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RESEARCH LETTER

Role of Genetic Testing for Cardiomyopathies in Pediatric Patients With Left Ventricular Dysfunction Secondary to Chemotherapy

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Improved cancer therapies have significantly increased survival in oncological pediatric patients. However, cardiac dysfunction secondary to chemotherapy represents a major complication that may affect long-term prognosis.[1] Anthracyclines are the most frequently used drugs, and their associated cardiotoxicity is well established. Several risk factors for cardiotoxicity have been identified, including cumulative drug dose, age at cancer diagnosis, female sex, race, and chest radiation. In addition, evidence of genetic susceptibility in determining anthracycline-related cardiomyopathy has recently been proposed.[2,3] In adults, dilated cardiomyopathy (DCM) develops according to a double-hit model in which environmental factors such as chemotherapy are superimposed on the presence of a rare pathogenic variant. In children, however, data are limited to a single study subset,[3] and the role of genetic screening in this setting is unresolved.

We retrospectively assessed children consecutively exposed to chemotherapy from 2016 to 2023 at our hospital. Among those who developed left ventricular (LV) systolic dysfunction, defined by an ejection fraction ≤55% by the Simpson biplane method, potential causes of reversible impairment were investigated and excluded. When dysfunction was persistent (on 2 different exams at least 1 year apart), genetic counseling and testing were offered to probands and their parents. Next-generation sequencing analysis was aimed at pathogenic or likely pathogenic variants in the 20 most prevalent DCM-related genes. Variant classification was performed according to the American College of Medical Genetics and Genomics guidelines. The data supporting the findings of this study are available from the corresponding author upon request. The study conforms to the principles of the Helsinki II Declaration and was approved by the institutional review board.

Of a total of 427 patients with cancer (mean age at the diagnosis of cancer, before starting chemotherapy, 11 years; range, 2–18; 41% female patients, 59% male patients), 47 (11%) developed systolic dysfunction. Of these 47, 3 died within a few days due to fulminant myocarditis (n=1) or sepsis (n=2). Of the remaining 44 children, 25 (57%) had a reversible form of LV impairment (in the context of sepsis in 10), while 19 (43%) had persistent systolic dysfunction, including 2 children who required hospitalization for heart failure. Of these 19, one patient with stable DCM died suddenly in 7 years following chemotherapy. One patient with persistent LV dysfunction had a positive family history of DCM (brother and maternal uncle) as previously reported.[4] In children with cardiac dysfunction correlated with sepsis, intensive care stay with inotropic support was necessary to overcome the acute heart failure phase.

Of the 19 patients with persistent dysfunction, 9 agreed to undergo genetic testing and 3 of these (33%) had pathogenic/likely pathogenic variants, including 2 with a truncating variant in *TTN* and one with a missense variant in *MYH7*, both associated with DCM in the literature (Table). In a fourth patient, a *DSP* (desmoplakin) variant of uncertain significance, but predicted to be potentially disruptive, was identified.

In our population of pediatric cancer survivors with postchemotherapy LV dysfunction, following a selection

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Nonstandard Abbreviations and Acronyms

DCM	dilated cardiomyopathy
LV	left ventricular

based on the persistence of systolic impairment >1 year, genetic testing for DCM-associated genes led to a 33% yield for potentially relevant variants in *TTN* and *MYH7*. Notably, only one of these patients had a clear family history of DCM. While the rarity of the association between pediatric cancer and persistent LV dysfunction unavoidably led to a small sample size, dictating caution in the interpretation of the results, our findings have a potential impact on management and warrant further understanding. In the study by Garcia-Pavia et al,[3] rare variants in genes causative of DCM were identified in 7.3% of 41 pediatric patients with chemotherapy-induced LV dysfunction, mostly comprising truncating *TTN* mutations. The lower yield in their cohort compared with ours (7.3% versus 33%) can be largely explained by the predominance of reversible LV dysfunction (68%), which was an exclusion criterion in our study. Thus, selecting patients with LV impairment persisting after at least a year after exposure to chemotoxic agents may considerably improve the appropriateness of genetic screening. Such criterion may obviously only be used with hindsight to evaluate the risk for subsequent chemotherapy cycles or perform cascade family screening. In terms of primary prevention, however, the identification of appropriate candidates for genetic screening prechemotherapy remains challenging. In this regard, the absence of genetic screening in cancer survivors without systolic dysfunction is a limitation of our study.

At present, we do not advocate a systematic approach by next-generation sequencing in patients with cancer (except in the presence of DCM family history or preexisting cardiac abnormalities) due to unjustified costs and limited actionability of the results. Nevertheless, further efforts may benefit from innovative approaches such as artificial intelligence approaches exploiting ECG-based techniques as a means to select potentially at-risk individuals.[5]

ARTICLE INFORMATION

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Disclosures

None.

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Table. Patients With Cardiac Dysfunction Underwent Genetic Testing

Sex	Age at CHT	Diagnosis	AC cumulative dose, mg	Other CHT drugs	LVEF (%) post-CHT	Gene variant	Variant type
F	12	EWS	524	CP, IF, VCR, Act D, ETO	40	*DSP* c.6275 C>T p. (Ala2092Val)	VOUS
M	14	OS	528	MTX, CIS	40	Negative	
F	5	OS	301	MTX, CIS, MTP	35	Negative	
M	14	OS	763	MTX, CIS, MTP	40	*TTN* c.85285_85289del p.(Lys28429*) and *TTN* c.97638C>G p.(Tyr32546*)	LP and LP
M	15	LH	0	CP, VCR, PC	45	*MYH7* c.1665C>G p.(Asn555Lys)	P
M	5	RMS	251	CP, IF, VCR, Act D, CARB	40	Negative	
M	12	BDA exposed to BMT	0	CP, Th, TREO, Flu	45	Negative	
M	10	OS	434	CIS, MTX, MTP	45	Negative	
M	1	MB exposed to BMT	0	CP, MTX, VCR, ETO, CARB	25	*TTN* c.54878 del p.(Lys18293Argfs*8)	LP

AC indicates anthracycline; Act D, actinomycin d; BDA, blackfan-diamond anemia; BMT, bone marrow transplant; CARB, carboplatin; CHT, chemotherapy; CIS, cisplatin; CP, cyclophosphamide; *DSP*, desmoplakin; ETO, etoposide; EWS, Ewing sarcoma; F, female; Flu, fludarabine; IF, ifosfamide; LH, lymphoma Hodgkin; LP, likely pathogenic; LVEF, left ventricular ejection fraction; M, male; MB, medulloblastoma; MTP, muramyl tripeptide; MTX, methotrexate; OS, osteosarcoma; P, pathogenic; PC, procarbazine; RMS, rhabdomyosarcoma; Th, thiotepa; TREO, treosulfan; VCR, vincristine; and VOUS, variant of uncertain significance.

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