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EDITORIAL COMMENT

Melanoma Treatment

The Heart Has Skin in the Game*

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Cancer and cardiovascular disease are neck and neck when it comes to leading causes of death worldwide. Many survivors who triumph over cancer will experience cardiovascular complications due to the undesired side effects of cancer treatment. The field of oncology has tirelessly pushed forward the development of as many new and effective cancer therapies as possible in order to improve the prognosis of patients with malignancies. Unfortunately, many of these newer therapies require further investigation into their cardiotoxic side effect profiles.

Melanoma is the most aggressive of all skin cancers, and its incidence is rising dramatically, especially in young adults.[1] As of today, melanoma diagnosis is the fifth most common malignancy overall and the second most common cancer in patients younger than 39 years of age.[1,2] The prognosis is even less encouraging, considering that the survival rate at 5 years following the diagnosis of stage IV metastatic melanoma can be as low as 30%, as reported by the American Cancer Society.

On a more positive note, treatment for stage IV melanoma is rapidly evolving. Targeting the mitogen-activated protein kinase (MAPK) pathway has shown promising results. Phase III clinical trials on the use of dual rapid accelerated fibrosarcoma B-type (BRAF) and mitogen-activated extracellular signal-related kinase 1 (MEK1) inhibition have both revolutionized the treatment of melanoma in the metastatic and adjuvant settings by increasing overall survival and/or cancer-free progression survival.[3-8] BRAF inhibitors have shown critical issues regarding cardiovascular toxicity. Patients receiving this class of drugs have displayed hypertension and QT-interval prolongation. MEK1 inhibitors have been developed to counteract the BRAF-induced treatment-related resistance; however, cardiovascular sequelae have been highlighted, including hypertension and decreased cardiac ejection fraction in up to 11% of patients leading to dose interruption in 3% or discontinuation in <1% of patients.[9]

Furthermore, the combination of BRAF and MEK inhibitors was the first Food and Drug Administration-approved combination for several malignancies such as malignant melanoma, non-small-cell lung cancer, anaplastic thyroid cancer, and more recently, for metastatic tumors with BRAFV600 mutations in a tumor-agnostic fashion.[10] Therefore, it is vital to understand the mechanisms behind the cardiotoxic side effects of MEK inhibitor-based therapies, in order to maximize the benefit for cancer patients affected by these life-threatening malignancies.

In this issue of *JACC: CardioOncology*, Beck et al[11] elegantly shed new light on this important topic. A murine model of chronic administration of trametinib, a MEK1 inhibitor, was used to induce cardiotoxicity in mice. According to clinical observations, the direct effect of MEK1 inhibition on the heart was measured as a significant reduction in cardiac function quantified as a decline in ejection fraction. Mice treated with trametinib had an almost 90% death rate after 80 days of treatment. The mortality rate observed by the investigators, however, was extremely high and fortunately does not represent the clinical observation in humans. Trametinib is

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usually prescribed in adult patients at a dosage of 2 mg orally once per day until disease progression or unacceptable toxicity. It is noteworthy that the percentage of patients who developed cardiomyopathy following treatment with trametinib was 11%, which may suggest that the investigators in the current animal study might have chosen too high a dosage. A lower dosage may prevent such an exacerbated cardiotoxic phenotype, but adjusting dosages from humans to mice is a widely known challenge.

Myocardial vacuolization, atrophy, and calcification were observed in almost one-third of the animals treated with trametinib. A proinflammatory response was investigated; increased M1 macrophage polarization was observed, whereas transcriptomic analysis revealed increased transcription of PI3K/AKT and JAK/STAT signaling, including interleukin (IL)-6. Increased plasma levels of pro-inflammatory IL-6 and C-X-C motif chemokines 11 and 13 were measured following the trametinib regimen. Trametinib also reduced cardiac ERK1/2 activation while increasing both transcriptional and protein levels of STAT3 and AKT. All these parameters were also associated with elevated genetic transcription of markers of mitochondrial biogenesis, mitophagy, and oxidative stress. However, it would have been extremely informative if mitochondrial biogenesis and mitophagy markers could have been assessed at the protein level. Transcriptomic changes associated with disturbances in cardiac pump function were also observed, which were in line with the functional assessments in mice and the clinical evidence in humans. On the other hand, it still remains unknown how the course of the trametinib-induced cardiotoxicity evolves through the entire experimental setting since both echocardiographic and transcriptomic data were collected as terminal assessments.

The inclusion of a tumor-bearing model would have also provided additional information on the role of cancer in the pathogenesis of trametinib cardiomyopathy, especially owing to what we know about the detrimental role of cancer and inflammation in the development of heart disease.[12] An elegant feature of this study is the employment of human cardiac organoids (hCOs) to model drug-induced cardiotoxicities. By using hCOs, the investigators were able to better understand the dynamics of trametinib-induced cardiotoxicity. Moreover, through the observation of a sustained recovery of cardiac function following the discontinuation of trametinib, measured in vivo as contraction amplitude of hCOs, the investigators were able to note the potentially transient effect of the drug on the heart. In fact, across clinical trials in patients who received trametinib in combination with dabrafenib, cardiomyopathy appears to often be reversible upon treatment discontinuation.[13] These data are very promising and might represent a valuable tool for clinicians to use in conjunction with early screening strategies.

However, as performed by Beck et al,[11] the measure of cardiac contraction alone might mask underlying compensatory mechanisms that often accompany many forms of cardiac disease, including cardiotoxicity consequent to cancer therapy, particularly in the early stages. Unfortunately, an unanswered clinical question is how trametinib compares with other currently approved MEK inhibitors (binimetinib, cobimetinib, selumetinib) from a cardiac safety profile, and how the combination of MEK and BRAF inhibitors would have affected cardiac function in the models proposed by the investigators while assessing the effect of anti-IL-6 on trametinib-induced cardiotoxicity. Trametinib, like other drugs in this class of therapies, is mostly used in combination with other targeted agents, because inhibition of MEK alone does not therapeutically provide sufficient disruption of the activated RAS-RAF-MEK-ERK cascade.[14] This suggests potential avenues for future investigation. As more is understood about trametinib and other MEK inhibitors, researchers can begin to explore the most efficient and safest combination to move forward across several malignancies.

In conclusion, this work by Beck et al[11] is an important first step forward in modeling the pharmacological inhibition of the MAPK pathway. However, several questions remain unanswered, including identifying the appropriate dosage and the characterization of a time course of trametinib-induced cardiomyopathy. This, combined with a better understanding of the tumor/heart axis in melanoma treatment and the use of a clinically relevant pharmacological approach comprising BRAF and MEK inhibition, will help pave the way for more in-depth mechanistic studies supporting a causal relationship between MEK inhibitor-based therapies and subsequent cardiovascular toxicity. Ideally, this will result in the discovery of tailored therapeutic strategies to

prevent cardiac complications and improve the overall quality of life in patients who derive clinical benefit from this important targeted therapeutic approach.

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REFERENCES

1. Indini A, Brecht I, Del Vecchio M, Sultan I, Signoroni S, Ferrari A. Cutaneous melanoma in adolescents and young adults. *Pediatr Blood Cancer*. 2018;65(11):e27292. https://doi.org/10.1002/pbc.27292

2. Scott JF, Conic RZ, Thompson CL, Gerstenblith MR, Bordeaux JS, Cleveland M. Stage IV melanoma of unknown primary: a population-based study in the United States from 1973 to 2014. *J Am Acad Dermatol*. 2018;79(2):258–265.e4. https://doi.org/10.1016/j.jaad.2018.03.021

3. Long GV, Stroyakovskiy D, Gogas H, et al. Dabrafenib and trametinib versus dabrafenib and placebo for Val600 BRAF-mutant melanoma: a multicentre, double-blind, phase 3 randomised controlled trial. *Lancet*. 2015;386(9992):444–451. https://doi.org/10.1016/S0140-6736(15)60898-4

4. Larkin J, Ascierto PA, Dréno B, et al. Combined vemurafenib and cobimetinib in BRAF-mutated melanoma. *N Engl J Med*. 2014;371(20):1867–1876. https://doi.org/10.1056/NEJMOA1408868

5. Long GV, Stroyakovskiy D, Gogas H, et al. Combined BRAF and MEK inhibition versus BRAF inhibition alone in melanoma. *N Engl J Med*. 2014;371(20):1877–1888. https://doi.org/10.1056/NEJMOA1406037

6. Hauschild A, Grob JJ, Demidov LV, et al. Dabrafenib in BRAF-mutated metastatic melanoma: a multicentre, open-label, phase 3 randomised controlled trial. *Lancet*. 2012;380(9839):358–365. https://doi.org/10.1016/S0140-6736(12)60868-X

7. Chapman PB, Hauschild A, Robert C, et al. Improved survival with vemurafenib in melanoma with BRAF V600E mutation. *N Engl J Med*. 2011;364(26):2507–2516. https://doi.org/10.1056/NEJMOA1103782

8. Balch CM, Gershenwald JE, Soong SJ, et al. Final version of 2009 AJCC melanoma staging and classification. *J Clin Oncol*. 2009;27(36):6199–6206. https://doi.org/10.1200/JCO.2009.23.4799

9. Bronte E, Bronte G, Novo G, et al. Cardiotoxicity mechanisms of the combination of BRAF-inhibitors and MEK-inhibitors. *Pharmacol Ther*. 2018;192:65–73. https://doi.org/10.1016/J.PHARMTHERA.2018.06.017

10. Mullard A. BRAF plus MEK inhibitor combo secures tumour-agnostic FDA approval. *Nat Rev Drug Discov*. 2022;21(8):548. https://doi.org/10.1038/D41573-022-00117-Y

11. Beck TC, Arhontoulis DC, Morningstar JE, et al. Cellular and molecular mechanisms of mek1 inhibitor-induced cardiotoxicity. *J Am Coll Cardiol CardioOnc*. 2022;4:535–548.

12. Lancellotti P, Marechal P, Donis N, Oury C. Inflammation, cardiovascular disease, and cancer: a common link with far-reaching implications. *Eur Heart J*. 2019;40(48):3910–3912. https://doi.org/10.1093/EURHEARTJ/EHZ645

13. Arangalage D, Degrauwe N, Michielin O, Monney P, Özdemir BC. Pathophysiology, diagnosis and management of cardiac toxicity induced by immune checkpoint inhibitors and BRAF and MEK inhibitors. *Cancer Treat Rev*. 2021;100:102282. https://doi.org/10.1016/J.CTRV.2021.102282

14. Zhao Y, Adjei AA. The clinical development of MEK inhibitors. *Nat Rev Clin Oncol*. 2014;11(7):385–400. https://doi.org/10.1038/NRCLINONC.2014.83

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