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LETTERS

RESEARCH LETTER

Cardiac Dysfunction in Children and Young Adults Treated With MEK Inhibitors

A Retrospective, Single-Center Study

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Ras-Raf-MEK-ERK alterations in cancer can be targeted using MEK inhibitors. In adults, MEK inhibitors cause left ventricular dysfunction, hypertension, and QT prolongation; however, few data exist for MEK inhibitor-associated cardiotoxicity in children, adolescents, and young adults (CAYAs).[1] In this single-center, retrospective study, we describe cardiotoxicity in CAYAs treated with MEK inhibitors.

Cincinnati Children's Hospital Institutional Review Board determined this study exempt (45CFR46.104 [d][4][iii]). Eligible patients were ≤30 years of age, had received at least 1 ≥3-week MEK inhibitor course for a hematologic/oncologic condition, had 1 pre-MEK inhibitor and ≥1 on-therapy echocardiogram, and a baseline left ventricular ejection fraction (LVEF) ≥55%. MEK inhibitor courses were considered separate if a patient switched MEK inhibitors and/or if there was a ≥16-week hiatus. LVEF values (using the 5/6 area-length method) were reviewed from baseline through 14 days post-MEK inhibitor. The primary outcome was the development of moderate International Cardio-Oncology Society (IC-OS) cancer therapy-related cardiac dysfunction (CTRCD), defined as an on-therapy LVEF decrease ≥10 points to <50%.[2] Given the limited pediatric data, a less stringent definition of CTRCD (on-therapy LVEF <55% and/or a decrease ≥10 points) was explored as a secondary outcome. For the primary outcome, LVEF recovery was defined as an improvement to >50%. For the secondary outcome, recovery was defined as LVEF >55% and/or improvement to within 10 points of baseline. If image quality was poor (14/604 echocardiograms), a blinded cardiologist (T.D.R.) assigned a qualitative LVEF. Post hoc longitudinal strain (LS) and circumferential strain (CS) were calculated by 3 sonographers using the apical 4-chamber and parasternal short-axis views at the papillary muscles (TomTec). For each course, strain was performed at baseline and the first on-therapy echocardiograms. Strain was considered abnormal if outside the 95% CI for age-based references.[3,4]

Univariable logistic regression with robust SEs clustered by patient was used to compare groups with or without CTRCD. The intraclass correlation coefficient with 2-way random effects was calculated to assess agreement between strain sonographers. Kaplan-Meier with jackknife variance was used to calculate the probability of freedom from CTRCD.

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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TABLE 1 Characteristics of MEK Inhibitor Courses With or Without CTRCD

	MEKi Courses With CTRCD (n = 6)	MEKi Courses Without CTRCD (n = 94)	*P* Value
Age at course, y	12.6 (7.81-14.8)	9.85 (5.85-14.4)	0.41
MEKi course			–
Trametinib (n = 65)	3 (50.0)	62 (66.0)	
Selumetinib (n = 31)	1 (16.7)	30 (31.9)	
Binimetinib (n = 4)	2 (33.3)	2 (2.1)	
Concurrent BRAFi (n = 10)	0 (0.00)	10 (10.6)	
LVEF at baseline, %	63.7 (62.8-65.3)	62.2 (59.7-65.5)	0.42
LVEF change from baseline at first echocardiogram, %	−2.89 (−9.46 to 1.56)	−2.43 (−5.22 to 0.90)	0.50
Days to first on-therapy echocardiogram	35.5 (22.2-67.6)	67.0 (41.4-102.9)	0.12
Observed follow-up time, d	455 (291-574)	388 (183-683)	0.35
Longitudinal strain, %			
Baseline	−19.8 (−23.9 to −18.0)	−21.9 (−24.8 to −19.8)	0.64
First on therapy	−18.2 (−20.5 to −16.0)	−21.2 (−23.8 to −18.9)	0.008
Circumferential strain, %			
Baseline	−25.0 (−25.6 to −24.7)	−30.0 (−32.8 to −27.0)	0.009
First on therapy	−20.7 (−24.2 to −18.8)	−27.1 (−30.7 to −24.3)	0.003

Values are median (Q1- Q3) or n (%). *P* values calculated using univariable logistic regression with clustered robust SEs.
BRAFi = BRAF inhibitor; CTRCD = cancer therapy-related cardiac dysfunction; LVEF = left ventricular ejection fraction; MEKi = MEK inhibitor.

Patients without CTRCD were censored at the last echocardiogram. $P < 0.05$ (2-sided) defined statistical significance. Continuous variables are presented as the median with the range or 25th and 75th percentiles (Q1-Q3). All statistical analyses were performed using R 4.4.0 (The R Foundation).

Eighty-one patients received MEK inhibitors between 2013 and 2021 for central nervous system tumors (n = 36), plexiform neurofibromas (n = 29), or other (n = 16) (100 total courses). The median age at the first MEK inhibitor was 8.9 years (range, 0.6-27.4 years). Five had prior anthracyclines (median cumulative doxorubicin equivalents = 150 mg/m^2 [range, 99-325 mg/m^2]); none had chest radiation.

CTRCD occurred in 5 of 81 (6%) patients (6/100 [6%] MEK inhibitor courses), was asymptomatic, and occurred at a median of 321 days (range, 29-700 days) on therapy. The median nadir LVEF was 47.8% (range, 32.4%-49.6%), representing a median 17.5-point (range, 13.7-25.6 points) decrease from baseline. The estimated freedom from CTRCD at 2 years was 88.1% (95% CI: 77.8%-99.8%).

LS was analyzable in 83 of 100 baseline and 84 of 100 on-therapy echocardiograms and CS in 85 of 100 baseline and 86 of 100 on-therapy studies. The median (Q1-Q3) LS and CS were significantly worse at the first on-therapy echocardiogram compared to baseline (LS: −21.0 [Q1-Q3: −23.6 to −18.8] vs −21.8 [Q1-Q3: −24.8 to −19.6]; $P = 0.036$ and CS: −26.9 [Q1-Q3: −30.5 to −23.9] vs −29.9 [Q1-Q3: −32.6 to −26.3]; $P < 0.001$). Abnormal LS on the first on-therapy echocardiograms occurred in 29 of 84 (35%) courses, whereas abnormal CS occurred in 5 of 86 (6%). The intraclass correlation coefficient was 0.50 (95% CI: 0.20-0.72) and 0.59 (95% CI: 0.32-0.77) for LS and CS, respectively. A QTc interval ≥450 milliseconds (Bazett's) occurred in 9 of 76 (12%) patients with electrocardiograms.

Characteristics according to CTRCD development were also compared (Table 1). The median (Q1-Q3) LVEF and LS did not differ between groups at baseline (LVEF: 63.7% [Q1-Q3: 62.8%-65.3%] vs 62.2% [Q1-Q3: 59.7%-65.5%]; $P = 0.42$; LS: −19.8 [Q1-Q3: −23.9 to −18.0] vs −21.9 [−24.8 to −19.8]; $P = 0.64$). At the first on-therapy echocardiograms, patients with subsequent CTRCD had worse median (Q1-Q3) LS (−18.2 [Q1-Q3: −20.5 to −16.0] vs −21.2 [Q1-Q3: −23.8 to −18.9]; $P = 0.008$) and CS (−20.7 [Q1-Q3: −24.2 to −18.8] vs −27.1 [Q1-Q3: −30.7 to −24.3]; $P = 0.003$) despite a similar median LVEF change (−2.89 [Q1-Q3: −9.46 to 1.56] vs −2.43 [Q1-Q3: −5.22 to 0.90] points; $P = 0.50$). Of 5 patients with CTRCD, all had MEK inhibitors temporarily held, and 2 (40%) additionally started an angiotensin-converting enzyme inhibitor. CTRCD recovered in 4 of 5 (80%) patients. The patient without recovery had no available echocardiograms post-CTRCD.

Using a less stringent CTRCD definition (LVEF <55% and/or a decrease ≥10 points), dysfunction occurred in 23 of 81 (28%) patients (25/100 [25%] MEK inhibitor courses). Of 23 patients with CTRCD, 11 (48%) had no intervention, 8 (35%) only had the MEK inhibitor held, and 4 (17%) started an

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angiotensin-converting enzyme inhibitor and/or a beta blocker. CTRCD resolved in 20 of 23 (87%). The 3 patients without resolution had no available echocardiograms post-CTRCD.

In adults, MEK inhibitor-associated CTRCD occurs in 2% to 12%, although this may be underestimated given inconsistent reporting.[1] One recent study using IC-OS definitions detected CTRCD in 27% (mild = 17%, moderate = 10%) of adults on combined MEK inhibitor/BRAF inhibitor.[2,5] This study also did not detect a difference in baseline LVEF or LS in patients who developed moderate CTRCD compared to those who did not.[5]

Identifying at-risk patients for MEK inhibitor-associated cardiotoxicity remains challenging. In adults, abnormal strain is associated with subsequent CTRCD; however, its role is not established in MEK inhibitors, particularly in children.[2] At the first on-therapy echocardiogram, strain was worse than at baseline, and patients who subsequently developed CTRCD showed significantly decreased strain compared to those without CTRCD. These data suggest that subclinical MEK inhibitor-associated cardiotoxicity occurs quickly and that patients with early, albeit subtle, changes in cardiac function may benefit from closer monitoring.

This study has several limitations, foremost its retrospective nature. Because many patients were treated according to trial protocols, echocardiogram timing and clinical care varied. Second, a primary outcome of IC-OS moderate CTRCD may miss milder cardiotoxicity. Notably, using a less conservative CTRCD definition, 28% of patients met the criteria, with 52% receiving an intervention to address cardiotoxicity. Without intervention, it is unknown how many with less severe CTRCD might have progressed to IC-OS moderate CTRCD. It is possible that the real-world incidence of MEK inhibitor-associated CTRCD in CAYAs lies between these 2 estimates.

In conclusion, IC-OS-defined moderate CTRCD occurred in 6% of CAYAs treated with MEK inhibitors, was asymptomatic, and resolved in nearly all cases. This may underestimate the true incidence of CTRCD in this population. Larger, longitudinal studies of MEK inhibitor-associated cardiotoxicity are needed, especially in CAYAs.

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