Continuous Versus Bolus Infusion of Doxorubicin in Children With ALL: Long-term Cardiac Outcomes

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KEY WORDS

anthracycline, cardiotoxicity, doxorubicin, leukemia, pediatrics

ABBREVIATIONS

ALL—acute lymphoblastic leukemia

DFCI—Dana-Farber Cancer Institute

LV—left ventricle

Drs Lipshultz, Sallan, Miller, Lipsitz, Silverman, Asselin, Clavell, Athale, Schorin, and Larsen were responsible for the concept and design of the study; Drs Lipshultz, Miller, Lipsitz, Neuberg, and Dahlberg and Ms Franco analyzed the data; Drs Lipshultz, Miller, Lipsitz, and Neuberg along with Ms Henkel, Franco, and Cushman drafted the manuscript; and all authors analyzed and interpreted the results, provided critical revision, and approved the final version of the report.

This clinical trial had patient enrollment before the requirement of registry.

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WHAT'S KNOWN ON THIS SUBJECT: Doxorubicin therapy, effective against many malignancies, is limited by cardiotoxicity. Continuous-infusion doxorubicin, compared with bolus-infusion, reduces early cardiotoxicity in adults. Its effectiveness in reducing late cardiotoxicity in children remains uncertain.

WHAT THIS STUDY ADDS: This multicenter randomized trial assessed whether continuous-infusion of doxorubicin in pediatric patients provides long-term cardioprotection or improvement in event-free survival over bolus-infusion in acute lymphoblastic leukemia. Continuous-infusion of doxorubicin provided no cardioprotection or improvement in event-free survival.

abstract

BACKGROUND AND OBJECTIVES: Doxorubicin, effective against many malignancies, is limited by cardiotoxicity. Continuous-infusion doxorubicin, compared with bolus-infusion, reduces early cardiotoxicity in adults. Its effectiveness in reducing late cardiotoxicity in children remains uncertain. We determined continuous-infusion doxorubicin cardioprotective efficacy in long-term survivors of childhood acute lymphoblastic leukemia (ALL).

METHODS: The Dana-Farber Cancer Institute ALL Consortium Protocol 91-01 enrolled pediatric patients between 1991 and 1995. Newly diagnosed high-risk patients were randomly assigned to receive a total of 360 mg/m² of doxorubicin in 30 mg/m² doses every 3 weeks, by either continuous (over 48 hours) or bolus-infusion (within 15 minutes). Echocardiograms at baseline, during, and after doxorubicin therapy were blindly remeasured centrally. Primary outcomes were late left ventricular (LV) structure and function.

RESULTS: A total of 102 children were randomized to each treatment group. We analyzed 484 serial echocardiograms from 92 patients ($n = 49$ continuous; $n = 43$ bolus) with ≥ 1 echocardiogram ≥ 3 years after assignment. Both groups had similar demographics and normal baseline LV characteristics. Cardiac follow-up after randomization (median, 8 years) showed changes from baseline within the randomized groups (depressed systolic function, systolic dilation, reduced wall thickness, and reduced mass) at 3, 6, and 8 years; there were no statistically significant differences between randomized groups. Ten-year ALL event-free survival rates did not differ between the 2 groups (continuous-infusion, 83% versus bolus-infusion, 78%; $P = .24$).

CONCLUSIONS: In survivors of childhood high-risk ALL, continuous-infusion doxorubicin, compared with bolus-infusion, provided no long-term cardioprotection or improvement in ALL event-free survival, hence provided no benefit over bolus-infusion. *Pediatrics* 2012;130:1003–1011

Anthracycline chemotherapy, although highly effective in treating hematologic malignancies and solid tumors, is limited by cardiotoxicity. Children receiving the anthracycline doxorubicin for acute lymphoblastic leukemia (ALL) can experience persistent and progressive cardiac injury that may lead to dysrhythmias, left ventricular (LV) dysfunction, heart failure, and death from cardiac causes.^{1–8} About 1% to 2% of children treated on front-line cancer protocols have symptomatic cardiac dysfunction within 1 year after treatment,⁹ and up to 65% have symptomatic or asymptomatic cardiac dysfunction 1 year or more after treatment.^{1–8} Delayed doxorubicin-induced cardiomyopathy is associated with female sex, younger age at exposure to doxorubicin, longer duration of follow-up after treatment, higher individual doxorubicin dose rate, and higher cumulative dosages of doxorubicin, with likely pharmacogenomic determinants of cardiac injury as well.^{1–8,10–15}

A retrospective study of 4122 5-year survivors of childhood cancer in France and the United Kingdom highlighted the association of anthracycline exposure with an increased risk of death from cardiac causes after an average follow-up of 27 years compared with the general population.⁷ The British Childhood Cancer Survivor Study of 17 981 5-year survivors of childhood cancer described an increased risk of death from cardiac causes after more than 45 years of follow-up since cancer diagnosis compared with the general population.⁸

These findings underscore the need to develop innovative cardioprotective strategies.¹⁶ Several cardioprotective methods have been explored,¹⁶ including altered doses and dose scheduling of doxorubicin, concomitant administration of cardioprotectant agents, and alternative delivery methods.^{15,16}

The risk of cardiac damage is dose dependent, and therefore investigators have varied dosing schedules and cumulative dosage. Continuous infusion of doxorubicin aims to reduce peak plasma doxorubicin levels by increasing the duration of infusion without reducing the dose.¹⁷ Replacing bolus administration with continuous infusion over 48 to 96 hours reduces early cardiotoxicity in adults,^{16–23} but apparently not in long-term survivors of childhood cancer.^{24,25} Despite the fact that continuous infusion has not demonstrated effectiveness in reducing cardiotoxicity in intermediate-term survivors of childhood cancer in randomized trials, it is still regarded as cardioprotective in children.^{26,27} Thus, we compared the late cardiac outcomes of continuous-infusion doxorubicin with those of bolus infusion in children with high-risk ALL in a randomized clinical trial.

METHODS

Study Participants

This study was part of the Dana-Farber Cancer Institute (DFCI) Childhood ALL Consortium Protocol 91-01, a multi-institutional, open-label, randomized clinical trial that enrolled patients <18 years of age with de novo ALL between December 1991 and December 1995.^{28,29} Patients were classified as having either standard-risk or high-risk ALL disease at the time of diagnosis. High-risk ALL disease was defined as having at least 1 of the following: white blood cell count at least 20 000 cells/ μ L, <2 years of age or 9 or more years of age, presence of leukemic blasts in a cytocentrifuged cerebrospinal fluid sample obtained at diagnosis, presence of a mediastinal mass or T-cell immunophenotype.

Patients were enrolled from 10 collaborating institutions as part of the DFCI Consortium. The study statistician, using a permuted-blocks algorithm

stratified by institution, prepared the allocation schedule. The allocation schedule was concealed by having investigators at each center call a centralized registrar at the DFCI when making group assignments. The nature of the treatments precluded blinding patients or treating physicians to assignment. The institutional review board of each participating institution approved the study, and informed consent was obtained from parents or guardians before treatment.

Therapy on Protocol 91-01 is described elsewhere.^{28,29} In high-risk patients, randomization to continuous or bolus infusion was done before initiation of therapy, but was not implemented until the patient was confirmed to be in complete remission postinduction. The planned maximum additional doxorubicin dose to be administered through either regimen was 300 mg/m². Therefore, all high-risk patients received 30 mg/m² of doxorubicin (by bolus infusion) on each of 2 days during the induction phase. In the postinduction consolidation phase, those patients in remission received doxorubicin either by continuous infusion over 48 hours or by bolus infusion (within 15 minutes) every 3 weeks until the cumulative doxorubicin dose was 360 mg/m² or until the patient had been in complete remission for 9 months, whichever came first. Standard-risk patients received doxorubicin only during the induction phase and were not included in this randomized study.

Echocardiographic Measurements

To evaluate late cardiac structure and function and be included in this analysis, patients had at least 1 follow-up echocardiogram at least 3 years after assignment. Patients who died or relapsed before undergoing follow-up echocardiography were excluded from analysis. Echocardiographic studies

were performed at local centers and then centrally remeasured at the echocardiographic core laboratory to reduce interobserver variability.³⁰ Sample echocardiographic strip-chart recordings and training sessions were provided to inform the collaborating institutions about required data. Echocardiographers at both the local and the central remeasurement sites were blinded to treatment assignments. Providers and patients remained blinded to remeasured data.

Patients underwent 2-dimensional and M-mode echocardiographic evaluations at baseline (before receiving doxorubicin) and during and after treatment. Patients were eligible for cardiac follow-up throughout their first continuous complete remission.

The primary outcomes were late echocardiographic assessments of LV end-diastolic and end-systolic dimensions, LV end-diastolic posterior wall thickness, and LV fractional shortening, which is an index of LV systolic function that is influenced by heart rate, preload, afterload, and contractility.^{30–32}

To adjust for the wide range of ages and developmental changes associated with growth, echocardiographic measurements were transformed to *z* scores from measurements of healthy children,^{30–32} as recommended by the Pediatric Measurements Writing Group of the American Society of Echocardiography Pediatric and Congenital Heart Disease Council.³¹ A *z* score of 0 corresponds to the mean value of the variable in similarly aged, healthy children, whereas *z* scores of 2 or –2 represent 2 standard deviations above or below this mean, respectively.

Statistical Analysis

Means of normally distributed outcome variables (eg, echocardiographic measurements) were compared with the use of *t* tests. Medians of non-normally

distributed variables (eg, age) were compared with the use of Wilcoxon rank-sum tests. Differences in proportions of dichotomous values (eg, percent female) between groups were compared with the use of Fisher exact tests.

To adjust for growth-related changes, echocardiographic data were standardized by age (LV fractional shortening) or body surface area (LV mass, LV dimensions, and LV wall thickness). A *z* score was then calculated from predicted values from a regression model using data from 285 healthy children³² in whom body-surface area ranged from 0.2 to 2.2 m², and who had normal percentiles for height, weight, and weight for height; whose blood pressures were normal; and who had no evidence of cardiac or other disorders.

This study was designed to obtain follow-up echocardiograms, although exact predetermined, fixed time points after assignment were not prescribed. We attempted to capture as much follow-up echocardiographic data on each patient as possible. Table 1 shows the number of echocardiograms and the number of patients from whom they were obtained at baseline and during the intervals >0 to <1, ≥1 to

<3, and 3 or more years after randomization.

Although we did not have a fixed set of time points (eg, yearly) at which to estimate mean *z* scores, we used all data in a mixed model to estimate a regression equation for the *z* scores as a function of time. We fit these data to a repeated-measures linear mixed model in SAS PROC MIXED (SAS Institute, Inc, Cary, NC), in which the mean *z* score was modeled as a linear, quadratic, and cubic function of time postrandomization, using all echocardiographic data at all different time points from all patients.

We modeled the correlation between *z* scores measured at a pair of times on the same subject using an autoregressive structure. Then, we used a mixed model to estimate the mean *z* score at time points 0 (baseline), 3, 6, and 8 years in each treatment arm and tabulated the mean *z* scores over time. We calculated 95% confidence intervals for mean *z* scores at each time point as the estimated mean plus and minus 1.96 times the SE from the mixed model.

Although the dropout rate did not differ between the treatment arms, the mixed-model approach protected against potential biases caused by patients on 1

TABLE 1 Description of 4 Cardiac Risk Factors Among 92 Children With High-Risk Acute Lymphoblastic Leukemia Treated With Doxorubicin and Any Posttreatment Echocardiographic Data Taken 3 or More Years After Baseline

Patient Characteristic	Bolus Infusion (<i>n</i> = 43)	Continuous Infusion (<i>n</i> = 49)	<i>P</i> Value
Age at diagnosis, median (range), y	4.6 (1.6 to 16.2)	3.7 (0.7 to 16.9)	.25
Female, <i>n</i> (%)	20 (47)	20 (41)	.67
Cumulative doxorubicin dose, median (range), mg/m ²	342 (196 to 360)	352 (204 to 360)	.29
Cardiac follow-up since randomization (range), y	8.3 (3.1 to 12.1)	8.2 (3.2 to 13.2)	.63
Echocardiograms by years since diagnosis (no. of echocardiograms/no. of patients)			
Baseline	49/49	61/61	
>0 to <1 y	33/23	29/24	
≥1 to <3 y	52/43	47/42	
≥3 y (total)	113/43	100/49	
≥3 to <6 y ^a	55/34 ^b	45/36 ^b	
≥6 to <8 y ^a	27/21 ^b	19/17 ^b	
≥8 y ^a	31/26 ^b	36/26 ^b	

^a Distribution of echocardiograms and patients with echocardiograms ≥3 y since ALL diagnosis.

^b Number of patients may not sum to total (see Methods-Echocardiographic Measurements).

treatment arm who might have been evaluated more often or followed for longer periods, as might occur with poorer LV function of children on a given treatment. The mixed-model formulation in SAS PROC MIXED adjusts for this type of missing follow-up data³³ and ensures that data from patients with poor cardiac function and more frequent testing are not given excessive weight and do not have a disproportionate influence on the mean z score at any time point.

Using a 2-sided .05 significance level, this study had at least 80% power to detect a difference of 1 SD unit in z scores between the continuous-infusion and bolus groups at the 6-year time point.

The α was set at 0.05, and all tests were 2-tailed. All data met the assumptions of the tests used to analyze them. Analyses were conducted with the SAS statistical software program.

RESULTS

Study Population

Between 1991 and 1995, 240 high-risk patients were enrolled, of whom 29 did not participate in the randomization (directly assigned to bolus infusion), and 7 did not achieve complete remission. Of the remaining 204 patients, 102 were randomly assigned to each treatment. Of these, 61 patients in the continuous-infusion group and 49 patients in the bolus-infusion group had baseline echocardiograms. For this analysis, we used serial echocardiograms from the 92 randomized patients (49 assigned to continuous infusion and 43 assigned to bolus infusion) with baseline echocardiograms and who had undergone at least 1 echocardiographic evaluation at least 3 years after assignment (Fig 1), totaling 484 echocardiograms. Thus, the minimum follow-up time was 3 years, the median was 8 years, and the maximum was 13 years for patients in continuous

FIGURE 1

Summary of the DFCI Childhood ALL Consortium Protocol 91-01 randomized controlled trial for long-term cardiotoxicity of doxorubicin in children with high-risk acute lymphoblastic leukemia.

complete remission and eligible for this late echocardiographic study. Eligible patients who did not have echocardiographic data after 3 years (12 in the continuous group and 6 in the bolus group) did not differ in baseline characteristics from those who did have these data. Ten-year ALL event-free survival rates did not differ between the 2 treatment arms (continuous infusion, 83% versus bolus infusion, 78%; $P = .24$).²⁹ No patient died of, or was detected to have, any clinical cardiac disease before, during, or after exposure to doxorubicin.

Patient Characteristics

Groups were compared by age at diagnosis, duration of follow-up, sex, and cumulative doxorubicin dose to determine whether these factors were associated with late doxorubicin

cardiotoxicity (Table 1). The groups did not differ significantly on any of these factors.

Treatment-Associated LV Effects

After controlling for duration of follow-up, sex, and age at diagnosis, we found no differences in LV echocardiographic characteristics between groups (Fig 2). Subgroup analysis of patients with cumulative doses based only on body surface area also revealed no differences between groups.

Echocardiographic Measurements

Baseline echocardiographic evaluations were performed before receiving doxorubicin for all patients, at a median of 2 days after group assignment for each group ($P = .52$). In both treatment groups, the estimated mean z scores at

FIGURE 2

Changes in estimated mean z-scores among 92 children with high-risk acute lymphoblastic leukemia receiving continuous or bolus infusions of doxorubicin as a cardioprotectant strategy. Years indicates time from date of diagnosis expressed in years. A, LV fractional shortening; B, LV end-diastolic posterior wall thickness; C, LV mass; D, LV end-systolic dimension; and E, LV end-diastolic dimension. Bars represent 95% confidence intervals; * indicates the P value for the difference between treatment arms; † indicates that there is a $P < .05$ for the difference between baseline and the follow-up time-point; ‡ indicates that there is a $P < .01$ for the difference between baseline and the follow-up time-point.

3, 6, and 8 years postrandomization were significantly lower from baseline for LV fractional shortening ($P < .01$ for each arm), LV end-diastolic posterior wall thickness ($P < .01$ for each arm), and LV mass ($P < .01$ for each arm) (Fig 2 A–C). For LV end-systolic

dimension, the estimated z scores were higher in each arm at 3, 6, and 8 years postrandomization compared with baseline, but the increase was statistically significant only for the continuous-infusion group at 6 and 8 years ($P < .05$ for both time points;

Fig 2D). Estimated z scores did not differ between groups for LV end-diastolic dimension at any time point (Fig 2E). Although both groups had significant abnormalities of LV structure and function when compared with baseline measurements and with

measurements in a healthy population, the groups did not differ significantly from each other.

DISCUSSION

We found no significant differences in LV structure or function between children and adolescents with high-risk ALL who were randomly assigned to receive doxorubicin as either a 48-hour continuous infusion or a bolus infusion after a median follow-up of 8 years. Echocardiographic measures of LV structure and function worsened over time in both arms. Continuous-infusion doxorubicin was also not associated with any advantage in ALL event-free survival compared with bolus infusion.

This is the only randomized trial assessing whether continuous-infusion doxorubicin in pediatric patients provides long-term cardioprotection compared with bolus infusion. We found that both continuous and bolus infusions were similarly associated with progressive subclinical cardiotoxicity, despite lower doxorubicin dose rates and lower cumulative dosages than those used in studies on adults.^{18,23,31,34} Previous studies of the cardioprotective effects of continuous doxorubicin infusion have been limited to adults or assessed during or shortly after therapy and have not reported long-term cardiac status.^{16–18,21,23,34–40} No clinical trial in pediatric oncology has demonstrated that continuous infusion of anthracycline prevents long-term cardiotoxicity. Our findings are in accord with another study comparing 2 sequential, nonconcurrent treatment protocols for childhood ALL using continuous or bolus infusion of daunorubicin (cumulative dose, 180 mg/m²), which found no advantage of administration by 6-hour infusion with respect to late cardiotoxicity, with a median follow-up of 5 years.⁴¹ Other pediatric studies have failed to find a statistically

significant cardioprotective effect of continuous infusion anthracycline in long-term survivors.^{25,37,40}

This study was conducted before our study assessing the use of dexrazoxane as a cardioprotective strategy.^{3,42} Therefore, dexrazoxane or other possible cardioprotective treatments, such as the administration of angiotensin-converting enzyme inhibitors or β -adrenergic receptor antagonists during anthracycline therapy, were not included.⁴³ In our subsequent randomized clinical trial, we demonstrated that dexrazoxane provided both early and long-term cardioprotection in high-risk ALL patients, as indicated by the serum cardiac troponin-T concentrations in the blood during doxorubicin therapy and the echocardiographic findings obtained years after treatment.⁴⁴ Dexrazoxane did not adversely affect ALL event-free survival. Thus, prevention of cardiomyocyte damage by dexrazoxane during therapy can also reduce delayed doxorubicin-associated cardiomyopathy in long-term survivors, without compromising the chances of oncologic cure.^{3,42} Survivors of pediatric sarcoma appeared to have less late cardiotoxicity when doxorubicin was administered with dexrazoxane than when administered by prolonged continuous doxorubicin infusion.⁴⁵

These results extend and strengthen our initial findings reported after a median follow-up of 18 months, that continuous infusions offered no cardioprotective advantage over bolus infusions.²⁴ The current findings highlight the persistence of the early abnormalities in LV dimension and LV wall thickness in this group of patients. These results are consistent with our previous findings that LV abnormalities rarely improve beyond the first few years after doxorubicin therapy.²⁴

In young children with HIV, we have found that some of these same

echocardiographic measurements are the strongest predictors of, and over time were associated with, subsequent death from any cause.⁴⁶ Thus, these echocardiographic measurements are validated as surrogate markers for subsequent death, in some cases identifying at-risk children 3 years before an event.⁴⁶

We used these echocardiographic measurements as a priori end points in this study. Since we made that decision, these measurements have been validated as surrogate end points for subsequent death in young children⁴⁶ and have been found to change over time in ways that correlate with cardiac outcomes in large, population-based studies of childhood cancer survivors in the United States, United Kingdom, France, and the Nordic countries with decades of follow-up.^{4–8,10,11}

Based on the epidemiologic literature, these interim echocardiographic assessments are the best outcomes to measure because clinical end points, such as congestive heart failure and death occur quite late. The current study may not have had a long enough follow-up period to provide evidence of symptomatic cardiovascular disease, but it does provide echocardiographic evidence of subclinical disease progression.

To prevent irreversible damage in patients exposed to cardiotoxic agents, cardioprotective strategies must continue to be developed, including sensitive cardiac monitoring to help guide treatment. Echocardiography is impractical for frequent serial monitoring and is limited by operator variability, its inability to detect early cardiomyocyte stress, and its lack of statistically significant association with concurrent measurements of cardiac troponins during therapy.^{3,44} Serial cardiac biomarkers, such as cardiac troponins and N-terminal probrain natriuretic peptide, have been useful in monitoring cardiotoxicity in pediatric patients.⁴⁴

Historically, continuous infusions have resulted in increased hospitalization, costs, and complications, such as mucositis and thromboembolic events.²⁴ With those considerations, as well as the absence of long-term cardioprotection, continuous infusion should not be considered a standard practice for childhood ALL.²⁴

Study Strengths and Limitations

The strengths of the study include the randomized study design, the large sample size, the long follow-up period, the use of echocardiographic z score measurements, and the central re-measurement of echocardiograms. This study had a median 8-year follow-up, the longest for any prospective randomized study in the field of pediatric cardiology where cardiac end points remained blinded. Yet the importance of late cardiac follow-up in patients treated with doxorubicin cannot be overstated in the assessment of disease burden in survivors of childhood cancer. A potential limitation of this study is the loss to echocardiographic follow-up, a general

problem in long-term studies on cured patients. As this study did have complete follow-up from an oncologic perspective, and a balance of follow-up between arms, we feel that any potential bias is low and does not affect the validity of our results. This study focused on LV structure and function and not assessment of global cardiovascular disease risk, which may be relevant to the increased cardiovascular morbidity and mortality in survivors. This study did not address whether continuous doxorubicin infusions at the higher dose rates used for solid tumors provides cardioprotection.

CONCLUSIONS

Continuous infusion of doxorubicin and other anthracyclines is currently included in pediatric treatment protocols on the basis of results from short-term studies of adults that suggest continuous anthracycline infusion is cardioprotective. Given that we found no difference in cardioprotection between continuous and bolus doxorubicin administration, and there was no

difference in ALL event-free survival between the 2 arms, we encourage pediatric oncology providers treating children with high-risk ALL to minimize or eliminate the use of continuous anthracycline infusion.

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