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Response to the letter "Cardio-oncology guidelines, structural heart disease and Kounis syndrome in the upcoming guidelines"

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Resposta à Carta ao Editor *Recomendações de cardio-oncologia, doença cardíaca estrutural e síndrome de Kounis nas próximas recomendações*

We appreciate the interest and kind remarks of Prof. Kounis regarding our recent position paper on interventional cardiology in cancer patients.[1]

When preparing our work, the main objective was to provide an overview of the most important specifics of the management of coronary and structural heart disease in patients with cancer, primarily from an interventional and practical perspective. Hence, a detailed review of the pathophysiology of coronary syndromes in cancer patients was beyond the scope of the paper. We did, however, strive to provide readers with the most significant mechanisms underlying coronary syndromes in cancer patients, together with the drugs most commonly associated with coronary toxicity, for proper contextualization. We therefore understand why some readers would have liked to see a more detailed review of this particular issue.

In his letter,[2] as well as another recent work,[3] Prof. Kounis and colleagues argue that Kounis syndrome and hypersensitivity in general play a major role in the occurrence of cardiac adverse events in patients

with cancer and should therefore be mentioned in the cardio-oncology guidelines and similar documents issued by medical societies. We believe the suggestion is interesting and merits reflection.

First, it is worth revisiting the actual definition of cardiac toxicity, or cardiotoxicity. The term has long been employed in different ways in cardio-oncology. Most commonly, it has been used to denote myocardial injury leading to left ventricular systolic dysfunction specifically as a result of cancer drugs, regardless of the exact pathophysiological mechanism. Notwithstanding, because many other adverse cardiovascular effects of cancer therapies were soon recognized, encompassing the full spectrum of cardiac disease, a broader term – cancer therapy-related cardiovascular toxicity – has been employed and is generally understood as a synonym for cardiotoxicity in cardio-oncology. This terminology has now been defined in a 2022 International Cardio-Oncology Society consensus statement[4] and endorsed by current international guidelines.[5] We believe it provides a useful umbrella term, and clearly harmonizes terminology for future research. The documents further identify five major subgroups, among them vascular toxicity. But regardless of clinical presentation, and in the words of the said consensus document,[4] the concept of cardiovascular toxicities of cancer therapies refers specifically to "those adverse CV events uniquely encountered during cancer therapy". Because cardio-oncology is mostly focused on the diagnosis, treatment, and prevention of cancer therapy-related cardiovascular toxicity, the guidelines and similar papers follow suit, as do both current international guidelines[5] and our own position paper.[1]

With the current international definition clearly in mind, it is now worth considering the pros and cons of bringing hypersensitivity, and in particular Kounis syndrome, into the spectrum of cardio-oncology.

Kounis syndrome refers to the occurrence of an acute coronary syndrome that results from hypersensitivity or anaphylactic reactions – the very elegant concept of 'allergic angina', as first coined by Prof. Kounis in 1991.[6] It can occur with any drug, whether cancer-related or not, and is therefore not "uniquely encountered during cancer therapy". As a result, this syndrome should not be construed as a form of cardiotoxicity, given that it is not covered by the aforementioned definition. Indeed, if such a reaction occurs in the setting of an allergic reaction to a cancer drug, the vascular toxicity is not directly caused by the cancer drug itself, but is rather an effect of the hypersensitivity reaction to the drug, and hence an indirect effect. Furthermore, the overarching clinical picture underlying such a presentation is the hypersensitivity reaction itself, not the cardiac manifestations of the disease. By contrast, in cancer therapy-related cardiovascular toxicity, cardiac disease is understood specifically as the result of cancer

therapies and is itself the overarching clinical picture. Furthermore, hypersensitivity reactions are rather unpredictable and are not dose-dependent. Thus, the classical cardio-oncology strategies of prevention and monitoring do not apply. In this line of reasoning, Kounis syndrome and hypersensitivity should be left outside the realm of cardio-oncology, as doing otherwise could add further unnecessary complexity to the field.

On the other hand, one could also argue that if a hypersensitivity reaction occurs during cancer therapy, and concomitantly Kounis syndrome develops, an adverse cardiac event is indeed, to some extent, the result of cancer therapy, even if indirectly. Additionally, considering hypersensitivity as a pathophysiological mechanism may indeed raise awareness of the very existence of the condition, thereby improving diagnosis and treatment. In addition, whatever the mechanism, if a cardiac adverse event develops during cancer therapy, it is of interest to the cardio-oncologist. Furthermore, some forms of cardiotoxicity, such as myocarditis, may be immune-mediated (even if not by hypersensitivity mechanisms), and are also not directly caused by cancer drugs. Moreover, of course, overlapping mechanisms in the development of cardiac adverse events during cancer therapy have been proposed, and a strict separation between cardiotoxicity and hypersensitivity may therefore not be feasible.

In conclusion, while our tendency is to align with the current understanding of cardio-oncology and its primary focus on cardiotoxicity (understood as cancer therapy-related cardiovascular toxicity[4]), leaving hypersensitivity reactions and Kounis syndrome to its own field, we do not believe a definitive answer can be provided in such a letter. The concerns raised by Professor Kounis are quite interesting and probably merit further discussion among colleagues in the field. We once again thank him for his kind remarks and look forward to further engaging in this discussion with colleagues from other parts of the world and in upcoming international meetings.

Ethics in publishing

1. Does your research involve experimentation on animals?:

No

2. Does your study include human subjects?:

No

3. Does your study include a clinical trial?:

No

4. Are all data shown in the figures and tables also shown in the text of the Results section and discussed in the Conclusions?:

Yes

Conflicts of interest

The authors have no conflicts of interest to declare.

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