to be the cause of toxicity in patients with DS. Since the *RFC* gene is located on the critical DS region of chromosome 21, increased *RFC* expression due to gene dosage effect may result in high intracellular MTX concentrations in normal and neoplastic cells. This could contribute to the increased incidence of adverse effects such as mucositis while not directly impacting pharmacokinetic parameters to any significant degree¹⁹.

It appears that the differential chemotherapy-related toxicity and efficacy observed in patients with leukemia and DS may be related to factors that alter the pharmacology of anticancer drugs in the DS setting. This notion has been explored for some drugs through *in vitro* studies. For example, cytarabine (ARA-C) is an antimetabolite chemotherapy agent used to treat hematological malignancies. ARA-C is converted into the active 1- β -D-arabinofuranosylcytosine-5'-triphosphate metabolite (ARA-CTP). ARA-CTP competitively inhibits DNA polymerase and prevents DNA strand elongation³². Clinical studies have shown pediatric patients with DS and AML are highly responsive to chemotherapy that includes ARA-C³³. Taub et al. (1996) investigated the metabolism and intracellular pharmacokinetics of ARA-C by performing *in vitro* experiments with myeloblasts isolated from leukemia patients with and without DS. The authors found that myeloblasts from patients with DS were 10-fold more sensitive to ARA-C (72-hour exposure) than myeloblasts from patients without DS. The intracellular levels of active ARA-CTP were higher in DS myeloblasts than in non-DS myeloblasts. It was suggested that increased expression of the enzyme cystathionine- β -synthase due to gene dosage effect may enhance the metabolism of ARA-C which in turn would contribute to increased drug sensitivity in cells with trisomy 21³⁴. Somatic mutations present in leukemic cells from patients with DS and megakaryocytic leukemia (AMkL), specifically in the transcription factor gene *GATA-1*, may also impact ARA-C therapy. The presence of somatic mutations in *GATA-1* found have been associated with increased sensitivity to ARA-C *in vitro*. It was shown that *GATA-1* mutations lead to reduced metabolism of ARA-C to the inactive metabolite ARA-U via decreased cytidine deaminase expression, which may partially explain the increased sensitivity to ARA-C seen in patients with DS and AMkL³⁵. To the best of our knowledge, pharmacokinetic studies with ARA-C in pediatric patients with DS have not been performed.

In the case of drugs that did not show differential pharmacokinetics between patients with and without DS, pharmacodynamic factors were often cited as the likely culprit to account for the observed distinctions in drug toxicities and/or treatment responses. For example, the pharmacokinetics of doxorubicin was not shown to be significantly altered in patients with DS; however, there are still doxorubicin-specific toxicities that have been reported to occur more often in these patients⁷. Specifically, patients with DS and leukemia may be at a higher

risk for anthracycline-related cardiotoxicity⁸. The intra-cardiac synthesis of anthracycline alcohol metabolites (e.g., daunorubicinol) by carbonyl reductases (CBRs) and aldo-keto reductases (AKRs) contributes to the pathogenesis of cardiotoxicity. The *CBR1* and *CBR3* genes are located in chromosome 21, and the resulting gene dosage effect from trisomy 21 impacts the metabolism of doxorubicin which may impact cardiotoxicity in DS. Studies in heart tissue documented increased *CBR1* mRNA and CBR1 protein expression in samples from donors with DS in comparison to samples from donors without DS. On average, heart tissue samples from donors with DS displayed a 1.7 fold increase in the rates of synthesis of cardiotoxic daunorubicinol^{36,37}.

The available literature on the pharmacokinetics of anticancer drugs in patients with DS is relatively scarce and should be interpreted with caution. Most of the reports have small sample sizes with some studies reporting data on fewer than 10 children with DS. This problem is further exacerbated by the retrospective nature of most of the studies. The deficits in statistical power make it difficult to draw confident conclusions from many of the studies provided. Small sample sizes also make the stratification of pediatric patients by age difficult. This hampers the ability to identify pharmacokinetic trends of potential clinical significance. Pediatric patients with leukemia may experience differential toxicities and treatment responses that vary by age^{38,39}. In pediatric patients, age may affect the expression and function of factors that can contribute to pharmacokinetic variability such as drug metabolizing enzymes and drug transporters⁴⁰. Small sample sizes make it difficult to extrapolate any findings to the entire continuum of age encompassing pediatric patients (i.e., from birth up to 18 – 21 years of age).

The limited number of reports available on pediatric patients with DS and leukemia have considered the pharmacokinetics of just a few drugs commonly utilized in therapy. The pharmacokinetic characteristics of other anti-leukemic drugs such as asparaginase, dexamethasone, and 6-mercaptopurine have not been reported in pediatric patients with DS. The current evidence suggests that the pharmacokinetics of specific antileukemic drugs may be altered in patients with DS. Other inherent factors present in the DS setting, such as differences in cellular sensitivity to chemotherapy and oxidative dysfunction, play a role in regards to response to therapy and susceptibility to adverse effects. The current paucity of well-powered pharmacokinetic studies precludes drawing definitive conclusions in regards to the impact of pharmacokinetic variability on specific toxicities and therapeutic outcomes.

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References

1. Hasle H, Clemmensen IH, Mikkelsen M. Risks of leukaemia and solid tumours in individuals with Down's syndrome. *The Lancet*. 2000; 355(9199):165–169.
2. Rowley JD. Down Syndrome and acute leukaemia: increased risk may be due to trisomy 21. *Lancet*. 1981; 2(8254):1020–2. [PubMed: 6118480]

3. Whitlock JA, Sather HN, Gaynon P, Robison LL, Wells RJ, Trigg M, Heerema NA, Bhatia S. Clinical characteristics and outcome of children with Down syndrome and acute lymphoblastic leukemia: a Children's Cancer Group study. *Blood*. 2005; 106(13):4043–9. [PubMed: 16109782]
4. Zwaan CM, Kaspers GJ, Pieters R, Hahlen K, Janka-Schaub GE, van Zantwijk CH, Huismans DR, de Vries E, Rots MG, Peters GJ, et al. Different drug sensitivity profiles of acute myeloid and lymphoblastic leukemia and normal peripheral blood mononuclear cells in children with and without Down syndrome. *Blood*. 2002; 99(1):245–51. [PubMed: 11756178]
5. O'Brien MM, Taub JW, Chang MN, Massey GV, Stine KC, Raimondi SC, Becton D, Ravindranath Y, Dahl GV. Cardiomyopathy in children with Down syndrome treated for acute myeloid leukemia: a report from the Children's Oncology Group Study POG 9421. *J Clin Oncol*. 2008; 26(3):414–20. [PubMed: 18202418]
6. Blatt J, Albo V, Prin W, Orlando S, Wollman M. Excessive chemotherapy-related myelotoxicity in children with Down syndrome and acute lymphoblastic leukaemia. *Lancet*. 1986; 2(8512):914. [PubMed: 2876340]
7. Palle J, Frost BM, Peterson C, Gustafsson G, Hellebostad M, Kanerva J, Schmiegelow K, Lonnerholm G. Doxorubicin pharmacokinetics is correlated to the effect of induction therapy in children with acute myeloid leukemia. *Anticancer Drugs*. 2006; 17(4):385–92. [PubMed: 16549995]
8. Hefti E, Blanco JG. Anthracycline-Related Cardiotoxicity in Patients with Acute Myeloid Leukemia and Down Syndrome: A Literature Review. *Cardiovasc Toxicol*. 2015
9. Peeters M, Poon A. Down syndrome and leukemia: unusual clinical aspects and unexpected methotrexate sensitivity. *Eur J Pediatr*. 1987; 146(4):416–22. [PubMed: 2958283]
10. Xavier AC, Taub JW. Acute leukemia in children with Down syndrome. *Haematologica*. 2010; 95(7):1043–5. [PubMed: 20595099]
11. O'Dwyer P, Stevenson J, Johnson S. Clinical Pharmacokinetics and Administration of Established Platinum Drugs. *Drugs*. 2000; 59(4):19–27. [PubMed: 10864227]
12. Ebadi MS, Kugel RB. Alteration in metabolism of acetylsalicylic acid in children with Down's syndrome: decreased plasma binding and formation of salicyluric acid. *Pediatr Res*. 1970; 4(2):187–93. [PubMed: 4246144]
13. Griener JC, Msall ME, Cooke RE, Corcoran GB. Noninvasive determination of acetaminophen disposition in Down's syndrome. *Clin Pharmacol Ther*. 1990; 48(5):520–8. [PubMed: 2146059]
14. Stowe CD, Phelps SJ. Altered clearance of theophylline in children with Down syndrome: a case series. *J Clin Pharmacol*. 1999; 39(4):359–65. [PubMed: 10197294]
15. Hemingway-Eltomey JM, Lerner AJ. Adverse effects of donepezil in treating Alzheimer's disease associated with Down's syndrome. *Am J Psychiatry*. 1999; 156(9):1470. [PubMed: 10484967]
16. Kondoh T, Nakashima M, Sasaki H, Moriuchi H. Pharmacokinetics of donepezil in Down syndrome. *Ann Pharmacother*. 2005; 39(3):572–3. [PubMed: 15701773]
17. Pui C-H, Mullighan CG, Evans WE, Relling MV. Pediatric acute lymphoblastic leukemia: where are we going and how do we get there?. 2012:1165–1174.
18. Garre ML, Relling MV, Kalwinsky D, Dodge R, Crom WR, Abromowitch M, Pui CH, Evans WE. Pharmacokinetics and toxicity of methotrexate in children with Down syndrome and acute lymphocytic leukemia. *J Pediatr*. 1987; 111(4):606–12. [PubMed: 2958611]
19. Buitenkamp TD, Mathot RA, de Haas V, Pieters R, Zwaan CM. Methotrexate-induced side effects are not due to differences in pharmacokinetics in children with Down syndrome and acute lymphoblastic leukemia. *Haematologica*. 2010; 95(7):1106–13. [PubMed: 20418240]
20. Stork LC, Matloub Y, Broxson E, La M, Yanofsky R, Sather H, Hutchinson R, Heerema NA, Sorrell AD, Masterson M, et al. Oral 6-mercaptopurine versus oral 6-thioguanine and veno-occlusive disease in children with standard-risk acute lymphoblastic leukemia: report of the Children's Oncology Group CCG-1952 clinical trial. 2010:2740–2748.
21. Palle J, Frost BM, Petersson C, Hasle H, Hellebostad M, Kanerva J, Schmiegelow K, Lonnerholm G. Thioguanine pharmacokinetics in induction therapy of children with acute myeloid leukemia. *Anticancer Drugs*. 2009; 20(1):7–14. [PubMed: 19342996]
22. Jordan MA, Thrower D, Wilson L. Mechanism of inhibition of cell proliferation by Vinca alkaloids. *Cancer Res*. 1991; 51(8):2212–22. [PubMed: 2009540]

23. Stewart CF. Treating children with acute lymphoblastic leukemia and Down syndrome: pharmacokinetics provides insight into vincristine therapy. *Pediatr Blood Cancer*. 2009; 52(1):1–2. [PubMed: 18816806]
24. Lonnerholm G, Frost BM, Soderhall S, de Graaf SS. Vincristine pharmacokinetics in children with Down syndrome. *Pediatr Blood Cancer*. 2009; 52(1):123–5. [PubMed: 18615507]
25. Griffin TC, Weitzman S, Weinstein H, Chang M, Cairo M, Hutchison R, Shiramizu B, Wiley J, Woods D, Barnich M, et al. A Study of Rituximab and Ifosfamide, Carboplatin, and Etoposide Chemotherapy in Children with Recurrent/Refractory B-cell (CD20+) Non-Hodgkin Lymphoma and Mature B-Cell Acute Lymphoblastic Leukemia: A Report from the Children's Oncology Group. *Pediatr Blood Cancer*. 2009; 52(2):177–181. [PubMed: 18816698]
26. Eksborg S, Soderhall S, Frostvik-Stolt M, Lindberg A, Liliemark E. Plasma pharmacokinetics of etoposide (VP-16) after i.v. administration to children. *Anticancer Drugs*. 2000; 11(4):237–41. [PubMed: 10898537]
27. Palle J, Frost BM, Gustafsson G, Hellebostad M, Kanerva J, Liliemark E, Schmiegelow K, Lonnerholm G. Etoposide pharmacokinetics in children treated for acute myeloid leukemia. *Anticancer Drugs*. 2006; 17(9):1087–94. [PubMed: 17001183]
28. Raj S, Franco VI, Lipshultz SE. Anthracycline-induced cardiotoxicity: a review of pathophysiology, diagnosis, and treatment. *Curr Treat Options Cardiovasc Med*. 2014; 16(6):315. [PubMed: 24748018]
29. Bishop JB, Wassom JS. Toxicological review of busulfan (Myleran). *Mutat Res*. 1986; 168(1):15–45. [PubMed: 3713721]
30. Rubin CM, Mick R, Johnson FL. Bone marrow transplantation for the treatment of haematological disorders in Down's syndrome: toxicity and outcome. *Bone Marrow Transplant*. 1996; 18(3):533–40. [PubMed: 8879614]
31. Shaw PJ, Scharping CE, Brian RJ, Earl JW. Busulfan pharmacokinetics using a single daily high-dose regimen in children with acute leukemia. *Blood*. 1994; 84(7):2357–62. [PubMed: 7919354]
32. Momparler R. Optimization of cytarabine (ARA-C) therapy for acute myeloid leukemia. *Experimental Hematology & Oncology*. 2013; 2(1):20. [PubMed: 23919448]
33. Ravindranath Y, Abella E, Krischer JP, Wiley J, Inoue S, Harris M, Chauvenet A, Alvarado CS, Dubowy R, Ritchey AK, et al. Acute myeloid leukemia (AML) in Down's syndrome is highly responsive to chemotherapy: experience on Pediatric Oncology Group AML Study 8498. *Blood*. 1992; 80(9):2210–4. [PubMed: 1384797]
34. Taub JW, Matherly LH, Stout ML, Buck SA, Gurney JG, Ravindranath Y. Enhanced metabolism of 1-beta-D-arabinofuranosylcytosine in Down syndrome cells: a contributing factor to the superior event free survival of Down syndrome children with acute myeloid leukemia. *Blood*. 1996; 87(8):3395–403. [PubMed: 8605357]
35. Taub JW, Ge Y. Down syndrome, drug metabolism and chromosome 21. *Pediatric Blood & Cancer*. 2005; 44(1):33–39. [PubMed: 15390307]
36. Kalabus JL, Sanborn CC, Jamil RG, Cheng Q, Blanco JG. Expression of the anthracycline-metabolizing enzyme carbonyl reductase 1 in hearts from donors with Down syndrome. *Drug Metab Dispos*. 2010; 38(12):2096–9. [PubMed: 20729274]
37. Quiñones-Lombrana A, Ferguson D, Blair RH, Kalabus JL, Redzematovic A, Blanco JG. Interindividual Variability in the Cardiac Expression of Anthracycline Reductases in Donors with and without Down Syndrome. *Pharm Res*. 2014; 31(7):1644–1655. [PubMed: 24562808]
38. Gamis AS, Woods WG, Alonzo TA, Buxton A, Lange B, Barnard DR, Gold S, Smith FO. Increased age at diagnosis has a significantly negative effect on outcome in children with Down syndrome and acute myeloid leukemia: a report from the Children's Cancer Group Study 2891. *J Clin Oncol*. 2003; 21(18):3415–22. [PubMed: 12885836]
39. Abildgaard L, Ellebaek E, Gustafsson G, Abrahamsson J, Hovi L, Jonmundsson G, Zeller B, Hasle H. Optimal treatment intensity in children with Down syndrome and myeloid leukaemia: data from 56 children treated on NOPHO-AML protocols and a review of the literature. *Ann Hematol*. 2006; 85(5):275–80. [PubMed: 16518605]
40. Wagner J, Abdel-Rahman SM. Pediatric Pharmacokinetics. *Pediatrics in Review*. 2013; 34(6):258–269. [PubMed: 23729775]

Table I

Summary of key studies on the pharmacokinetics of chemotherapeutic drugs in pediatric patients with leukemia and DS.

Study	Drug of focus	Main findings
Peters and Poon (1987)	Methotrexate	The 2 patients with DS in the study showed normal clearance of methotrexate
Garre et al. (1987)	Methotrexate	Patients with DS had higher 42-hour plasma concentrations of methotrexate, no difference was seen in clearance
Buitenkamp et al. (2010)	Methotrexate	Retrospective NONMEM analysis showed a 5% reduction in methotrexate clearance in patients with DS
Palle et al. (2009)	Thioguanine	Higher intracellular concentration of active TGN metabolite seen in DS
Lönnnerholm et al. (2009)	Vincristine	No pharmacokinetic differences between patients with and without DS
Eksborg et al. (2000)	Etoposide	The 2 patients with DS considered for the study showed no pharmacokinetic differences compared to the NDS group
Palle et al. (2006)	Etoposide	Patients with DS had a non-significant 20% decrease in etoposide clearance compared to the patients without DS
Shaw et al. (1994)	Busulfan	DS status is not likely to impact busulfan pharmacokinetics in pediatric patients
Palle et al. (2006)	Doxorubicin	There was no significant clearance or plasma concentration differences between DS and NDS groups