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Anthracycline-Related Cardiotoxicity in Patients with Acute Myeloid Leukemia and Down Syndrome: A Literature Review

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Anthracycline-Related Cardiotoxicity in Patients with Acute Myeloid Leukemia and Down Syndrome: A Literature Review

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Abstract Pediatric patients with Down syndrome (DS) are at an increased risk of developing certain cancers. Specifically, patients with DS have a reported 10–20-fold increased risk of developing acute myeloid leukemia (AML). Anthracycline-based treatment regimens achieve good results in patients with DS and AML. It has been proposed that DS status constitutes a risk factor for the cardiotoxicity associated with the use of anthracyclines in the pediatric setting. However, published evidence pointing toward an increased risk of cardiotoxicity in patients with DS is relatively scarce and conflictive. This concise review compiles literature relating to the incidence of anthracycline-related cardiotoxicity in pediatric patients with DS. In general, reports from trials using anthracyclines at the maximum recommended dose showed increases in the incidence of anthracycline-related cardiotoxicity in patients with DS in comparison with trials that used anthracyclines at reduced doses. Evidence from the literature suggests that patients with DS can achieve favorable therapeutic outcomes after receiving treatment with reduced doses of anthracyclines to minimize the potential for cardiotoxicity. Further prospective trials, along with the available evidence, would assist the design of treatment protocols for patients with pediatric leukemias and DS.

Keywords Anthracycline · Cardiotoxicity · Pediatric · AML · Leukemia · Down syndrome · Doxorubicin

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Introduction

Children with Down syndrome (DS) have a 10–20-fold increase in the incidence of acute myeloid leukemia (AML) as compared to patients without DS [1, 2]. Patients with DS and AML are treated with anthracycline-based chemotherapeutic regimens that typically include doxorubicin, daunorubicin, or idarubicin. In general, the treatment for pediatric AML can be divided in two main phases: induction and consolidation. Most chemotherapeutic regimes incorporate anthracyclines during the induction phase at varying dose intensities. Cytarabine-based therapy and/or other approaches such as allogenic stem cell transplants are utilized during the consolidation phase [3]. Chemotherapy regimens in patients with DS and AML are efficacious and often result in superior therapeutic endpoints as compared to patients with AML and without DS [4–7]. Leukemic cells from patients with DS have increased sensitivity to the cytotoxic effects of anthracycline chemotherapeutics which may contribute to more effective elimination of the leukemia [6]. Unfortunately, the clinical use of anthracyclines is limited by the development of adverse side effects in some patients. Anthracyclines can trigger various adverse side effects such as immunosuppression, nausea, and mucositis. These toxicities are shared with other chemotherapeutic agents. Anthracyclines can also cause dose-limiting cardiotoxicity. The cardiotoxicity exerted by anthracyclines spans a spectrum of signs and symptoms ranging from relatively minor perturbations in cardiac rhythm and myocardial function to severe cardiomyopathy and congestive heart failure (CHF) [8]. The incidence of CHF secondary to anthracycline-induced cardiomyopathy is related to the total cumulative dose of the drug, and an empirically determined threshold of 300–500 mg/m^2 has often been used for adult patients.

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Reports have shown that children treated with higher cumulative doses (especially children exposed to >300 mg/m^2) are at increased risk of subclinical cardiovascular dysfunction and clinically significant cardiomyopathy [9]. These data have not been helpful for selecting an appropriate dose for individual patients, given that doses in excess of 1,000 mg/m^2 have been well tolerated by some patients, whereas a dose as low as 150 mg/m^2 has resulted in a significant decrease in the left ventricular ejection fraction and other signs of cardiac toxicity (e.g., arrhythmias) in others [10, 11].

The cardiotoxicity of anthracycline chemotherapeutic agents is mediated by a combination of different mechanisms. Anthracyclines are metabolized to alcohol metabolites that can disrupt iron and calcium homeostasis in the cardiomyocytes via interactions with iron(II) and the calcium transporter SERCA2, respectively. Anthracyclines can cause an irreversible decrease in mitochondrial Ca^{+2} loading and ATP content. This, when combined with impairment of mitochondrial creatine kinase activity, can lead to mitochondrial dysfunction in the cardiomyocyte. Anthracyclines can also cause mitochondrial dysfunction due to increased generation of reactive oxygen species in cardiac mitochondrion [12, 13]. The oxidative stress triggered by anthracyclines is not effectively controlled in cardiomyocytes due to decreased levels of detoxifying enzymes such as superoxide dismutase [14]. Anthracycline treatment can also alter nitric oxide regulation in the cardiomyocyte and lead to the disruption of normal heart function [15].

Since 15 % of all pediatric patients with AML have DS, many of the clinical trials have focused on the outcomes and efficacy of AML treatments [16]. However, when considering the reported data on treatment-related toxicity in patients with DS and AML, there are discrepancies between the published reports. Specifically, the incidence of anthracycline-related cardiotoxicity in patients with DS and AML has not been reported in a consistent manner. Often, the analysis of anthracycline-related cardiotoxicity in patients with DS and AML has not been a primary aim of the studies; therefore, the data were not detailed and rarely included quantitative estimates of prevalence. The purpose of this concise review is to explore the published literature in an attempt to shed light on the following question "Do pediatric patients with AML and DS treated with anthracyclines experience more or less cardiotoxicity than equally treated patients with AML and without DS?"

Literature Analysis

Published reports that consider anthracycline-based therapy for pediatric patients (i.e., patients under the age range of 18–21 years old) with AML were considered for inclusion in this manuscript. Specifically, articles that reported data on incidences of anthracycline-related cardiotoxicity in pediatric patients with DS and AML were considered for this review. The online databases PubMed and OVID Medline were searched using the keywords "Down syndrome," "cardiotoxicity," "anthracycline," "pediatric," "acute myeloid leukemia," "daunorubicin," "doxorubicin," "adriamycin," and "AML" between August 15 and September 15, 2014. This search resulted in 16 primary peer-reviewed articles for analysis that either focused on cardiotoxicity in patients with DS that received anthracycline-based therapy or reported cardiotoxicity as an adverse effect in a clinical study. These reports were published between 1990 and 2012, and the patient data presented ranged from the early 1970s to the 2000s. Other primary literature that discussed cardiotoxicity in pediatric patients with DS and AML were also considered. The published primary reports utilized in this review are summarized and compiled in Table 1.

Studies that Suggest Elevated Relative Incidence of Anthracycline-Related Cardiotoxicity in Patients with DS

One of the first reports to examine the treatment and outcomes of children with DS and leukemia that also mentioned anthracycline-related cardiotoxicity was published by Levitt et al. [17] in 1990 (Table 1). In this study, 90 patients under 15 years of age with DS and either AML or acute lymphoblastic leukemia (ALL) were recruited and treated with the UKALL X protocol. The study did not aim to measure the incidence of anthracycline-related cardiotoxicity directly. The authors mentioned that irreversible cardiomyopathy was seen in two out of a total of 26 patients with DS and AML. Both patients died while off treatment due to unspecified cardiomyopathy presumably associated with daunorubicin. It was noted that one patient had a normal electrocardiogram (EKG), while the other had a heart defect. One of the children with fatal cardiomyopathy had been re-treated with daunorubicin due to bone marrow relapse. The authors did not set the criteria used to determine cardiotoxicity, and the dose of anthracycline was not specified [17].

Arguably, one of the first reports that established DS status as a significant risk factor for anthracycline-related cardiotoxicity was published in 1997 by Krischer et al. [1]. The report was a retrospective analysis that compiled data on 6,493 children with and without DS and with various types of cancer (e.g., leukemias, sarcomas, and brain tumors) who had received anthracycline chemotherapy per protocols from the Pediatric Oncology Group (POG) from

Table 1 Summary of select published studies that report cardiotoxicity in pediatric patients with DS and AML

Protocol	First author	Year	Anthracycline dose	Patients with DS and AML		Patients without DS with AML		Summarized cardiotoxicity details
				n	Reported cardiotoxicity	*n*	Reported cardiotoxicity	
UKALL X	Levitt	1990	Daunorubicin dose not specified	26	Cardiomyopathy: 2 (7.6 %)	713	Cardiotoxicity not reported or mentioned in this group	Both children had irreversible cardiomyopathy, one had a congenital defect, one had a normal EKG, both died while off treatment
POG 8498	Ravindranath	1992	Cumulative anthracycline (daunorubicin) dose = 225 mg/m^2, induction only)	12	No incidences reported	273	No incidences reported	It was noted that 50 % of DS patients had congenital heart defects, but that did not affect unreported cardiotoxicity
AML-BFM 87/93	Creutzig	1996	Cumulative anthracycline dose (doxorubicin and daunorubicin) was 220–400 mg/m^2	21	Cardiotoxicity: 2 (9.5 %)	589	Cardiotoxicity not reported or mentioned in this group	One patient had cardiac failure and the other died of congestive heart failure in remission
POG protocols 1974–1990	Krischer	1997	Doxorubicin, daunorubicin, or mitoxantrone at a cumulative dose up to 550 mg/m^2	66	Cardiotoxicity: 4 (6 %)	6,427	Cardiotoxicity: 102 (1.6 %)	The relative risk of cardiotoxicity was 3.37 ($p = 0.02$)
AML-10, other recognized intensive protocols, individualized protocols	Craze	1999	Anthracycline dose based on protocol used	45	Cardiomyopathy or decreased cardiac function: 9 (20 %)	114	Cardiotoxicity not reported or mentioned in this group	Four of the patients with DS experienced cardiac failure, one patient died
Institutional specific AML-Down protocol	Kojima	2000	Mean anthracycline (daunorubicin, pirarubicin, or mitoxantrone) dose = 300 mg/m^2	33	Cardiotoxicity: 2 (6.1 %)	0	Not considered in the study	The two individuals died of congestive heart failure, one during consolidation, the other after 38 months in remission
CCG 2891	Gamis	2003	Daunorubicin 20 mg/m^2 days 0–4, 4 cycles (320 mg/m^2 cumulative dose)	161	Cardiotoxicity, intensive chemotherapy patients: 1 % Cardiotoxicity, standard chemotherapy patients: 2 %	947	Cardiotoxicity, intensive chemotherapy patients: 4.5 % Cardiotoxicity, standard chemotherapy patients: 1 %	Nonsignificant difference in the grade III/IV cardiac toxicity rates in AML patients with DS vs. patients without DS
AML-BFM 93/98	Creutzig	2005	Cumulative anthracycline dose for DS–AML patients = 220–240 mg/m^2, for non-DS–AML patients = 320–450 mg/m^2	118	Cardiotoxicity: 1 (0.08 %)	907	Cardiotoxicity not reported or mentioned in this group	The patient who experienced late cardiotoxicity received a cumulative anthracycline dose of $\sim$ 400 mg/m^2

Table 1 continued

Protocol	First author	Year	Anthracycline dose	Patients with DS and AML		Patients without DS with AML		Summarized cardiotoxicity details
				n	Reported cardiotoxicity	*n*	Reported cardiotoxicity	
NOPHO-AML84, NOPHO-AML88 and NOPHOAML93	Zeller	2005	Anthracycline dose based on protocol used	62	Cardiotoxicity was not reported or mentioned in this group	435	Cardiotoxicity not reported or mentioned in this group	Cardiotoxicity in patients with DS and AML not noted
MRC AML-10,12	Rao	2006	Cumulative 300 mg/m^2 daunorubicin, 50 mg/m^2 mitoxantrone	46	Cardiomyopathy: 2 (4.3 %)	822	Cardiotoxicity not reported or mentioned in this group	One patient died within 5 years of clinical remission, one died 13 years post diagnosis of cardiomyopathy
NOPHO-AML88,93	Abildgaard	2006	Cumulative anthracycline (doxorubicin, mitoxantrone) dose = 300–450 mg/m^2	56	Cardiotoxicity: 0 (0 %)	0	This group was not considered for this study	Cardiotoxicity in patients with DS and AML not noted
AML-BFM 93/98	Creutzig	2007	Cumulative anthracycline dose of 300–450 mg/m^2	74 (early) 69 (late)	Early-onset cardiomyopathy: 3 (4.1 %), Late-onset cardiomyopathy: 2 (2.9 %)	811 (early) 478 (late)	Early-onset cardiomyopathy: 35 (4.3 %) Late-onset cardiomyopathy: 14 (2.9 %)	Cardiotoxicity presented as decreased shortening fraction and arrhythmia, no increased cardiotoxicity was seen in patients with DS and AML
AML 99	Kudo	2007	Pirarubicin 25 mg/m^2 (cumulative dose = 250 mg/m^2)	68	Cardiotoxicity: 4 (5.9 %)	0	This group was not considered for this study	Cardiotoxicity was seen during induction, all patients recovered
POG 9421	O'Brien	2008	Cumulative anthracycline dose = 535 mg/m^2	57	Cardiomyopathy: 10 (17.5 %)	565	Cardiomyopathy: 6 (1.1 %)	Cardiotoxicity was found to be higher in the DS group, three deaths were related to CHF
JCCLSG AML 9805	Taga	2011	Pirarubicin 25 mg/m^2 on days 2, 4, then in remission patients: mitoxantrone 3.5 mg/m^2 on days 2–4 and pirarubicin 35 mg/m^2 on day 2	24	Cardiotoxicity: 0 (0 %)	0	This group was not considered for this study	Cardiotoxicity in patients with DS and AML not noted
COG A2971	Sorrell	2012	Cumulative daunorubicin dose = 20 mg/m^2	131	Cardiotoxicity (induction): 5 (3.8 %) Cardiotoxicity (intensification): 2 (1.7 %)	0	The number of patients or toxicity in this group was not reported	Cardiotoxicity was not specified beyond " > grade III ", intensification patients did not receive additional anthracyclines

The above table summarizes the primary literature examined in this review. Only patients that received treatment are included when presenting number of patients (*n*) and when calculating cardiotoxicity percentages when not calculated in the original article

1974 to 1990. Patients with cardiac malformations or with evidence of myocardial dysfunction, arrhythmias, or conduction abnormalities were excluded from the analysis. From a total of 66 patients with DS, four patients developed congestive heart failure or sudden death associated with the use of anthracyclines (Table 1). In univariate analysis, the relative risk conferred by DS status was 3.55 (95 % confidence interval 1.31–9.76, $p = 0.01$), whereas multivariate analysis showed a relative risk of 3.37 for the presence of DS (95 % confidence interval 1.24–9.18, $p = 0.02$). It should be noted that this study was one of the few that specifically concluded that DS was a risk factor for anthracycline-related cardiotoxicity with statistical significance ($p \leq 0.05$). It should also be noted that this study's objective was to identify risk factors for anthracycline-related cardiotoxicity in patients with DS, which is not a common goal of many of the reports reviewed. This is the most cited study presented in this review (approximately 335 citations), which highlights the impact this report has had on the field of pediatric oncology.

In 1999, Craze et al. conducted a retrospective study that considered the outcomes of children with DS and AML treated in the UK between 1987 and 1995. The authors reported that nine out of the 45 patients (20 %) with DS and AML exhibited cardiomyopathy or asymptomatic deterioration of cardiac function, and four of those had episodes of cardiac failure related to anthracycline use, one of which was fatal. The criteria for the diagnosis of cardiomyopathy were not defined, and neither doses nor the type of anthracycline drug were specified. Four patients (44 %) had congenital heart disease. Statistical analysis for the cardiomyopathy data was not provided. The authors noted that follow-up echocardiographic data were incomplete [4].

A more recent report (2008) by O'Brien et al. [18] from the North American Children's Oncology Group (COG) was based on retrospective chart reviews from cases treated in the POG protocol 942. In POG 9421, echocardiograms were required at enrollment, before each chemotherapy cycle, and at the end of therapy. Cardiomyopathy was defined as clinically symptomatic CHF that required medical intervention (e.g., diuretics, inotropic therapy, and afterload reduction) or dilated cardiomyopathy at autopsy. The report noted a higher incidence of anthracycline-related cardiotoxicity in patients with DS and AML as compared to patients without DS and AML, although statistical comparisons were not reported. Ten (17.5 %) out of 57 patients with DS and AML developed cardiomyopathy associated with the use of daunorubicin and three patients died of CHF (Table 1). Fifty percent of the patients with symptomatic cardiomyopathy had congenital heart defects, and the three cardiomyopathy-related deaths occurred in children with congenital heart defects. The total dose of daunorubicin for non-infant patients was 135 mg/m^2, and the authors noted that dose adjustments for infant patients were preformed "as prescribed" [18]. POG 9421 also included the anthracenedione mitoxantrone (total dose: 80 mg/m^2), and the authors reported a total cumulative exposure to anthracyclines of 535 mg/m^2, after using an empirical 5:1 conversion factor for mitoxantrone.

Studies that do not Suggest Elevated Relative Incidence of Anthracycline-Related Cardiotoxicity in Patients with DS

Not all published reports documented increases in the incidence of anthracycline-related cardiotoxicity in patients with DS and AML. In 1992, a report by Ravindranath et al. from the POG highlighted favorable responses to chemotherapy for AML in patients with DS. Although not a primary endpoint of the study, the authors also touched on the subject of anthracycline-related cardiotoxicity. However, the criteria for reporting cardiotoxicity were not specified. The study did not show increased cardiotoxicity in patients with DS and AML treated with daunorubicin at a total cumulative dose of 225 mg/m^2 (Table 1). The authors acknowledged that follow-up toxicity data were limited [19].

In 1996, Creutzig et al. reported the outcomes of 40 patients with DS and AML, 21 of which were treated with chemotherapy according to protocols by the German cooperative group AML-BFM (Berlin–Frankfurt–Münster). The authors noted that six patients received major dose or protocol reductions. This study reported cardiac insufficiency in two patients with AML and DS that were treated with chemotherapy (Table 1). It was noted that one of the patients received a cumulative anthracycline dose of approximately 400 mg/m^2 [20].

In 2000, Kojima et al. conducted a study that included 33 children with DS and AML with the intent to develop a safe and effective chemotherapeutic regimen for these patients. The study showed that good results with low toxicity rates could be achieved with less intensive chemotherapeutic regimens that included mean cumulative anthracycline doses of 300 mg/m^2. In this study, there were two cases of heart failure noted (Table 1). One patient received an anthracycline dose of 400 mg/m^2 and died during clinical remission 38 months after therapy, while the other patient died during consolidation therapy. Of note, 13 out of the 33 patients were treated with pirarubicin or mitoxantrone, while the other 20 patients received daunorubicin. Toxicity was graded with NCI criteria [21].

Gamis et al. [22] reported a 2 % incidence of grade III or grade IV cardiac toxicity in patients with DS and AML treated with "standard-timing" induction chemotherapy

versus a 1 % incidence of cardiac toxicity in the control group of patients without DS ($p = 0.708$). In the group of patients with DS and AML that received intensification of their chemotherapy regimen (84 % of the total), 1 % exhibited grade III or grade IV toxicity (Table 1). Grade III/IV cardiotoxicity was seen in 4.5 % on the patients without DS ($p = 0.148$, Table 1). The specifics of the grading criteria for recording cardiotoxicity were not reported. Daunorubicin-based induction was used at a dose of 20 mg/m^2/day for the first 4 days of each cycle for four induction cycles. The result was a 320 mg/m^2 total cumulative dose of daunorubicin. The authors concluded that patients with DS and AML showed no overall increase in toxicity when given chemotherapy regimens at a lower intensity but with an equal total cumulative dose in comparison with patients without DS [22].

In 2005, a second study by Creutzig et al. considered cure rates of AML in patients with DS treated with AML-BFM protocols 93 and 98. Only one case of clinical cardiotoxicity was noted in the group of 118 patients with DS and AML (Table 1). The patient who experienced the cardiotoxicity received a cumulative anthracycline dose of $\approx$400 mg/m^2, while the other patients with DS were given relatively lower doses of anthracyclines (220–240 mg/m^2). The patient was reported to have developed CHF with progressive cardiomegaly and has been also described in the previous study [23]. In a population-based study on patients with leukemia, Zeller et al. [24] considered the treatment outcomes in a group of 62 patients with DS and AML. The report did not include any specifics on the incidence of anthracycline-related cardiotoxicity. The authors noted that 48 % of the patients with DS were treated with decreased doses of anthracyclines (Table 1) [24].

In 2006, Abildgaard et al. reported data on 56 children with DS treated on the Nordic Society for Pediatric Hematology and Oncology-acute myeloid leukemia (NOPHO-AML) protocols NOPHO-AML88 and NOPHO-AML93. The authors reported no cardiotoxicity using protocols that, in general, included cumulative anthracycline doses of 300–450 mg/m^2 (Table 1). It was noted that 29 % of the patients with DS were given reduced doses that were on average 75 % of the scheduled dose of anthracycline. The study did show that patients that were given full-dose anthracycline-based therapy had a higher rate of treatment-related death [25].

The report by Rao et al. [5] focused on patients with DS and AML treated in the UK in Medical Research Council trials AML 10 and AML 12. Patients were treated with 300 mg/m^2 of daunorubicin, and two cases of cardiac failure due to myopathy at 13 and 15 years post-cancer diagnosis were listed (Table 1). The mortality rate during the induction phase in patients with DS and AML was 11 % versus a 4 % mortality rate for the group of patients with AML and without DS ($p = 0.02$). Cardiotoxicity was not listed as a distinct cause of mortality. Criteria and specifics concerning non-lethal cardiotoxicity were not discussed [5].

A study in 2007, also conducted by Creutzig et al., is one of the few reports to consider early- and late-onset anthracycline-related cardiotoxicity in patients with DS and AML. The study defined early toxicity as transient tachycardias, dysrhythmias, or non-specific EKG changes within 1 year of receiving the anthracycline. Late toxicity was defined as occurring 1 year after receiving the anthracycline, and it was characterized by CHF or pericardial effusion. Two out of 69 patients (2.9 %) with DS and AML showed late cardiotoxicity, and three out of 74 patients (4.1 %) experienced early cardiotoxicity (Table 1). The patients with early cardiotoxicity showed reduced shortening fraction and arrhythmias, while the patients with late cardiotoxicity displayed reduced shortening fraction. One patient developed both early and late cardiotoxicity after receiving a cumulative anthracycline dose of over 400 mg/m^2. The report noted that liposomal daunorubicin was used to treat four patients with AML and without DS [26].

In 2007, a report by Kudo et al. from the Japanese Childhood AML Cooperative Study Group presented data from a reduced dose pirarubicin-based chemotherapy regimen on 72 patients (68 of which were assessed for toxicity during induction) with DS and AML, many of the patients had acute megakaryocytic leukemia (AMKL). Four individuals (5.9 %) displayed unspecified grade III/IV treatment-related cardiac dysfunction upon induction therapy (Table 1). It was noted that all of those patients recovered after the induction phase, but the length of follow-up was not specified [27]. Likewise, a report from the Japanese Children's Cancer and Leukemia Study Group (2011) by Taga et al. did not document any increased incidence of undefined grade III/IV cardiotoxicity in a total of 24 patients with DS and AML with a mean follow-up period of 75 months. In this study, all patients were younger than 4 years of age and had a phenotype of AMKL. The therapy for remission induction included pirarubicin (25 mg/m^2) on days 2 and 4. The authors noted that reduced anthracycline doses were used in patients with DS due to the concern for cardiac insufficiency [28].

A recent report by Sorrell et al. from the COG (2012) compiled results from the phase 3 trial A2971, the first trial designed to provide uniform therapy to children with DS and myeloid leukemia in North America. The A2971 protocol did not include etoposide and dexamethasone in the induction phase, eliminated the 3 months of systemic maintenance chemotherapy, which left three intrathecal doses of cytarabine as maintenance. The study enrolled 132

patients, 91 patients had DS and AML, and 41 patients had DS and myelodysplastic syndrome. The total cumulative dose of anthracycline was 320 mg/m^2. Seven individuals (5.3 %) experienced grade ≥3 cardiotoxicity, five patients during the induction phase and two in the intensification phase. Further details on the cardiotoxicities were not specified; however, it was mentioned that there was no difference in the incidence of toxicity in comparison with the results from the trial CCG 2891. The median follow-up time was 4.8 years [22, 29].

Conclusions

There are divergent findings in the literature concerning the incidence of anthracycline-related cardiotoxicity in pediatric patients with DS and AML. There seems to be a trend toward high-dose or high-intensity conventional anthracycline chemotherapy being linked to increased rates of cardiotoxicity in patients with DS and AML compared to patients without DS and AML. Likewise, studies that showed relatively low incidences of cardiotoxicity tended to use lower cumulative doses of anthracyclines, anthracyclines with potentially reduced cardiotoxic potential, or liposomal anthracycline dosage forms. Similar findings were also reported in studies focused on the chemotherapy for pediatric patients with ALL and DS. For example, Bassal et al. [30] reported no increases in grade III or grade IV cardiotoxicity (NCI CTC 2.0 grading criteria) in patients with ALL and DS treated with a cumulative dose of anthracycline of 150 mg/m^2 [30]. Other reports involving pediatric ALL patients without DS showed that doses of anthracyclines >300 mg/m^2 significantly increased the risk of cardiac complications and toxicity [31].

Differences in the specific anthracycline used may impact the incidence of clinical cardiotoxicity. For example, Japanese trials documented very low cardiotoxicity associated with the use of pirarubicin, which is reported to have less cardiotoxic potential compared to doxorubicin or daunorubicin (Table 1) [27, 28, 32]. Likewise, liposomal doxorubicin is known to have reduced toxicity (including cardiotoxicity) which may have impacted the rates of cardiotoxicity reported by Creutzig et al. [26] [33]. Anthracyclines are very rarely given as monotherapy, and patients are often exposed to cytotoxic drugs with cardiotoxic potential. The anthracenedione mitoxantrone may induce cardiotoxicity [34]. The use of mitoxantrone and other chemotherapeutic agents in the presented studies may have had an impact on the rates of reported cardiotoxicity.

It is important to consider potential confounders when comparing different reports, including the demographics of the patient population. The reports included patients younger than 18–21 years of age. However, the mean ages between studies were different. Some reports had patient populations with mean ages at the high and low ends of the "pediatric" spectrum. For example, the report by Kudo et al. included infant patients of around 1 year of age, while 57 % of the patients in the report by Krischer et al. [1, 27] were over 6 years of age. Age discrepancies may be a confounder when comparing the incidence of toxicities between protocols, since the susceptibility to specific toxicities might vary with age [31]. It has already been shown that age can affect clinical outcomes in patients with leukemia and DS, so it is reasonable to suspect that age may be also a factor when considering the risk of anthracycline-related toxicity in this group of subjects [22, 25]. The definition of cardiac toxicity is another potential confounding factor when comparing data from various studies. Some of the studies did not contain explicit definitions for the terms cardiotoxicity or cardiac dysfunction, while others used grading systems based on combinations of symptoms and objective measurements that may not communicate the specific nature of the cardiac dysfunction to the reader. There are different grading criteria available, and the use of unspecified grading systems in some studies makes comparison difficult [35]. Depending on the study, early- or late-onset cardiotoxicity may not be accounted for, or differentiated. Often, the reports noted relatively limited follow-up periods that may have been inadequate to capture late-onset cardiotoxicity [36]. This leads to the possible issue of underreporting the incidence of cardiotoxicity in patients with DS and leukemia, as put forth by O'Brien et al. [18]. Few reports have included comparative cardiotoxicity data from patients with and without DS and AML, which precludes the exploration of potential differences in susceptibility between groups. Some studies focused on treatment efficacy in patients with DS and leukemia have not included data or comments on the topic of anthracycline-related cardiotoxicity [7, 25]. Recently, van der Pal et al. [36] noted that one in eight survivors of pediatric cancers will develop severe cardiac disease (e.g., CHF) 30 years after the initial treatment with anthracyclines and radiation therapy. The current average life expectancy for individuals with DS is 55 years, with many living into their sixties and seventies [37]. It is not known whether the cumulative incidence of cardiac adverse events associated with cardiotoxic chemotherapy is different between long-term cancer survivors with DS and without DS.

There have been hypotheses put forth on the factors that may be involved during the pathogenesis of anthracycline-related cardiotoxicity in the DS setting. For example, several lines of evidence suggest that individuals with DS have mitochondrial dysfunction [38, 39]. Since anthracyclines can be toxic to the mitochondria, it is possible that patients with DS may be more susceptible to cardiotoxicity

due to underlying mitochondrial dysfunction [40]. The increase in cardiac oxidative stress resulting from anthracycline chemotherapy may be less tolerated in patients with DS compared to patients without DS, leading to increased cardiotoxicity in the DS setting. The reduced capability to tolerate oxidative stress may also contribute to the increased sensitivity of AML–DS cells to the cytotoxic effects of anthracyclines [6]. It is known that patients with DS have high rates of congenital heart defects (CHDs). While it is plausible that CHDs may impair the heart's ability to function properly while exposed to a cardiotoxic stimulus, the presence of CHDs has not been shown to impart a greater risk of cardiotoxicity in patients with DS. None of the reviewed studies that take CHDs into account have documented significant correlations between CHDs and anthracycline-related cardiotoxicity in patients with DS [4, 17, 18, 20, 28].

Despite the complications involved in reaching a definitive consensus about anthracycline-related cardiotoxicity in the DS setting, the omnipresent message in most of the published reports is that reduced anthracycline exposure in patients with DS and AML is preferable. The studies presented suggest that decreasing the anthracycline dose in patients with DS did not decrease the therapeutic efficacy of the treatment. Further prospective clinical trials would contribute to solidifying a definitive answer to the issue of anthracycline-related cardiotoxicity in patients with DS and AML. There are multiple limiting factors that make this clinical research difficult but also crucial to continue the development and implementation of more efficacious and less toxic treatment protocols for patients with DS and AML.

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