Anthracycline-induced cardiotoxicity: Is there a role for myocardial ^{123}I-*m*IBG scintigraphy?

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In general, it is safe to claim that advances in treatment of cancer have led to improved survival of patients.[1,2] However, this success does not go without collateral damage. The increased survival is in part counterbalanced by side effects of the treatment, both acute and late, sometimes leading to increased morbidity and even increased mortality. This means that although patients are more likely to survive their cancer, they are more likely to be confronted with the late side effects of the treatment. In case of lymphoma patients, this is illustrated by the fact that as a result of the advances in treatment cure rates have improved survival. This in combination with the globally increased incidence of malignant lymphoma, causes the lymphoma survivor population to grow. As the diagnosis in lymphoma patients is often made at a relative young age (late) side effects of the treatment are of concern.[3,4] Cardiovascular diseases (CVDs) are one of the most frequent of these side effects, and there is a growing concern that they may lead to premature morbidity and death among cancer survivors.[5] This may be the result of cardiotoxicity, which involves direct effects of the cancer treatment on heart function and structure, or may be due to accelerated development of CVD, especially in the presence of traditional cardiovascular risk factors.[6]

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Anthracyclines (doxorubicin, idarubcin, epirubicin, and liposomal anthracyclines) are among the most widely used chemotherapeutic agents and have been shown to be effective in a wide range of cancers, in particular, breast cancer and lymphoma.[7,8] On the other hand, anthracyclines may cause irreversible cardiac damage, which in turn affects prognosis.[9]

Left ventricular (LV) dysfunction and heart failure (HF) are relatively common and should be considered as serious side effects. Survivors of paediatric cancer, treated with anthracyclines and/or mediastinal radiotherapy, have a 15-fold increased lifetime risk for developing HF compared with matched controls.[10] In older patients with pre-existing cardiovascular risk, the short-term risk for developing HF is also increased. For example, survivors of aggressive non-Hodgkin lymphoma have a 17% incidence of clinical HF at 5 years.[11] Furthermore, doxorubicin is associated with a 5% incidence of congestive HF when a cumulative lifetime dose of 400 mg·m^2 is reached, and higher doses lead to an exponential increase in risk, up to 48% at 700 mg·m^2.[12] However, there is considerable variability among patients in their susceptibility to anthracyclines. While many tolerate standard-dose anthracyclines without long-term complications, treatment-related cardiotoxicity may occur as early as after the first dose in other patients.[13]

Cardiotoxicity can be specified according to the time of occurrence after the treatment i.e., acute, early and late. Acute cardiotoxicity is rare (< 1% of patients) and occurs immediately after treatment and is usually reversible. Early cardiotoxicity is defined to the first year of treatment and late cardiotoxicity occurs with a median of 7 years after treatment.[14,15] A recent study by Cardinale et al., involving 2625 patients (mean follow-up 5.2 years), showed a 9% overall incidence of cardiotoxicity after anthracycline treatment.[16] Of interest is that 98% of cardiotoxicity occurred within the first year without any symptoms in these patients.

Anthracycline-induced cardiotoxicity is most likely a phenomenon characterized by continuous progressive decline in left ventricular ejection fraction (LVEF). Many affected patients may initially be asymptomatic, with clinical manifestations appearing years later, often in the context of other triggering factors, which may indicate that anthracyclines negatively affect compensatory mechanisms.[17]

Although there is variation between patients in the occurrence of anthracylcine-related cardiotoxicity, there are some factors associated with an increased risk of cardiotoxicity i.e., cumulative anthracycline dose, female sex, age (> 65 years old and children (< 18 years old)), renal failure, concomitant or previous radiation therapy involving the heart, concomitant chemotherapy (alkylating or antimicrotubule agents, immune- and targeted therapies), cardiac diseases with increased wall stress, arterial hypertension and genetic factors.[18]

In clinical practice, these considerations cause clinicians to balance between treating cancer with a maximum effect and limiting possibly cardiotoxicity. Therefore, there is a need to diagnose and monitor for cardiotoxicity by imaging of LV function and biomarkers. Assessment of the LVEF has been considered the most common parameter. However, LVEF as a prognostic and diagnostic tool has several limitations, including inter-observer and intra-observer variability and a lack of sensitivity to detect early subclinical changes.[19] Although the more conventional biomarkers such as Troponin (Tn), brain-type natriuretic peptide (BNP) and myeloperoxidase seem promising they are so far limited by for example the lack of thresholds for risk prediction and the unknown timing and frequency of assessment.[20]

As stated earlier, symptoms of HF may be masked for years due to the substantial compensatory myocardial reserve which is to a large extent a result of sympathetic nervous system activation. Hence, the manifestation of clinical HF does not occur until compensatory mechanisms are no longer adequate, at which point the prognosis has worsened considerably. Functional and structural injury to myocardial adrenergic neurons may be part of the pathophysiology of doxorubicin cardiotoxicity.[21–23] Assessment of adrenergic nervous system function of the heart may, therefore, represent a possible tool for detection of subclinical cardiotoxicity. Iodine-123 *meta*-iodobenzylguanidine (^{123}I-*m*IBG) is a radiolabelled norepinephrine analogue. ^{123}I-*m*IBG mimics the presynaptic uptake, storage and release mechanisms of noradrenaline, but has no effect on postsynaptic adrenergic receptors. Myocardial ^{123}I-*m*IBG scintigraphy has been primarily used as a prognostic marker in HF patients.[24–26] Although there is a limited number of studies that have evaluated myocardial ^{123}I-*m*IBG scintigraphy as a prognostic marker for cardiotoxicity, these studies have limitations that hamper extrapolation of the study findings.[27]

In this issue of the Journal of Nuclear Cardiology Laursen et al. performed planar myocardial ^{123}I-*m*IBG scintigraphy in 37 lymphoma patients scheduled for doxorubicin treatment prior to chemotherapy and after a median of 4 cycles of doxorubicin. At 1-year follow-up, LVEF decreased but stayed, on average, within normal ranges (64 vs. 58%, $p = 0.03$). The change in LVEF was not associated with any of the planar-assessed parameters of myocardial ^{123}I-*m*IBG uptake or washout (WOR). The authors conclude that, therefore, the presented data do not provide sufficient evidence to promote ^{123}I-*m*IBG myocardial scintigraphy as a clinical tool to detect doxorubicin-induced cardiotoxicity. However, this conclusion does not completely justify their findings.

The authors showed that at baseline WOR was significantly lower in younger patients compared to elderly patients. This difference in baseline ^{123}I-*m*IBG WOR is line with the fact that WOR increases with advancing age.[28,29] Of interest is that this difference in WOR was no longer present at 1-year follow-up (i.e., WOR increased in the younger patients). From a pathophysiological perspective, this increase in WOR in the younger patients at 1-year follow-up may represent a compensatory response to cardiotoxic injury by an appropriate increase in sympathetic activity, which declines with age. In addition it is tempting to speculate that the slowly degrading sympathetic response with age may explain the fact the elderly are more prone to anthracylcine cardiotoxicity.

Disclosure

Hein J. Verberne and Derk O. Verschure have no conflict of interest to declare.

References

1. Ferlay J, Steliarova-Foucher E, Lortet-Tieulent J, Rosso S, Coebergh JW, Comber H, et al. Cancer incidence and mortality patterns in Europe: estimates for 40 countries in 2012. Eur J Cancer 2013;49:1374-403.
2. Siegel R, DeSantis C, Virgo K, Stein K, Mariotto A, Smith T, et al. Cancer treatment and survivorship statistics, 2012. CA Cancer J Clin 2012;62:220-41.
3. Carver JR, Shapiro CL, Ng A, Jacobs L, Schwartz C, Virgo KS, et al. American Society of Clinical Oncology clinical evidence review on the ongoing care of adult cancer survivors: cardiac and pulmonary late effects. J Clin Oncol 2007;25:3991-4008.
4. van Dalen EC, Caron HN, Kremer LC. Prevention of anthracycline-induced cardiotoxicity in children: the evidence. Eur J Cancer 2007;43:1134-40.

5. Ewer MS, Ewer SM. Cardiotoxicity of anticancer treatments. Nat Rev Cardiol 2015;12:620.
6. Armstrong GT, Oeffinger KC, Chen Y, Kawashima T, Yasui Y, Leisenring W, et al. Modifiable risk factors and major cardiac events among adult survivors of childhood cancer. J Clin Oncol 2013;31:3673-80.
7. Smith LA, Cornelius VR, Plummer CJ, Levitt G, Verrill M, Canney P, et al. Cardiotoxicity of anthracycline agents for the treatment of cancer: systematic review and meta-analysis of randomised controlled trials. BMC Cancer 2010;10:337.
8. Yang F, Teves SS, Kemp CJ, Henikoff S. Doxorubicin, DNA torsion, and chromatin dynamics. Biochim Biophys Acta 2014;1845:84-9.
9. Felker GM, Thompson RE, Hare JM, Hruban RH, Clemetson DE, Howard DL, et al. Underlying causes and long-term survival in patients with initially unexplained cardiomyopathy. N Engl J Med 2000;342:1077-84.
10. Oeffinger KC, Mertens AC, Sklar CA, Kawashima T, Hudson MM, Meadows AT, et al. Chronic health conditions in adult survivors of childhood cancer. N Engl J Med 2006;355:1572-82.
11. Limat S, Daguindau E, Cahn JY, Nerich V, Brion A, Perrin S, et al. Incidence and risk-factors of CHOP/R-CHOP-related cardiotoxicity in patients with aggressive non-Hodgkin's lymphoma. J Clin Pharm Ther 2014;39:168-74.
12. Swain SM, Whaley FS, Ewer MS. Congestive heart failure in patients treated with doxorubicin: a retrospective analysis of three trials. Cancer 2003;97:2869-79.
13. Bristow MR, Thompson PD, Martin RP, Mason JW, Billingham ME, Harrison DC. Early anthracycline cardiotoxicity. Am J Med 1978;65:823-32.
14. Steinherz LJ, Steinherz PG, Tan CT, Heller G, Murphy ML. Cardiac toxicity 4 to 20 years after completing anthracycline therapy. JAMA 1991;266:1672-7.
15. Von Hoff DD, Layard MW, Basa P, Davis HL Jr, Von Hoff AL, Rozencweig M, et al. Risk factors for doxorubicin-induced congestive heart failure. Ann Int Med 1979;91:710-7.
16. Cardinale D, Colombo A, Bacchiani G, Tedeschi I, Meroni CA, Veglia F, et al. Early detection of anthracycline cardiotoxicity and improvement with heart failure therapy. Circulation 2015;131:1981-8.
17. Eschenhagen T, Force T, Ewer MS, de Keulenaer GW, Suter TM, Anker SD, et al. Cardiovascular side effects of cancer therapies: a position statement from the Heart Failure Association of the European Society of Cardiology. Eur J Heart Fail 2011;13:1-10.
18. Zamorano JL, Lancellotti P, Rodriguez Munoz D, Aboyans V, Asteggiano R, Galderisi M, et al. 2016 ESC Position Paper on cancer treatments and cardiovascular toxicity developed under the auspices of the ESC Committee for Practice Guidelines: the Task Force for cancer treatments and cardiovascular toxicity of the European Society of Cardiology (ESC). Eur Heart J 2016;37:2768-801.
19. Shah AM, Solomon SD. Myocardial deformation imaging: current status and future directions. Circulation 2012;125:e244-8.
20. Yu AF, Ky B. Roadmap for biomarkers of cancer therapy cardiotoxicity. Heart 2016;102:425-30.
21. de Geus-Oei LF, Mavinkurve-Groothuis AM, Bellersen L, Gotthardt M, Oyen WJ, Kapusta L, et al. Scintigraphic techniques for early detection of cancer treatment-induced cardiotoxicity. J Nucl Med 2011;52:560-71.
22. Flotats A, Carrio I. Cardiac neurotransmission SPECT imaging. J Nucl Cardiol 2004;11:587-602.
23. Lekakis J, Prassopoulos V, Athanassiadis P, Kostamis P, Moulopoulos S. Doxorubicin-induced cardiac neurotoxicity: study with iodine 123-labeled metaiodobenzylguanidine scintigraphy. J Nucl Cardiol 1996;3:37-41.
24. Jacobson AF, Senior R, Cerqueira MD, Wong ND, Thomas GS, Lopez VA, et al. Myocardial iodine-123 meta-iodobenzylguanidine imaging and cardiac events in heart failure. Results of the prospective ADMIRE-HF (AdreView Myocardial Imaging for Risk Evaluation in Heart Failure) study. J Am Coll Cardiol 2010;55:2212-21.
25. Verberne HJ, Brewster LM, Somsen GA, van Eck-Smit BL. Prognostic value of myocardial 123I-metaiodobenzylguanidine (MIBG) parameters in patients with heart failure: a systematic review. Eur Heart J 2008;29:1147-59.
26. Verschure DO, de Groot JR, Mirzaei S, Gheysens O, Nakajima K, van Eck-Smit BLF, et al. Cardiac (123)I-mIBG scintigraphy is associated with freedom of appropriate ICD therapy in stable chronic heart failure patients. Int J Cardiol 2017;248:403-8.
27. Dos Santos MJ, da Rocha ET, Verberne HJ, da Silva ET, Aragon DC, Junior JS. Assessment of late anthracycline-induced cardiotoxicity by (123)I-mIBG cardiac scintigraphy in patients treated during childhood and adolescence. J Nucl Cardiol 2017;24:256-64.
28. Estorch M, Carrio I, Berna L, Lopez-Pousa J, Torres G. Myocardial iodine-labeled metaiodobenzylguanidine 123 uptake relates to age. J Nucl Cardiol 1995;2:126-32.
29. Sakata K, Iida K, Mochizuki N, Ito M, Nakaya Y. Physiological changes in human cardiac sympathetic innervation and activity assessed by (123)I-metaiodobenzylguanidine (MIGB) imaging. Circ J 2009;73:310-5.