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Cardiac Failure 30 Years after Treatment Containing Anthracycline for Childhood Acute Lymphoblastic Leukemia

John M. Goldberg, MD[1,2], **Rebecca E. Scully, BA**[1,3], **Stephen E. Sallan, MD**[4], and **Steven E. Lipshultz, MD**[1,2]

[1]Department of Pediatrics, University of Miami Leonard M. Miller School of Medicine, Miami, FL

[2]Holtz Children's Hospital of the University of Miami/Jackson Memorial Medical Center and the Sylvester Comprehensive Cancer Center, Hanover, NH

[3]Dartmouth Medical School, Hanover, NH

[4]Department of Pediatric Oncology, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA

Abstract

In 1977, a 5-year-old girl diagnosed with acute lymphoblastic leukemia (ALL) was treated on DFCI Childhood ALL Protocol 77-01, receiving a cumulative doxorubicin dose of 465 mg/m^2, cranial radiation, and other drugs. After being in continuous complete remission for 34 months, she developed heart failure (HF) and was treated with digoxin and furosemide. At 16, she was diagnosed and treated for dilated cardiomyopathy. Over the years she continued to have bouts of HF, which became less responsive to treatment. At 36, she received a heart transplant. Six months later, she stopped taking her medications and suffered a sudden cardiac death.

Keywords

Heart failure; cancer survivorship; late-effects

Case

In 1977, a 5-year-old girl was diagnosed as having acute lymphoblastic leukemia (ALL). She was treated on DFCI ALL Protocol 77-01[1] that included induction therapy with vincristine, prednisone, and doxorubicin. Post-induction therapy included an initial dose rate of 60 mg/m^2 of doxorubicin every 3 weeks, but was reduced after unacceptable cardiac toxicity to 45 mg/m^2 every 3 weeks until a total dose of 465 mg/m^2 was reached.[1] Central nervous system treatment consisted of 24 Gy cranial radiation and intrathecal methotrexate. Additional chemotherapy consisted of courses of vincristine, prednisone, and 6-mercaptopurine, methotrexate and asparaginase. Therapy ended in 1979 after 30 months of continuous complete remission.

Corresponding Author: Steven E. Lipshultz, MD, Department of Pediatrics (D820), University of Miami Leonard M. Miller School of Medicine, P.O. Box 016820, Miami, FL 33101, slipshultz@med.miami.edu, Telephone: 305-243-3993, Fax: 305-243-3990.

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Four months after completing ALL-directed therapy, she developed shortness of breath that led to the diagnosis of heart failure (HF). At that point, she had been in continuous complete remission from leukemia for 34 months. Her left ventricular fractional shortening (LVFS) was approximately 14%, as measured by echocardiography. She was begun on digoxin and furosemide, and 6 months later her LVFS was 24%. She did well after that and was followed by pediatric cardiology and oncology physicians.

She was weaned off furosemide approximately 5 years later, at the age of 13 years, and one year after that weaned off digoxin. At age 14 her LVFS was 28%. At age 16, shortness of breath recurred concomitant with an upper respiratory viral infection. Her LVFS was 18%. She was diagnosed with a dilated cardiomyopathy and treated with digoxin, furosemide, and enalapril. She remained on the enalapril and was gradually weaned off the digoxin and furosemide. Over the next 10 years she continued to have bouts of HF during episodes of mild respiratory illnesses. She received digoxin and furosemide during each of these bouts.

In her late twenties, her care was transferred from a pediatric cardiologist to an adult cardiologist. She never became pregnant, did not smoke, use drugs, or drink excessive amounts of alcohol. At age 27 she underwent bariatric surgery after her BMI reached 39.7; post-operatively, her BMI stabilized at approximately 20. She subsequently developed persistent vitamin D deficiency and iron deficiency anemia, for which she received vitamin D_3 and periodic IV iron supplementation.

Throughout her early thirties, her overall health declined and she developed type II diabetes, amenorrhea, chronic migraine headaches, and hip and back pain. Her acute episodes of HF became less responsive to treatment and she had progressively worsening LVFS. After runs of paroxysmal atrial fibrillation, an implantable defibrillator and pacemaker were considered. She was started on carvedilol, in addition to digoxin and furosemide. Whereas in her twenties her LVFS was 24%, by her early thirties it was only 16% even when she was not acutely ill. Her HF was characterized by a dilated pattern, suggesting remodeling early in the course of her condition. She received a heart transplant at age 36. Six months following cardiac transplant, the patient electively stopped taking her medications, refused follow-up, and suffered a sudden cardiac death within 2 weeks of stopping her treatment.

Discussion

This patient illustrates several recently reviewed[2] key issues pertaining to the late occurring cardiac effects and other sequelae of anthracycline cardiotoxicity presented at a consensus conference in Como, Italy.[3] First, the patient was treated with doxorubicin and survived childhood cancer. Anthracyclines have played a substantial role in improving cancer survivorship over the past 45 years.[4] She also demonstrates that patients who suffer from acute cardiac toxicity soon after doxorubicin therapy are more likely to suffer from marked late HF.[5]

In addition to cardiotoxicity, per se, her case also exemplifies the added risks of female sex, young age at the time of anthracycline treatment, and receiving high dose-rates and high cumulative doxorubicin doses.[6–8] The risk of doxorubicin toxicity in females is thought to be greater because of the lower expression of *p*-glycoprotein (hepatic *p*-glycoprotein is 2.4-fold lower in females than in males on gene expression array) and the associated higher intracellular exposures to the drug. *P*-glycoprotein is also known as multi-drug resistance gene and pumps doxorubicin and other toxins out of cells and into the biliary tract to be eliminated in feces.[9] Body composition is also implicated in increased toxicity. Skin and body fat show low uptake of doxorubicin as compared to muscle, suggesting that females

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are predisposed to higher cellular concentrations of doxorubicin for any given body-surface area determined dose.[10]

Younger patients may be more susceptible because of inhibited cardiac growth.[7] Because time is required for somatic growth to outstrip myocardial growth, the myocardial effects of doxorubicin on left ventricular mass and afterload become more obvious over time.[7]

She received a relatively high cumulative dose of doxorubicin, a significant risk factor for toxicity. The risk of HF for children who receive a cumulative dose of 100 to 399 mg/m^2 is 1.7% compared with 9% for those who receive 500 mg/m^2 or more.[11] She also received doxorubicin at a relatively high dose-rate, which has typically been associated with increased afterload and decreased LVFS.[7]

Cranial radiation, a component of her CNS treatment, is associated with significant sequelae, particularly in women. Compared with men who received the same treatment, women show greater increases in BMI over time, increased neurocognitive impairment, and greater reductions in final height.[12,13]

The interaction between weight and cardiac disease progression remains unclear.[14,15] Higher BMI has been shown to be associated with better cardiac outcomes in the setting of a chronic systolic HF diagnosis.[16] However, alternative measures of body composition and improved understanding of the heterogeneity of obesity[17] may help to clarify what until now has been a paradoxical relationship.[18,19]

Persistent vitamin D deficiency, which has been increasingly implicated in elevated cardiovascular risk, may also have accelerated her declining heart function.[20] Among adult Caucasians routinely referred for cardiac angiography, vitamin D deficiency was found to be associated with worse New York Heart Association classification and greater impairments in left ventricular function.[21]

This patient showed that ACE inhibitor therapy can delay the progression of chronic HF caused by doxorubicin and can postpone end-stage HF for many years.[22] However, clinical cardiomyopathy associated with anthracycline chemotherapy often becomes refractory to treatment and carries a poor prognosis.[22–24]

Cardiac transplantation is an increasingly acceptable treatment option for long-term cancer survivors with end-stage cardiomyopathy following anthracycline chemotherapy.[25–29] A concern specific to cancer survivors is that cancer might recur. The Pediatric Committee of the American Society of Transplantation notes that cancer treatment within the past five years is a relative contraindication for transplantation.[30] Results of long-term follow-up of 17 survivors who received cardiac transplant 9.2 years (range, 0.4 to 15.2 years) after cancer treatment showed a 1 year survival rate of 100% and a 5-year rate of 60%.[29]

This case underscores the extent of the health-related burden carried by long-term survivors of anthracycline-treated childhood ALL; thirty years after treatment, the cumulative incidence of chronic health conditions in this population reaches 73%; more than 40% of adult survivors of childhood cancer have a severe, disabling, or life threatening condition.[31]

In light of the unique demands of chronic, particularly cardiac, disease, patients such as ours may benefit from the services of a dedicated comprehensive multidisciplinary treatment program. While the data are limited, comprehensive HF programs appear to limit both hospitalizations and length of hospital stay, while also providing a cost benefit to families.[32]

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Although most survivors report satisfaction with their lives, certain subgroups show increased rates of poor health-related quality of life. Those include patients who received cranial radiation or surgery during treatment and those with a major medical condition during follow-up; women are at the highest risk.[33] Intensive chemotherapy is a significant risk factor for depression and somatic distress among survivors of leukemia or lymphoma.[34]

In the setting of extreme disease burden, the question of suicidality among adult survivors of childhood cancer has recently emerged. Among a large cohort who were at least 5 years post-treatment, 7.8% of cancer survivors reported suicidal ideation as opposed to only 4.6% of controls.[35] In a single site study, that percentage reached 12.8%.[36] In addition, bariatric surgery has also been shown to be associated with elevated rates of suicide.[37]

Conclusion

Each year, about 12,400 children are diagnosed with cancer in the United States.[38] Overall 5-year survival rate is 80%. Thus, 1 in every 540 adults aged 20 to 34 years in the United States is a survivor of childhood cancer.[38,39] Therefore, an increasing number of patients treated with anthracyclines are expected to be at risk for late-occurring cardiac morbidity, although not every child with cancer is treated with anthracyclines and in modern protocols, the total dose and dose rate tends to be lower than that described for our patient.[40] Because these patients are at risk for HF and other long-term complications of childhood cancer and its therapy, it is crucial for primary care physicians, cardiologists, and oncologists caring for adults to be aware of the therapy received by their patients and its long-term risks.[31]

Many survivors will require long-term monitoring of cardiac function, and among them, some will inevitably require more definitive therapy for HF. Patients with anthracycline-induced cardiotoxicity might present to the long-term oncology follow-up clinic or to the cardiologist without a clear history of HF; up to 6% of such asymptomatic patients have clinically relevant, long-term cardiac effects.[41]

Areas for pediatric cardiologists to explore include new biomarkers of early signs of cardiac toxicity and genetic variations that increase susceptibility to anthracycline toxicity, as well as strategies for cardioprotection during treatment. Hopefully, new genetic research, facilitated by the complete sequencing of the human genome, may identify gene mutations and polymorphisms that increase an individual's cardiac sensitivity to doxorubicin. Perhaps the success of these drugs can be also be improved by modulating their cardiotoxicity, either through cardioprotectants, such as dexrazoxane, or through new agents that maintain the efficacy of the original class of compounds while reducing their toxicity.[8,42,43]

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References

1. Sallan SE, Hitchcock-Bryan S, Gelber R, et al. Influence of Intensive Asparaginase in the Treatment of Childhood Non-T-Cell Acute Lymphoblastic Leukemia. Cancer Res. 1983; 43:5601–5607. [PubMed: 6352020]
2. Lipshultz SE, Lipsitz SR, Sallan SE, et al. Chronic progressive cardiac dysfunction years after doxorubicin therapy for childhood acute lymphoblastic leukemia. J Clin Oncol. 2005; 23:2629–2636. [PubMed: 15837978]

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3. Gianni L, Herman EH, Lipshultz SE, et al. Anthracycline cardiotoxicity: from bench to bedside. J Clin Oncol. 2008; 26:3777–3784. [PubMed: 18669466]
4. Furman L, Camitta BM, Jaffe N, et al. Development of an effective treatment program for childhood acute lymphocytic leukemia: a preliminary report. Med Pediatr Oncol. 1976; 2:157–166. [PubMed: 822270]
5. Lipshultz SE. Heart failure in childhood cancer survivors. Nat Clin Pract Oncol. 2007; 4:334–335. [PubMed: 17457311]
6. Lipshultz SE, Colan SD, Gelber RD, et al. Late cardiac effects of doxorubicin therapy for acute lymphoblastic leukemia in childhood. N Engl J Med. 1991; 324:808–815. [PubMed: 1997853]
7. Lipshultz SE, Lipsitz SR, Mone SM, et al. Female sex and drug dose as risk factors for late cardiotoxic effects of doxorubicin therapy for childhood cancer. N Engl J Med. 1995; 332:1738–1743. [PubMed: 7760889]
8. Lipshultz SE, Rifai N, Dalton VM, et al. The effect of dexrazoxane on myocardial injury in doxorubicin-treated children with acute lymphoblastic leukemia. N Engl J Med. 2004; 351:145–153. [PubMed: 15247354]
9. Davis M. Gender differences in p-glycoprotein: drug toxicity and response. J Clin Oncol. 2005; 23:6439–6440. [PubMed: 16155032]
10. Thompson PA, Rosner GL, Matthay KK, et al. Impact of body composition on pharmacokinetics of doxorubicin in children: a Glaser Pediatric Research Network study. Cancer Chemother Pharmacol. 2009; 64:243–251. [PubMed: 19020877]
11. Krischer JP, Epstein S, Cuthbertson DD, et al. Clinical cardiotoxicity following anthracycline treatment for childhood cancer: the Pediatric Oncology Group experience. J Clin Oncol. 1997; 15:1544–1552. [PubMed: 9193351]
12. Garmey EG, Liu Q, Sklar CA, et al. Longitudinal changes in obesity and body mass index among adult survivors of childhood acute lymphoblastic leukemia: a report from the Childhood Cancer Survivor Study. J Clin Oncol. 2008; 26:4639–4645. [PubMed: 18824710]
13. Armstrong GT, Sklar CA, Hudson MM, et al. Long-term health status in adult survivors of childhood cancer: Does gender matter? J Clin Oncol. 2007; 25:4477–4489. [PubMed: 17906209]
14. Kenchaiah S, Evans JC, Levy D, et al. Obesity and the risk of heart failure. N Engl J Med. 2002; 347:305–313. [PubMed: 12151467]
15. Qureshi, MY.; Wilkinson, JD.; Lipshultz, SE. The Relationship of Childhood Obesity with Cardiomyopathy and Heart Failure. In: Lipshultz, SE.; Miller, TL.; Messiah, SE., editors. Pediatric Metabolic Syndrome: Comprehensive Clinical Review and Related Health Issues. London, United Kingdom: Springer; 2011.
16. Lavie CJ, Osman AF, Milani RV, et al. Body composition and prognosis in chronic systolic heart failure: the obesity paradox. Am J Cardiol. 2003; 91:891–894. [PubMed: 12667583]
17. Miller TL, Lipsitz SR, Lopez-Mitnik G, Hinkle AS, Constine LS, Adams MJ, French C, Proukou C, Rovitelli A, Lipshultz SE. Characteristics and determinants of adiposity in pediatric cancer survivors. Cancer Epidemiol Biomarkers Prev. 2010; 19:2013–2022. [PubMed: 20647396]
18. Ashrafian H, le Roux CW, Darzi A, et al. Effects of bariatric surgery on cardiovascular function. Circulation. 2008; 118:2091–2102. [PubMed: 19001033]
19. Oreopoulos A, Ezekowitz JA, McAlister FA, et al. Association between direct measures of body composition and prognostic factors in chronic heart failure. Mayo Clin Proc. 2010; 85:609–617. [PubMed: 20592169]
20. Lee JH, O'Keefe JH, Bell D, et al. Vitamin D deficiency: an important, common, and easily treatable cardiovascular risk factor? J Am Coll Cardiol. 2008; 52:1949–1956. [PubMed: 19055985]
21. Pilz S, März W, Wellnitz B, et al. Association of vitamin D deficiency with heart failure and sudden cardiac death in a large cross-sectional study of patients referred for coronary angiography. J Clin Endocrinol Metab. 2008; 93:3927–3935. [PubMed: 18682515]
22. Lipshultz SE, Lipsitz SR, Sallan SE, et al. Long-term enalapril therapy for left ventricular dysfunction in doxorubicin-treated survivors of childhood cancer. J Clin Oncol. 2002; 20:4517–4522. [PubMed: 12454107]

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23. Felker GM, Thompson RE, Hare JM, et al. Underlying causes and long-term survival in patients with initially unexplained cardiomyopathy. N Engl J Med. 2000; 342:1077–1084. [PubMed: 10760308]
24. Silber JH, Cnaan A, Clark BJ, et al. Enalapril to prevent cardiac function decline in long-term survivors of pediatric cancer exposed to anthracyclines. J Clin Oncol. 2004; 22:820–828. [PubMed: 14990637]
25. Arico M, Pedroni E, Nespoli L, et al. Long term survival after heart transplantation for doxorubicin induced cardiomyopathy. Arch Dis Child. 1991; 66:985–986. [PubMed: 1929498]
26. Levitt G, Bunch K, Rogers CA, et al. Cardiac transplantation in childhood cancer survivors in Great Britain. Eur J Cancer. 1996; 32A:826–830. [PubMed: 9081361]
27. Levitt G, Anazodo A, Burch M, et al. Cardiac or cardiopulmonary transplantation in childhood cancer survivors: an increasing need? Eur J Cancer. 2009; 45:3027–3034. [PubMed: 19744853]
28. McManus RP, O'Hair DP. Pediatric heart transplantation for doxorubicin-induced cardiomyopathy. J Heart Lung Transplant. 1992; 11 375–356.
29. Ward KM, Binns H, Chin C, et al. Pediatric heart transplantation for anthracycline cardiomyopathy: cancer recurrence is rare. J Heart Lung Transplant. 2004; 23:1040–1045. [PubMed: 15454169]
30. Fricker FJ, Addonizio L, Bernstein D, et al. Heart transplantation in children: indications. Report of the Ad Hoc Subcommittee of the Pediatric Committee of the American Society of Transplantation (AST). Pediatr Transplant. 1999; 3:333–342. [PubMed: 10562980]
31. Oeffinger KC, Mertens AC, Sklar CA, et al. Chronic health conditions in adult survivors of childhood cancer. N Engl J Med. 2006; 355:1572–1582. [PubMed: 17035650]
32. Bublik N, Alvarez JA, Lipshultz SE. Pediatric cardiomyopathy as a chronic disease: a perspective on comprehensive care programs. Prog Pediatr Cardiol. 2008; 25:103–111. [PubMed: 19122765]
33. Zeltzer LK, Recklitis C, Buchbinder D, et al. Psychological status in childhood cancer survivors: a report from the Childhood Cancer Survivor Study. J Clin Oncol. 2009; 27:2396–2404. [PubMed: 19255309]
34. Zebrack BJ, Zeltzer LK, Whitton J, et al. Psychological outcomes in long-term survivors of childhood leukemia, Hodgkin's disease, and non-Hodgkin's lymphoma: a report from the Childhood Cancer Survivor Study. Pediatrics. 2002; 110(1 Pt 1):42–52. [PubMed: 12093945]
35. Recklitis CJ, Diller LR, Li X, et al. Suicide ideation in adult survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. J Clin Oncol. 2010; 28:655–661. [PubMed: 19841325]
36. Recklitis CJ, Lockwood RA, Rothwell MA, et al. Suicidal ideation and attempts in adult survivors of childhood cancer. J Clin Oncol. 2006; 24:3852–3857. [PubMed: 16921037]
37. Tindle HA, Omalu B, Courcoulas A, et al. Risk of suicide after long-term follow-up from bariatric surgery. Am J Med. 2010; 123:1036–1042. [PubMed: 20843498]
38. Jemal A, Siegel R, Ward E, et al. Cancer statistics, 2008. CA Cancer J Clin. 2008; 58:71–96. [PubMed: 18287387]
39. Ries, LAG.; Eisner, MP.; Kosary, CL., et al. SEER Cancer Statistics Review, 1975–2004, based on November 2006 SEER data submission, posted to the SEER Web site 2007. Bethesda, MD: National Cancer Institute; 2006.
40. Ries, LAG.; Smith, MA.; Gurney, JG., et al., editors. Cancer Incidence and Survival among Children and Adolescents: United States SEER Program 1975–1995. Bethesda, MD: National Cancer Institute; 1999. SEER program. NIH Pub No 99-4649,99-4649. Bethesda, MD
41. Pein F, Sakiroglu O, Dahan M, et al. Cardiac abnormalities 15 years and more after adriamycin therapy in 229 childhood survivors of a solid tumour at the Institut Gustave Roussy. Br J Cancer. 2004; 91:37–44. [PubMed: 15162142]
42. Booser DJ, Perez-Soler R, Cossum P, et al. Phase I study of liposomal annamycin. Cancer Chemother Pharmacol. 2000; 46:427–432. [PubMed: 11127949]
43. Barry E, Alvarez JA, Scully RE, et al. Anthracycline-induced cardiotoxicity: course, pathophysiology, prevention and management. Expert Opin Pharmacother. 2007; 8:1039–1058. [PubMed: 17516870]