

Editorial

Targeting Interleukin-1: Implications on Long-Term Cardiovascular Management Following Radiotherapy

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This editorial refers to ‘Prevention of radiotherapy-induced arterial inflammation by IL-1 blockade’, by T. Christersdottir, et al.

Radiotherapy is a central component of the management portfolio in oncology, comprising a critical role in effective cancer treatment. In high-income countries, radiotherapy is applied in more than half of cancer cases in an effort to eliminate cancer stem cells in the primary tumor and regional lymph nodes, ameliorate symptoms and manage the disease in incurable cases¹. This expanding use of radiation in cancer treatment has led to the emergence of a new field, namely cardio-oncology, which pertains to cardiovascular disorders induced by radiation injury in healthy tissue^{2, 3}. Indeed, despite great advances in planning and delivery, acute and long-term toxicity resulting from normal tissue injury in organs at risk, remain key aspects of radiotherapy⁴.

An expanding body of clinical evidence has linked radiotherapy with increased risk of coronary artery disease, congestive heart failure, pericardial disease, ischemic stroke, and others. The pathophysiology underlying these clinical observations is not fully understood but radiation induced vascular damage seems to be a critical factor. During the acute phase, radiation leads to vasodilation and an increase in capillary wall permeability causing the characteristic radiation erythema⁵. Later on, the coagulation cascade is activated, forcing the vascular wall into a pro-thrombotic state characterized by elevated tissue factor levels and thrombomodulin downregulation⁴. In addition, irradiation has been implicated with vascular cellular cycle arrest and senescence, caused by genetic instability resulting from either direct or indirect, reactive oxygen species-induced DNA damage⁶. However, the main and most studied modulator of the mechanisms governing ionizing radiation’s damage to the healthy

vessels is the activation of the inflammatory cascade. Following radiation, the endothelium responds with a wide range of transcriptional, translational and post-translational changes, which lead to complex molecular network alterations, phenotypic changes, production and secretion of chemokines, cytokines, and growth-factors⁷. Consequently, endothelial activation arising from these pro-thrombotic and pro-inflammatory phenotypes, leads to thrombosis and recruitment of leukocytes. At the same time, irradiated endothelial cells have the potential to undergo an endothelial-to-mesenchymal differentiation into activated myofibroblasts secreting collagen and contributing to fibrosis⁷. On the other hand, the upregulation of growth factors, such as VEGF, PlGF, and G-CSF, may deem radiation beneficial, as an innovative method of inducing therapeutic neovascularization, especially when targeting ischemia⁸.

In this issue of the European Heart Journal, Christersdottir et al elucidate further the critical role of inflammation in radiation induced vascular damage, with a special focus on chronic long-term effects. Global transcriptional profiling on pairs of irradiated and non-irradiated arteries from cancer patients revealed upregulation of inflammasome-related transcripts for NLRP3, IL-1a, IL-1b, pro-caspase-1 and caspase-1. This important observation confirms that vascular inflammation persists years after irradiation, as the median time post injury for the arteries used in the study cohort was 3 years. Furthermore, chemoattractant proteins CCL2 and CCL5 were also found upregulated, whereas tissue immunochemistry revealed increased CD68⁺ macrophage infiltration. The novelty of these findings underlines that the inflammatory response induced by radiation doesn't dissolve with time, but rather triggers the initiation of a chronic process that maintains vascular tissue damage and may therefore explain the long-term cardiovascular risk linked with radiotherapy in clinical studies. Previous reports have highlighted the presence of sustained inflammation in irradiated arteries, evidenced by activation of the NF-kB pathway and IL-1b upregulation⁹. Human umbilical vein

endothelial cells irradiated in vitro secreted IL-6 and IL-8, while inhibition of the TNF- α and TGF- β signaling pathways, resulted in attenuation of radiation related pathologies in mouse models¹⁰. An increase in monocyte and platelet adhesion to the activated endothelial cells caused by overexpression of proteins such as VCAM-1, ICAM-1, PECAM-1, E-selectin and P-selectin, is also part of the vascular response to radiation⁷. In summary, ionizing radiation in the normal vasculature, is firstly responsible for DNA damage, senescence and late cellular death. It triggers the production of reactive oxygen species, promotes coagulation and the release of pro-inflammatory cytokines. These in turn activate endothelial cells, which overexpress and release chemokines and adhesion molecules. Recruitment and activation of diverse immune cells follows with concomitant transition of endothelial cells to myofibroblasts. The microenvironment of the vascular wall therefore changes, adapting a chronic inflammatory profile, primarily characterized by increased inflammasome-related activity and transcripts, that persists throughout time, and constitutes a promising treatment target.

In an effort to investigate this very interesting prospect, Christersdottir et al hypothesized that inhibition of IL-1 receptor activity for a period of two weeks after radiation exposure, will reduce the inflammatory activity observed in the vascular wall years after dose delivery (Figure). Using the atherosclerosis-prone apolipoprotein E deficient (ApoE^{-/-}) mouse model, the authors observed a reduction in CD68⁺ macrophage infiltration of the aortic root of animals receiving anakinra (IL-1 receptor antagonist), as well as reduced expression levels of VCAM and chemokines CCL2 and CCL5. The authors are to be congratulated for these noteworthy findings, which suggest that treatment with anti-inflammatory agents immediately after radiotherapy, may intercept the development of chronic low-grade inflammation processes and perhaps reverse the underlying pathophysiology of vascular damage.

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There are, however, some aspects that deserve to be considered. The animal model used may depict a similar inflammatory phenotype to that of the irradiated human arteries, but nevertheless remains an atherosclerosis model, and therefore the mouse aortas obtained 20 weeks after radiation exposure may not accurately reflect the chronic inflammatory profile in the human arteries years after radiation exposure. In addition, while the prospect of pre-treating cancer survivors post radiation with anakinra to improve vascular health and outcomes is revolutionary, the time-frame for treatment deployment in humans is unclear. The authors used a two-week intervention period in the mouse model they deployed but human timings may differ. Clinical decision-making on treatment duration can benefit gravely from recently developed and validated non-invasive imaging modalities¹¹, which track vascular inflammation and can be used as companion diagnostics to guide targeted deployment of these treatments. Moreover, the applicability and safety of anakinra and novel anti-inflammatory drugs in general, in the clinical setting is still not very well-documented. Undoubtedly, inflammation has emerged as a very promising target in the battle against cardiovascular disease and cancer, evidenced by large clinical trials, such as the CANTOS trial¹², which reported for the first time in humans that targeting IL-1 β using canakinumab reduces the risk for cardiovascular events as well as fatal cancer (particularly lung cancer).¹³ However, fatal infections and sepsis were more common in the anti-inflammatory treatment group, raising safety concerns regarding innate immunity targeting, a finding that may become particularly relevant if these treatments are administered to patients with cancer undergoing radiotherapy. Importantly, inflammation should not be perceived as a singular therapeutic target, but rather as a spectrum of many and diverse signaling pathways, each one constituting a separate target, with variant therapeutic potential¹⁴. This was underlined by the recently published CIRT trial¹⁵, in which low-dose methotrexate failed to reduce events versus placebo. Therefore, it is crucial

that the IL-1 pathway is further investigated in randomized clinical trials to uncover its actual potential in not just reducing inflammatory burden, but long-term events as well. In conclusion, with this work Christersdottir et al introduce for the first time the notion that preventive IL-1 blockade following radiation, can reduce chronic vascular inflammation with the prospect of improving cardiovascular outcomes for cancer patients.

Conflict of interest: CA is a founder, shareholder and director of Caristo Diagnostics, a spinout company of the University of Oxford. CA is also director of the Oxford Academic Cardiovascular CT Core lab.

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References

1. Atun R, Jaffray DA, Barton MB, Bray F, Baumann M, Vikram B, Hanna TP, Knäul FM, Lievens Y, Lui TY. Expanding global access to radiotherapy. *The Lancet Oncology* 2015;**16**(10):1153-1186.
2. Lancellotti P, Suter TM, López-Fernández T, Galderisi M, Lyon AR, Van der Meer P, Cohen Solal A, Zamorano J-L, Jerusalem G, Moonen M. Cardio-Oncology Services: rationale, organization, and implementation: A report from the ESC Cardio-Oncology council. *European Heart Journal* 2018.
3. Chow EJ, Leger KJ, Bhatt NS, Mulrooney DA, Ross CJ, Aggarwal S, Bansal N, Ehrhardt MJ, Armenian SH, Scott JM. Paediatric cardio-oncology: epidemiology, screening, prevention, and treatment. *Cardiovascular Research* 2019.
4. Moding EJ, Kastan MB, Kirsch DG. Strategies for optimizing the response of cancer and normal tissues to radiation. *Nature Reviews Drug Discovery* 2013;**12**(7):526.
5. Jaworski C, Mariani JA, Wheeler G, Kaye DM. Cardiac complications of thoracic irradiation. *Journal of the American College of Cardiology* 2013;**61**(23):2319-2328.
6. Hatoum OA, Otterson MF, Kopelman D, Miura H, Sukhotnik I, Larsen BT, Selle RM, Moulder JE, Gutterman DD. Radiation induces endothelial dysfunction in murine intestinal arterioles via enhanced production of reactive oxygen species. *Arteriosclerosis, Thrombosis, and Vascular Biology* 2006;**26**(2):287-294.
7. Guipaud O, Jaillet C, Clément-Colmou K, François A, Supiot S, Milliat F. The importance of the vascular endothelial barrier in the immune-inflammatory response induced by radiotherapy. *The British Journal of Radiology* 2018;**91**(1089):20170762.
8. Ministro A, de Oliveira P, Nunes RJ, dos Santos Rocha A, Correia A, Carvalho T, Rino J, Faísca P, Becker JD, Goyri-O'Neill J. Low-dose ionizing radiation induces therapeutic neovascularization in a pre-clinical model of hindlimb ischemia. *Cardiovascular Research* 2017;**113**(7):783-794.
9. Halle M, Christersdottir T, Bäck M. Chronic adventitial inflammation, vasa vasorum expansion, and 5-lipoxygenase up-regulation in irradiated arteries from cancer survivors. *The FASEB Journal* 2016;**30**(11):3845-3852.
10. Hill RP, Zaidi A, Mahmood J, Jelveh S. Investigations into the role of inflammation in normal tissue response to irradiation. *Radiotherapy and Oncology* 2011;**101**(1):73-79.
11. Oikonomou EK, Marwan M, Desai MY, Mancio J, Alashi A, Centeno EH, Thomas S, Herdman L, Kotanidis CP, Thomas KE. Non-invasive detection of coronary inflammation using computed tomography and prediction of residual cardiovascular risk (the CRISP CT study): a post-hoc analysis of prospective outcome data. *The Lancet* 2018;**392**(10151):929-939.
12. Ridker PM, Everett BM, Thuren T, MacFadyen JG, Chang WH, Ballantyne C, Fonseca F, Nicolau J, Koenig W, Anker SD. Antiinflammatory therapy with canakinumab for atherosclerotic disease. *New England Journal of Medicine* 2017;**377**(12):1119-1131.
13. Ridker PM, MacFadyen JG, Thuren T, Everett BM, Libby P, Glynn RJ, Ridker P, Lorenzatti A, Krum H, Varigos J. Effect of interleukin-1 β inhibition with canakinumab on incident lung cancer in patients with atherosclerosis: exploratory results from a randomised, double-blind, placebo-controlled trial. *The Lancet* 2017;**390**(10105):1833-1842.
14. Vromman A, Ruvkun V, Shvartz E, Wojtkiewicz G, Santos Masson G, Tesmenitsky Y, Folco E, Gram H, Nahrendorf M, Swirski FK. Stage-dependent differential effects of interleukin-1 isoforms on experimental atherosclerosis. *European Heart Journal* 2019.
15. Ridker PM, Everett BM, Pradhan A, MacFadyen JG, Solomon DH, Zaharris E, Mam V, Hasan A, Rosenberg Y, Iturriaga E. Low-dose methotrexate for the prevention of atherosclerotic events. *New England Journal of Medicine* 2019;**380**(8):752-762.

Figure legend

The effects of ionizing radiation on the vascular wall. Increased permeability and production of pro-inflammatory cytokines are initial responses of healthy vessels to radiation damage. Later stages include increased production of reactive oxygen species (ROS), senescence and late apoptosis due to DNA damage, production and release of chemokines and growth factors, adaptation of a pro-coagulant state, endothelial cell activation with increased adhesion molecule expression, immunity cells infiltration, differentiation of endothelial cells to fibroblasts. Years later the vascular wall has altered its microenvironment, adapting a pro-inflammatory, pro-thrombotic, pro-fibrotic profile. IL-1 blockade, ameliorates the localized chronic inflammation response. EC: endothelial cell