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Letters

TO THE EDITOR

Cardiotoxicity of BRAF/MEK Inhibitors According to HFA/ICOS Cardiotoxicity Risk Category

The study by Glen et al[1] characterizes the incidence, time course, and risk factors for cancer therapy-related cardiac dysfunction (CTRCD) in patients with melanoma receiving rapidly accelerated fibrosarcoma B-type (BRAF) and mitogen-activated extracellular signal-regulated kinase (MEK) inhibitors in the real world. Based on the recent definition of the International Cardio-Oncology Society, they observed 27% (n = 17) of mild or moderate CTRCD among their 63 patients. The baseline risk stratification according to the Heart Failure Association/International Cardio-Oncology Society tool was not able to predict CTRCD. A few years ago, our group described a longitudinal cohort of 88 patients receiving BRAF and MEK inhibitors.[2] At that time, the criteria for CTRCD were different, and global longitudinal strain (GLS) was not routinely performed. We observed 13.6% (n = 12) had left ventricular ejection fraction (LVEF) decrease, which was defined as a reduction in LVEF ≥10% from baseline to a value <55%. All patients had transthoracic echocardiograms performed at baseline, at 1 month, and every 3 months after BRAF and MEK inhibitor initiation. We performed a new analysis of our data using the new CTRCD criteria (of note, GLS was not available in our cohort starting in 2014 and patients without moderate or severe CTRCD criteria were classified into the same category of "no or mild CTRCD") and the assessment of the cardiotoxicity baseline risk category (Table 1). Moderate CTRCD was mainly observed in patients in the low and medium baseline risk category, similarly to the study by Glen et al.[1] We observed in our cohort 1 case of severe CTRCD in a high-risk patient with prior radiotherapy to the mediastinum and anthracycline exposure. The absence of GLS assessment in our cohort did not influence the classification of our patients in the moderate CTRCD subgroups because the new reduction observed in LVEF to 40% to 49% was always associated with an absolute LVEF reduction ≥10% from baseline. In our cohort, all patients who benefited from angiotensin-converting enzyme inhibitors or beta-blockers had a normalization of LVEF at the end of the follow-up. By combining both cohorts, we can observe that severe and moderate CTRCD occurred in <1% and 7%, respectively. To conclude, we agree in entirety with Glen et al[1] that new tools are necessary to predict CTRCD in this population. With our current understanding, performing transthoracic echocardiography every 3 to 4 months in all patients receiving BRAF and MEK inhibitors may be the best option so as to not miss CTRCD.[3,4] However, the low frequency of CTRCD, along with the recovery of LVEF, raises the question of whether there is benefit of systematic cardiac monitoring in asymptomatic, low-risk patients.

TABLE 1 Patients Categorized According to HFA/ICOS Cardiotoxicity Baseline Risk Category in Lyon's Cohort

	All Patients (N = 88)	No or Mild CTRCD (n = 83)	Moderate CTRCD (n = 4)	Severe CTRCD (n = 1)
Low	46 (52.3)	45 (54.2)	1 (25)	0 (0)
Medium	38 (43.2)	35 (42.2)	3 (75)	0 (0)
High	4 (4.5)	3 (3.6)	0 (0)	1 (100)
Very high	0 (0)	0 (0)	0 (0)	0 (0)

Values are n (%).
CTRCD = cancer therapy-related cardiac dysfunction; HFA = Heart Failure Association; ICOS = International Cardio-Oncology Society.

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REFERENCES

1. Glen C, Adam S, McDowell K, et al. Cardiotoxicity of BRAF/MEK inhibitors: a longitudinal study incorporating contemporary definitions and risk scores. *J Am Coll Cardiol CardioOnc*. 2023;5(5):628–637.

2. Berger M, Amini-Adlé M, Maucort-Boulch D, et al. Left ventricular ejection fraction decrease related to BRAF and/or MEK inhibitors in metastatic melanoma patients: a retrospective analysis. *Cancer Med*. 2020;9(8):2611–2620.

3. Glen C, Tan YY, Waterston A, et al. Mechanistic and clinical overview cardiovascular toxicity of BRAF and MEK inhibitors: JACC: CardioOncology state-of-the-art review. *J Am Coll Cardiol CardioOnc*. 2022;4(1):1–18.

4. Courand PY, Berger M, Bouali A, et al. Cardiac effects of BRAF and MEK inhibitors: mechanisms and clinical management. *Curr Oncol Rep*. 2022;24(3):265–271.