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LETTERS

RESEARCH LETTER

Carvedilol to Improve Cardiac Remodeling in Anthracycline-Exposed Childhood Cancer Survivors

Subgroup Analysis of COG ALTE1621

Saro H. Armenian, DO, MPH,[a,b] Melissa M. Hudson, MD,[c,d] Lanie Lindenfeld, MA,[a,b] Sitong Chen, MS,[a] Eric J. Chow, MD, MPH,[e] Steven Colan, MD,[f] Meagan Echevarria, MPH,[a] F. Lennie Wong, PhD,[a] Ming Hui Chen, MD,[f] Smita Bhatia, MD, MPH[g]

ALTE1621 (PREVENT-HF [Pharmacologic Reversal of Ventricular Remodeling in Childhood Cancer Survivors at Risk for Anthracycline-related Heart Failure]) was a multicenter, randomized phase IIb, double-blinded, placebo-controlled trial of carvedilol at a 6.25 mg twice daily vs placebo administered for 2 years in childhood cancer survivors. Survivors had received ≥250 mg/m^2 cumulative anthracycline (doxorubicin equivalent) exposure by age 21 years, were ≥2 years from completion of cancer treatment, and had preserved cardiac function (ie, left ventricular ejection fraction [LVEF] ≥50% and/or fractional shortening [FS] ≥25%).[1] The primary endpoint was to determine the impact of carvedilol on standardized left ventricular wall thickness/dimension ratio *z*-score (LVWT/Dz), an established marker of adverse cardiac remodeling in survivors that precedes changes in conventional measures such as LVEF/FS.[2] The secondary endpoints included the left ventricular end-systolic diameter (LVESD), left ventricular end-diastolic diameter (LVEDD), left ventricular end-systolic volume (LVESV), and left ventricular end-diastolic volume (LVEDV); left ventricular end-systolic wall stress; left ventricular mass; LVEF; FS; and diastolic function (E/A wave ratio). The parent PREVENT-HF trial[1] showed that although low-dose carvedilol was safe and well tolerated, it did not result in significant improvement in the primary endpoint of LVWT/Dz compared with placebo nor were there significant changes in other secondary endpoints of cardiac remodeling such as LVESD/LVEDD and LVESV/LVEDV.[1]

Recent studies have highlighted the prognostic role of N-terminal pro-B-type natriuretic peptide (NT-proBNP) in determining risk of cardiomyopathy/heart failure in asymptomatic childhood cancer survivors.[3,4] Specifically, elevated (age- and sex-specific >97.5th percentile) NT-proBNP was independently associated with >2-fold risk of cardiomyopathy in high-risk survivors,[3] representing a group that would have likely been eligible for the PREVENT-HF study. With that in mind, we performed a post hoc analysis to examine the efficacy of carvedilol in the subset of

From the [a]Division of Outcomes Research, City of Hope, Duarte, California, USA; [b]Department of Pediatrics, City of Hope, Duarte, California, USA; [c]Department of Oncology, St. Jude Children's Research Hospital, Memphis, Tennessee, USA; [d]Department of Epidemiology and Cancer Control, St. Jude Children's Research Hospital, Memphis, Tennessee, USA; [e]Clinical Research and Public Health Sciences Divisions, Fred Hutchinson Cancer Center, Seattle, Washington, USA; [f]Department of Cardiology, Boston Children's Hospital, Boston, Massachusetts, USA; and the [g]Institute for Cancer Outcomes and Survivorship, University of Alabama at Birmingham, Birmingham, Alabama, USA.

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TABLE 1 Comparison of the Study Primary and Secondary Endpoints and the Differences Between Arms at 2 Years Among Those With Elevated Baseline N-Terminal Pro-B-Type Natriuretic Peptide

	Carvedilol (95% CI)[a]	Placebo (95% CI)[a]	Difference (95% CI)	*P* Value
LV wall thickness to dimension ratio (*z*-score)	2.35 (0.12-4.57)	0.85 (−1.41 to −3.10)	1.5 (0.41-2.59)	0.007
LV end-systolic wall stress	−10.41 (−31.71 to 10.9)	6.75 (−17.23 to 30.72)	−17.15 (−30.28 to −4.03)	0.011
Ejection fraction, %	2.31 (−3.79 to 8.42)	1.04 (−4.79 to 6.86)	1.28 (−1.3 to 3.85)	0.33
Fractional shortening, %	2.10 (−2.19 to 6.40)	0.15 (−3.41 to 3.72)	1.95 (−0.76 to 4.66)	0.16
E/A ratio	−0.84 (−1.31 to −0.37)	−0.79 (−1.61 to −0.43)	−0.05 (−0.34 to 0.25)	0.75
LV end-diastolic diameter in diastole, cm	−0.05 (−0.55 to 0.44)	0.21 (−0.33 to 0.75)	−0.26 (−0.49 to −0.02)	0.032
LV end-diastolic diameter in systole, cm	−0.15 (−0.58 to 0.28)	0.16 (−0.31 to 0.64)	−0.31 (−0.51 to −0.12)	0.002
LV mass (BSA adjusted)	16.47 (1.58-31.37)	15.88 (0.67-31.10)	0.59 (−5.44 to 6.63)	0.85
LV end-diastolic volume, mL	−3.30 (−33.67 to 27.07)	20.52 (−11.1 to 52.13)	−23.82 (−38.28 to −9.36)	0.002
LV end-systolic volume, mL	−3.02 (−17.41 to 11.37)	9.24 (−6.66 to 25.14)	−12.26 (−21.29 to −3.22)	0.008

[a]Linear mixed-effects model-based mean and 95% CI. Each model was adjusted for age at diagnosis (<5 years, ≥5 years), time since diagnosis (<10 years, ≥10 years), chest radiation (any, none), and age at study enrollment.

BSA = body surface area; LV = left ventricular.

PREVENT-HF participants who had elevated NT-proBNP at baseline.

The methodology of the trial has been described elsewhere.[1] In brief, all echocardiograms were read independently at the core cardiology lab by 1 reader (M.H.C.) blinded to treatment allocation. NT-proBNP was measured centrally using quantitative immunochromatography (RAMP NT-proBNP, Response Biomedical Corp), for which the lower limit of detection was 18 pg/mL. In our statistical analyses, echocardiogram-derived outcomes, measured every 6 months for 2 years, were verified as normally distributed and compared longitudinally by treatment group using a linear mixed-effects model for repeated measures (MMRM). Outcomes were assumed to vary linearly with time (continuous variable). The model also included baseline randomization stratification factors (age at and time since diagnosis and chest radiotherapy) and age at enrollment. A comparison of baseline values for substudy participants revealed no significant differences, and the inclusion of interactions between time and covariates did not alter the results. Thus, these terms were not considered in the MMRM. The activity of carvedilol was determined by testing the statistical significance of the treatment group (carvedilol: 1, placebo: 0) by time interaction in the MMRM for LVWT/Dz using a 2-sided 1 degree of freedom *t*-test at $P \leq 0.05$, requiring the estimated mean LVWT/Dz to be higher for carvedilol than placebo with time. The secondary echocardiographic endpoints were analyzed similarly using MMRM. The Central Institutional Review Board provided approval, and all participants provided written informed consent.

There were 146 participants (96.0% of the parent modified intention-to-treat cohort) who had both a baseline and a follow-up NT-proBNP. Of these, 32 (n = 16 carvedilol, n = 16 placebo) had elevated (age- and sex-specific >97.5th percentile)[3,4] baseline NT-proBNP and were included in this subanalysis. Participant characteristics, baseline echocardiographic measures, and NT-proBNP levels were balanced ($P > 0.05$) between the treatment groups (data not shown). The mean time since cancer diagnosis was 22.4 ± 10.7 years, and the age at study participation was 34.0 ± 9.8 years. The majority were male patients (22 [68.8%]), and 22 (68.8%) were non-Hispanic White. The most common cancer diagnosis was acute lymphoblastic leukemia (7 [21.9%]), and bone and soft tissue sarcomas constituted 31% of cancer diagnoses. The mean cumulative anthracycline dose was 415 ± 120 mg/m^2. Ten (31.3%) participants had previously been treated with chest radiation; the mean radiation dose was 19.4 ± 19.4 Gy.

Of the participants in this subanalysis, compared to placebo, carvedilol arm participants had significantly better LVWT/Dz (+1.5 in the carvedilol arm; 95% CI: 0.41-2.59; $P = 0.007$) at 2 years. In addition, carvedilol arm participants had significantly better left ventricular end-systolic wall stress (−17.15; 95% CI: −30.28 to −4.03; $P = 0.0011$), LVEDD (−0.26; 95% CI: −0.49 to −0.02; $P = 0.032$), LVESD (−0.31; 95% CI: −0.51 to −0.12; $P = 0.002$), LVEDV (−23.82; 95% CI: −38.28 to −9.36; $P = 0.002$), and LVESV (−12.26; 95% CI:

−21.29 to −3.22; $P = 0.008$) (Table 1). Longer follow-up is ongoing to determine the clinical implications of these statistically significant differences.

It is noteworthy that compared to the parent study, participants included in this subanalysis were older at enrollment (34.0 ± 9.8 years vs 27.3 ± 10.2 years), had higher cumulative anthracycline exposure (415 ± 120 mg/m^2 vs 385 ± 96 mg/m^2), and were more likely to have been treated with chest radiation (31% vs 19%). As such, they would be considered at higher risk. That said, in the parent study, stratified analyses by anthracycline dose and chest radiation exposure did not reveal significant treatment effects, suggesting that clinical risk factors alone may not differentiate individuals in whom pharmacologic intervention would be most efficacious. In this context, readily available cardiac blood biomarkers such as NT-proBNP may help discern those who may benefit most from low-dose carvedilol.

A recent study of nearly 1,500 long-term childhood cancer survivors with normal baseline LVEF (≥50%) suggested that NT-proBNP and echocardiography-derived global longitudinal strain (GLS) may provide independent and additive prognostic information for long-term cardiomyopathy/heart failure risk prediction compared with clinical factors alone (area under the curve [AUC]: clinical model + GLS/NT-proBNP [AUC: 0.74] vs clinical model [AUC: 0.70]).[3] Of note, GLS was not prospectively measured in the PREVENT-HF trial; therefore, we are not able to comment on its impact in the current subanalysis. Regardless, given the findings from the recent observational studies evaluating the independent prognostic role of NT-proBNP in this population combined with our preliminary data, we would advocate for continued efforts toward developing more precision-based interventions to reduce heart failure risk in long-term survivors. The findings from this study will need to be confirmed in a larger randomized trial, focusing on the subgroup of survivors highlighted in the current report who may derive the greatest benefit from neurohormonal blockade with carvedilol.

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ADDRESS FOR CORRESPONDENCE: Dr Saro H. Armenian, Departments of Pediatrics and Population Sciences, City of Hope, 1500 East Duarte Road, Duarte, California 91010, USA. E-mail: sarmenian@coh.org.

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