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Response by Herrmann et al to Letter Regarding Article, "Vascular Toxicities of Cancer Therapies: The Old and the New—An Evolving Avenue"

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In Response:

We deeply appreciate the comments by Giuseppina and Giovanni emphasizing an important point: the overlap between disease conditions and chemotherapeutic agents with regard to vascular toxicities. In our article,[1] we alluded to the parallels among vascular endothelial growth factor signaling pathway inhibitor effects, peripartum cardiomyopathy, and preeclampsia. This aspect was outlined in even greater detail in an article by Bellinger et al[2] in this journal. The current perception is that the placental release of soluble fms-related tyrosine kinase 1 and endoglin leads to vascular endothelial growth factor signaling pathway and transforming growth factor-beta signaling pathway inhibition with profound effects on endothelial cells and pericytes. The interplay of those 2 cell populations is crucial for the maintenance of vascular health; if perturbed, endothelial dysfunction with hypertension and proteinuria and dysfunction of the myocardial microvasculature and cardiomyopathy can evolve as mentioned in pregnancy-related conditions.[1–3]

Accordingly, Giuseppina and Giovanni postulate that cancer patients are at an enhanced risk of cardiovascular side effects with any baseline and therapy-related additional impairment of signaling pathways of functional significance for vascular cells. This view is intuitive and in agreement with the current concept of the multiple hit theory, exhausting the cardiovascular reserve in any cancer patient undergoing therapy with cardiovascular injury potential. A number of cardiovascular diseases and risk conditions go into this conceptual model, and in cases of cardiomyopathy with vascular endothelial growth factor signaling pathway inhibitors, coronary artery disease has been identified as the strongest risk factor so far. To our knowledge, there are no published studies defining a history of preeclampsia as a risk factor for cardiovascular events with cancer therapy in specific terms. Neither has there been a study on the association between circulating soluble fms-related tyrosine kinase 1 levels at baseline and the risk of cardiovascular events with chemotherapy. These objectives would be interesting for future studies and the refinement of cardiovascular risk prediction with cancer therapies.

Although this link is being investigated further, one may welcome the suggestion of Giuseppina and Giovanni to include an inquiry about a history of preeclampsia and peripartum cardiomyopathy before the initiation of chemotherapy with cardiovascular toxicity potential. This meets general recommendations of the American Heart Association and the American Stroke Association in recognition of preeclampsia as a women-specific risk factor for cardiovascular disease that emerges in the fifth and sixth decade in life, shows a linear correlation with the severity of preeclampsia, and imposes an overall 2-fold higher risk.[4] As further reviewed recently, recommendations on screening and prevention for this patient population are, however, based on a low level of evidence.[4] This poses an even greater challenge in the cancer population, and the key question becomes how such information should influence patient care. Would any such positive screening results translate into specific therapy or

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monitoring recommendations? Would we advise to withhold cancer therapy to prevent additive injury? Would this be a general recommendation or only for those patients with a history of preeclampsia or peripartum cardiomyopathy who have evidence of persistent perturbations or higher levels of circulating anti-angiogenic factors? Much still needs to be defined for (cardiooncology) practice to become refined, but the initiatives as proposed are truly exciting.

DISCLOSURES

Dr Herrmann participated in the 2014 and 2016 Ponatinib in CML Cardio-Oncology Advisory Board meeting organized by ARIAD Pharmaceuticals and is a member of the Institute for Cardio-Oncology advisory panel sponsored by Bristol-Myers Squib.

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