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Concepts in cardiac oncology

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Cardiac oncology is a subspecialty of cardiology engaging cardiologists and oncologists alike, in order to provide the best possible oncologic treatment for patients at high cardiovascular risk or developing cardio-toxicity during the course of their treatment, thus avoiding discontinuing it, and aiming at improving survival and quality of life. Early diagnosis and the effectiveness of the newer cancer treatments delivered an increasing number of long-term survivors (presently almost 30 million worldwide), at high risk of developing cardiovascular diseases. This predisposition has been correlated not only to the toxic side effects of the oncologic treatment but also to a real vulnerability to the risk factors in this patients population. For decades, the concept of cardio-toxicity in cardiac oncology has been restricted to ventricular dysfunction, but during the last few years the Food and Drug Administration has approved hundreds of new molecules and cardiac oncology has escalated its complexity. The introduction of new target therapy, proteasome inhibitors, immunomodulators, and inhibitors of the immunitary checkpoint, magnified the concept of cardio-toxicity to a wider definition of 'cardiovascular toxicity' incorporating arterial hypertension, ischaemia, cardiomyopathy, myocarditis, arrhythmic complications, long QT, and arterial and venous thrombosis. We are still lacking guidelines on the new and varied forms of toxicity, as well as monitoring strategies in the short- and long-term follow-up.

Ventricular dysfunction

In 2017, the ASCO[1] guidelines were published concerning the prevention and monitoring strategies of ventricular dysfunction that defined as patients at risk, those undergoing treatment with high doses of anthracyclines and/or RT, sequential treatments of anthracyclines, and trastuzumab, treatments with doses of anthracyclines or trastuzumab but associated with two or more cardiovascular risk factors, patients aged $\geq$60 years, left ventricular function at the limits (FE value 50–55%), previous myocardial infarction, and moderate-severe valvulopathy. Cardio-protection strategies include the use of prolonged anthracycline infusion regimens, less cardiotoxic dexrazoxane and liposomal anthracyclines, the use of conformational modulated radiation therapy and breathing control techniques. In cardiology, the pharmacological strategies of primary prevention with the use of angiotensin-converting enzyme (ACE) inhibitors, sartans, beta blockers have not shown satisfactory results in clinical studies for a number of reasons: low number of patients enrolled, selection of low-risk populations, heterogeneity in the outcome measures, short duration of follow-ups. As part of the monitoring, it has been observed that cardiotoxicity from anthracyclines occurs in 98% of cases within 12 months and therefore an echocardiographic evaluation is necessary 6–12 months after the end of the anthracycline chemotherapy and the early treatment carried out with enalapril and beta blockers allow normalization of left ventricular function in 82% of cases even if only 11% of patients show complete recovery of ventricular function at baseline.[2]

The diagnosis of cardiotoxicity is currently defined with a $>$10% reduction in the ejection fraction (EF) and an absolute value of less than 53% according to the American Society of Echocardiography (ASE) and the European Society of Cardiovascular Imaging (EACVI), while the cut-off is 50% according to the European Society of Cardiology

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(ESC)[3] Position Paper. However, traditional echocardiography with the standard measurement of the EF shows a low diagnostic sensitivity and a low predictive value in identifying subclinical cardiotoxicity. Subclinical ventricular dysfunction can be detected early by the study of the global longitudinal strain (GLS) even after administration of low doses of anthracyclines (150 mg/m^2) and it has been observed that a reduction compared to the baseline value >15% has a high predictive value of symptomatic and asymptomatic ventricular dysfunction in the following months.[4] The use of troponin (Tn) has shown in several studies that it is able to identify cardiotoxicity early and to stratify the risk in the short and long term. In particular, the persistent increase in Tn after treatment with high-dose anthracyclines has proven to be a fairly reliable parameter for the identification of high-risk patients thanks to a high negative predictive value. In a recently published European prospective register, 865 cancer patients treated mainly with anthracyclines and/or trastuzumab were analysed. Patients with cardiac toxicity were divided into four groups: (i) normal, with both cardiac markers (Tn and N-terminal pro B-type natriuretic peptide) within the normal range and preserved EF; (ii) mild, with increased markers and EF ≥50%; (iii) moderate, with EF value of 40–49% with or without biomarkers increase; and (iv) severe, with EF value ≤40%. Cardiac toxicity was defined as the appearance of a new dysfunction or the worsening of the left ventricular function and was found in 37.5% of patients in the 24-month follow-up period but in only 3.1% of the cases it was severe and significantly correlated with total mortality.[5] The use of Tn is not part yet of the guidelines because of a partial lack of data of cut-off value for the troponins (troponin T, ultra-sensitive troponins), timing of withdrawals, duration of follow-up, and definition of cardiac endpoints.

Trastuzumab, a humanized anti-HER2 monoclonal antibody, was developed for the treatment of breast cancer women who overexpress HER2 and which represents 25% of cases and is associated with molecular, histopathological and clinical characteristics of aggression and unfavourable prognosis. Trastuzumab changed the scenario of HER2 positive disease allowing improved prognosis and survival both when used in neoadjuvant (preoperative), adjuvant (postoperative), and in metastatic forms. Surprisingly, however, trastuzumab caused an 'unexpected' cardiotoxicity related to anthracycline toxicity and potentiated when trastuzumab is administered concomitantly or shortly after anthracyclines. Monitoring should be carried out every 3 months, according to the studies that led to the approval of the drug, if the FE value remains >50%. In centres where the GLS is measured, a variation of more than 15% could involve the adoption of cardio-protection strategies as already happens in cases where the EF becomes less than 50%.[6]

A new toxicity is emerging in recent years: myocarditis induced by immune checkpoint inhibitors. The clinical syndrome associated with myocarditis is extensive and can include a spectrum of symptoms including palpitations, chest pain, acute or chronic heart failure, pericarditis, and pericardial effusion. In addition, myocarditis can occur indolently with mild ventricular dysfunction. In diagnosis, necrosis markers such as troponins and CPK-MB, ultrasound alterations with ST anomalies, arrhythmias, conduction disturbances, echocardiographic alterations with anomalies of the segmental motion and of the global function, altered strain, pericardial effusion but the diagnosis of certainty of myocarditis is accomplished through magnetic resonance imaging (MRI). The certainty diagnosis requires a positive endomyocardial biopsy (EMB) or diagnostic criteria for myocarditis at MRI associated with clinical syndrome and positivity of electrocardiogram or markers or the presence of echocardiographic anomalies plus clinical syndrome, in the absence of coronary artery disease at the angiographic study. The treatment includes, in addition to the therapy of decompensation, high-dose steroids, plasmapheresis; immunoglobulins; infliximab, mycophenolate mofetil, tacrolimus if EMB positive for severe myocarditis or failure of heart failure therapy and mechanical support if haemodynamic instability.[7]

Vascular toxicity

The vascular toxic effects, unlike ventricular dysfunction, are very varied and less well characterized and cancer itself represents a risk factor for vascular disease, above all increasing the risk of thromboembolic events. Many traditional therapies such as fluoropyrimidines, platinum, and radiation therapy still represent the cornerstone of many treatment protocols today. Fluoropyrimidines 5-fluorouracil and its oral pro-drug capecitabine can induce ischaemia (angina, heart attack, arrhythmia, and sudden death) by coronary vasospasm, endothelial damage, and endothelin vasoconstriction, in the absence of coronary artery disease and the symptoms are reversible upon discontinuation of treatment and treatment with vasodilators; Platinum components can induce vascular damage by endothelial damage, platelet hyperaggregability, and reduced availability of NO. Finally, radiation therapy can cause progressive microvascular and large vessel damage through inflammatory mechanisms and one of the main side effects of mediastinal radiation therapy is accelerated coronary atherosclerosis. In addition to vascular damage, mediastinal radiation can cause autonomic changes in the regulation of the cardiovascular system, valvulopathies, constrictive pericarditis, therefore, in patients undergoing mediastinal RT, periodic surveillance with functional non-invasive stress tests is recommended, which should be performed starting from 5 years after treatment. The introduction of target therapy has significantly amplified treatment options in cancer patients. In particular, small molecule tyrosine kinase inhibitors, both directed towards vascular endothelial growth factor (VEGF) (Sorafenib, Sunitinib, Pazopanib, and Regorafenib) and towards the mutated protein Bcr-ABL (Nilotinib, Dasatinib, and Ponatinib) that can be administered orally, have shown efficacy for multiple types of cancer and have dramatically changed the natural history of several malignant tumours but the vascular toxicities that can occur with the new agents are manifold and include arterial hypertension, pulmonary hypertension, ischaemic arterial events such as myocardial infarction, stroke, and ischaemic limbs, as well as venous thromboembolic events

(VTE). Other classes of new cancer therapies such as immunomodulators (thalidomide and lenalidomide) and proteasome inhibitors (bortezomib and carfilzomib) currently used in the treatment of myeloma are associated with a risk of significant vascular toxicity.[8]

Hypertension

The management of high blood pressure in patients with cancer is a very frequent problem and involves up to one-third of the patients treated, both for problems related to the age of the population and for the use of drugs, especially VEGF inhibitors and of the proteasome.

The inhibition of VEGF reduces the production of NO, suppresses vasodilating molecules such as prostacyclines and induces a rarefaction of the capillary bed with consequent hypertension. Hypertension occurs more frequently during the first months of starting therapy and careful monitoring is therefore recommended in the initial phase of the first cycle of treatment with anti-VEGF. Treatment must be undertaken even before the start of cancer therapy according to the criteria established by the recent ESC guidelines. The general practice is to avoid the calcium channel blockers diltiazem and verapamil due to the risk of drug–drug interaction related to the induction of CYP3A4 and the use of inhibitors of the ACE inhibitor and amlodipine is preferred.[9]

Acute coronary syndrome management

Cancer patients were generally excluded from clinical trials on ischaemic heart disease. In the management of acute coronary syndromes, the recommendations of the acute coronary syndrome consensus document that sets the value of 10 000 platelets (PLT) as a cut-off for aspirin therapy and 30 000 and for double antiplatelet therapy (DAPT) with aspirin and clopidogrel are of reference. Ticagrelor and prasugrel should be avoided unless the PLT number is $>$50 000.[10] The durability of DAPT in cancer patients raises further problems that have led bare metal stent to be preferred over DES (drug-eluting stent) for decades in this population. Premature discontinuation of DAPT is often related to clinical or pharmacological problems or to the need for diagnostic or surgical procedures. However, studies conducted with the latest generation drug-eluting stent without polymer and DES have shown safety and efficacy data of DAPT for 1 month.[11] From a practical point of view, patients without active disease should be treated according to general guidelines. In cases of active cancer (and mainly in the first 6 months from diagnosis) a multidisciplinary and multi-parametric assessment is necessary, that takes into account the prognosis related to cancer, the need for surgery or an invasive diagnosis in the immediate future, of drug interactions—drug and cancer-related comorbidities. The key is a multidisciplinary approach. It is essential that in acute and unstable cases, where it may not be possible to interact with the oncologist, cardiac treatment should not be delayed 'a priori' only on the basis of a cancer diagnosis.

Management of venous thromboembolism

The use of LMWH (low molecular weight heparin) has always been the reference in thromboprophylaxis and in the treatment of venous thromboembolism (VTE) of cancer. Thromboprophylaxis with direct oral anticoagulant (DOAC) in high-risk outpatients (defined as Khorana score $\geq$2) has recently been studied in two important clinical trials: the AVERT study conducted with apixaban (2.5 mg $\times$ 2/day) and the CASSINI with rivaroxaban (10 mg/day), both up to 180 days.[12,13] When considered together, the two trials showed a significant benefit of DOACs in the prevention of VTE with a low incidence of major bleeding and the results made it possible to insert DOACs together with LMWHs in the indications of thromboprophylaxis of VTE in the latest ASCO guidelines.[14] In the treatment of the initial VTE phase, the results of the Hokusai VTE cancer study conducted with edoxaban vs. dalteparin and the SELECT-D study which compared rivaroxaban vs. dalteparin demonstrated adequate efficacy and safety of DOACs.[15,16] The results made it possible to insert rivaroxaban in the indications of acute phase therapy as monotherapy and edoxaban after 5–10 days of treatment with LMWH; in the long-term treatment, intended up to 6 months for rivaroxaban and 12 months for edoxaban, the use of these DOACs is envisaged in the absence of tumours with a high risk of bleeding such as gastrointestinal or genitourinary ones or of pharmacological interaction. Recently, the Caravaggio study comparing apixaban vs. dalteparin confirmed the efficacy and safety of the treatment with DOACs in cancer patients.[17]

Management of atrial fibrillation

Cancer and atrial fibrillation (AF) share a state of hypercoagulability and in patients with cancer, the risk of AF is increased. A heart rate control strategy is generally preferred in stable patients and especially in elderly patients, patients with heart disease, with good symptom control and those with an unfavourable prognosis or in palliative care.[18]

In the absence of specific risk stratification scales tested in cancer patients, the $CHAD_2S_2$-VASc score is used for thrombotic risk along with the HAS-BLED which must be periodically re-evaluated. In the initial evaluation, it is essential to exclude a high bleeding risk (intracranial tumour, haematological malignancies with coagulation defects, severe thrombocytopenia, severe metastatic liver disease) and therefore evaluate the thrombotic risk. The option to be proposed is that of a treatment with DOAC in the presence of $CHAD_2S_2$-VASc $>$1 in the absence of high bleeding risk;[19] in cases of high thrombotic and haemorrhagic risk, the hypothesis of closing the auricle with devices can be evaluated.

For the anticoagulant treatment, the analysis of phase III subgroups of studies has shown constant safety and efficacy of DOAC in cancer patients. An analysis of ENGAGE AF-TIMI 48 included 1153 patients who had developed post-randomization cancer and showed conserved efficacy and safety of edoxaban compared to warfarin.[21] Apixaban has been shown to be superior in safety and efficacy in patients

with active cancer enrolled in ARISTOTLE compared to warfarin in reducing stroke and other thromboembolic events.[21] Observational experience has shown that rivaroxaban, when used in patients with active cancer and AF, is associated with low rates of ischaemic stroke and clinically relevant bleeding. Although there is no direct data on the use of DOAC in patients with cancer and non-valvular AF, available evidence suggests that they represent a safe and effective option. The choice must take into account age, weight, kidney function, increased risk of bleeding in patients with gastrointestinal and genitourinary tumours, the need for concomitant antiplatelet treatment and risk of interactions with anticancer drugs.

The recent ISHT recommendations propose the adoption of an individualized and shared therapeutic regimen with the patient and propose in patients already on anticoagulant treatment the continuation of the ongoing therapy, in the absence of drug interactions, with close checks of the international normalized ratio in case of vitamin K antagonists therapy. In the case of the onset of FA during chemotherapy, preference is given to DOACs except in gastrointestinal or genitourinary tumours and in the presence of drug interactions where the use of EBPM[22] is preferred.

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References

1. Armenian SH, Lacchetti C, Barac A, Carver J, Constine LS, Denduluri N, Dent S, Douglas PS, Durand J-B, Ewer M, Fabian C, Hudson M, Jessup M, Jones LW, Ky B, Mayer EL, Moslehi J, Oeffinger K, Ray K, Ruddy K, Lenihan D. Prevention and monitoring of cardiac dysfunction in survivors of adult cancers: American Society of Clinical Oncology Clinical Practice Guideline. *J Clin Oncol* 2017;**35**:893–911.
2. Cardinale D, Colombo A, Bacchiani G, Tedeschi I, Meroni CA, Veglia F, Civelli M, Lamantia G, Colombo N, Curigliano G, Fiorentini C, Cipolla CM. Early detection of anthracycline cardiotoxicity and improvement with heart failure therapy. *Circulation* 2015;**131**:1981–1988.
3. Zamorano JL, Lancellotti P, Rodriguez Muñoz D, Aboyans V, Asteggiano R, Galderisi M, Habib G, Lenihan DJ, Lip GYH, Lyon AR, Lopez Fernandez T, Mohty D, Piepoli MF, Tamargo J, Torbicki A, Suter TM; ESC Scientific Document Group. 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**:2768–2801.
4. Plana JC, Thavendiranathan P, Bucciarelli-Ducci C, Lancellotti P. Multi-modality imaging in the assessment of cardiovascular toxicity in the cancer patient. *JACC Cardiovasc Imaging* 2018;**11**:1173–1186.
5. López-Sendón J, Álvarez-Ortega C, Zamora Auñon P, Buño Soto A, Lyon AR, Farmakis D, Cardinale D, Canales Albendea M, Feliu Batlle J, Rodríguez Rodríguez I, Rodríguez Fraga O, Albaladejo A, Mediavilla G, González-Juanatey JR, Martínez Monzonis A, Gómez Prieto P, González-Costello J, Serrano Antolín JM, Cadenas Chamorro R, López Fernández T; on behalf of the CARDIOTOX Registry Investigators. Classification, prevalence, and outcomes of anticancer therapy-induced cardiotoxicity: the CARDIOTOX registry. *Eur Heart J* 2020;**41**:1720–1729.
6. Tarantini L, Gulizia MM, Di Lenarda A, Maurea N, Giuseppe Abrignani M, Bisceglia I, Bovelli D, De Gennaro L, Del Sindaco D, Macera F, Parrini I, Radini D, Russo G, Beatrice Scardovi A, Inno A. ANMCO/AIOM/AICO Consensus Document on clinical and management pathways of cardio-oncology: executive summary. *Eur Heart J* 2017;**19**:D370–D379.
7. Bonaca MP, Olenchock BA, Salem J-E, Wiviott SD, Ederhy S, Cohen A, Stewart GC, Choueiri TK, Di Carli M, Allenbach Y, Kumbhani DJ, Heinzerling L, Amiri-Kordestani L, Lyon AR, Thavendiranathan P, Padera R, Lichtman A, Liu PP, Johnson DB, Moslehi J. Myocarditis in the setting of cancer therapeutics: proposed case definitions for emerging clinical syndromes in cardio-oncology. *Circulation* 2019;**140**:80–91.
8. Guha A, Armanious M, Fradley MG. Update on cardio-oncology: novel cancer therapeutics and associated cardiotoxicities. *Trends Cardiovasc Med* 2019;**29**:29–39.
9. Katsi V, Magkas N, Georgiopoulos G, Athanasiadi E, Virdis A, Masi S, Kliridis P, Hatziyanni A, Tsioufis C, Tousoulis D. Arterial hypertension in patients under antineoplastic therapy: a systematic review. *J Hypertens* 2019;**37**:884–901.
10. Iliescu CA, Grines CL, Herrmann J, Yang EH, Cilingiroglu M, Charitakis K, Hakeem A, Toutouzas KP, Leesar MA, Marmagkiolis K. SCAI Expert consensus statement: evaluation, management, and special considerations of cardio-oncology patients in the cardiac catheterization laboratory (endorsed by the Cardiological Society of India, and Sociedad Latino Americana de Cardiología Intervencionista). *Catheter Cardiovasc Interv* 2016;**87**:E202–E223.
11. Garot P, Morice M-C, Tresukosol D, Pocock SJ, Meredith IT, Abizaid A, Carrié D, Naber C, Iñiguez A, Talwar S, Menown IBA, Christiansen EH, Gregson J, Copt S, Hovasse T, Lurz P, Maillard L, Krackhardt F, Ong P, Byrne J, Redwood S, Windhövel U, Greene S, Stoll H-P, Urban P, Urban P, Morice M-C, Abizaid A, Meredith IT, Pocock SJ, Carrié D, Naber C, Greene S, Stoll H-P. 2-Year outcomes of high bleeding risk patients after polymer-free drug-coated stents. *J Am Coll Cardiol* 2017;**69**:162–171.
12. Carrier M, Abou-Nassar K, Mallick R, Tagalakis V, Shivakumar S, Schattner A, Kuruvilla P, Hill D, Spadafora S, Marquis K, Trinkaus M, Tomiak A, Lee AYY, Gross PL, Lazo-Langner A, El-Maraghi R, Goss G, Le Gal G, Stewart D, Ramsay T, Rodger M, Witham D, Wells PS; AVERT Investigators. Apixaban to prevent venous thromboembolism in patients with cancer. *N Engl J Med* 2019;**380**:711–719.
13. Khorana A, Vadhan-Raj S, Kuderer N, Wun T, Liebman H, Soff G, Belani C, O'Reilly E, McBane R, Eikelboom J, Damaraju CV, Beyers K, Dietrich F, Kakkar A, Riess H, Peixoto R, Lyman G. Rivaroxaban for preventing venous thromboembolism in high-risk ambulatory patients with cancer: rationale and design of the CASSINI Trial. Rationale and design of the CASSINI Trial. *Thromb Haemost* 2017;**117**:2135–2145.
14. Key NS, Khorana AA, Kuderer NM, Bohlke K, Lee AYY, Arcelus JI, Wong SL, Balaban EP, Flowers CR, Francis CW, Gates LE, Kakkar AK, Levine MN, Liebman HA, Tempero MA, Lyman GH, Falanga A. Venous thromboembolism prophylaxis and treatment in patients with cancer: ASCO Clinical Practice Guideline Update. *J Clin Oncol* 2020;**38**:496–520.
15. van Es N, Di Nisio M, Bleker SM, Segers A, Mercuri MF, Schwocho L, Kakkar A, Weitz JI, Beyer-Westendorf J, Boda Z, Carrier M, Chlumsky J, Décousus H, Garcia D, Gibbs H, Kamphuisen PW, Monreal M, Ockelford P, Pabinger I, Verhamme P, Grosso MA, Büller HR, Raskob GE. Edoxaban for treatment of venous thromboembolism in patients with cancer. Rationale and design of the Hokusai VTE-cancer study. *Thromb Haemost* 2015;**114**:1268–1276.
16. Young AM, Marshall A, Thirlwall J, Chapman O, Lokare A, Hill C, Hale D, Dunn JA, Lyman GH, Hutchinson C, MacCallum P, Kakkar A, Hobbs FDR, Petrou S, Dale J, Poole CJ, Maraveyas A, Levine M. Comparison of an oral factor Xa inhibitor with low molecular weight heparin in patients with cancer with venous thromboembolism: results of a randomized trial (SELECT-D). *J Clin Oncol* 2018;**36**:2017–2023.
17. Agnelli G, Becattini C, Meyer G, Muñoz A, Huisman MV, Connors JM, Cohen A, Bauersachs R, Brenner B, Torbicki A, Sueiro MR, Lambert C, Gussoni G, Campanini M, Fontanella A, Vescovo G, Verso M; Caravaggio Investigators. Apixaban for the treatment of venous thromboembolism associated with cancer. *N Engl J Med* 2020;**382**:1599–1607.
18. Farmakis D, Parissis J, Filippatos G. Insights into onco-cardiology: atrial fibrillation in cancer. *Am Coll Cardiol* 2014;**63**:945–953.
19. López-Fernández T, Martín-García A, Roldán Rabadán I, Mitroi C, Mazón Ramos P, Díez-Villanueva P, Escobar Cervantes C, Alonso Martín C, Alonso Salinas GL, Arenas M, Arrarte Esteban VI, Ayala de La Peña F, Castro Fernández A, García Pardo H, García-Sanz R, González Porras JR, López de Sá E, Lozano T, Marco Vera P, Martínez Marín V, Mesa Rubio D, Montero Á, Oristrell G, Pérez de Prado A, Velasco del Castillo S, Virizuela Echaburu JA, Zatarain-Nicolás E,

Anguita Sánchez M, Tamargo Menéndez J, Marín F, López-Sendón JL, Zamorano JL; Expert reviewers. Atrial fibrillation in active cancer patients: expert position paper and recommendations. *Rev Esp Cardiol (Engl Ed)* 2019;**72**:749–759.

20. Fanola CL, Ruff CT, Murphy SA, Jin J, Duggal A, Babilonia NA, Sritara P, Mercuri MF, Kamphuisen PW, Antman EM, Braunwald E, Giugliano RP. Efficacy and safety of edoxaban in patients with active malignancy and atrial fibrillation: analysis of the ENGAGE AF-TIMI 48 trial. *J Am Heart Assoc* 2018;**7**:e008987.
21. Melloni C, Dunning A, Granger CB, Thomas L, Khouri MG, Garcia DA, Hylek EM, Hanna M, Wallentin L, Gersh BJ, Douglas PS, Alexander JH, Lopes RD. Efficacy and safety of apixaban versus warfarin in patients with atrial fibrillation and a history of cancer: insights from the ARISTOTLE trial. *Am J Med* 2017;**130**:1440–1448.
22. Delluc A, Wang T-F, Yap E-S, Ay C, Schaefer J, Carrier M, Noble S. Anticoagulation of cancer patients with non-valvular atrial fibrillation receiving chemotherapy: guidance from the SSC of the ISTH. *J Thromb Haemost* 2019;**17**:1247–1252.