JACC: CARDIOONCOLOGY VOL. 5, NO. 2, 2023

EDITORIAL COMMENT

Tumor Genetics Are Thrombogenic

The Need for Action*

Isabelle Mahé, MD, PhD,[a,b,c,d] Florian Scotté, MD, PhD,[e] Ismail Elalamy, MD, PhD[d,f,g]

Patients with cancer are at high risk for subsequent venous and arterial thrombosis. This risk is based on multifactorial, synergistic associations involving patient comorbidities, cancer characteristics, and antitumor treatment. In their study in this issue of *JACC: CardioOncology*, Feldman et al[1] highlight a strong association between tumor genomic alterations and the risk for 1-year arterial thromboembolism (ATE) in a large retrospective tumor-profiling registry involving 14,223 adult patients with solid malignancies (1,044 were excluded because of history of ATE). Among the 341 genes tested, *KRAS* and *STK11* cancer somatic genetic alterations were associated with an increased risk for ATE, irrespective of tumor site. This is one of the few studies investigating the role of genetic alterations in ATE risk. The same group previously reported in a similar cohort that somatic tumor mutations of *STK11*, *KRAS*, *CTNNB1*, *KEAP1*, *CDKN2B*, and *MET* predicted an increased incidence of venous thromboembolism (VTE) up to 1 year before diagnosis.[2]

The risk for arterial complications in patients with cancer was recently identified and compared with the well-established risk for VTE.[3] Identification of such high-risk patients remains a challenge.[4,5] The increase in prevalence and improved life expectancy among patients with cancer warrants further investigation of the prevention, management, and awareness of ATE.[6] Tumor genetic profiling has a clear influence on vascular disease and adds another dimension to ATE prognostication.

In this study, the investigators used a large database of patients with cancer without a history of ATE to limit bias related to the higher risk for recurrence in patients with prior ATE. Overall, the population was representative of patients with cancer, with a median age of 61 years; most had metastatic disease (74%) and cardiovascular risk factors (hypertension in 42%, diabetes in 13%, and hypercholesterolemia in 33%). The cumulative 12-month ATE incidence of 1.9% was lower than previously reported; this is possibly due to the relatively short-term follow-up, the inclusion of low-risk patients, and the exclusion of patients with a history of ATE. Patients with cancer and cardiovascular disease share similar risk factors, but in this study, they were not associated with increased risk for ATE. However, the temporality of ATE occurrence (higher in the months preceding and following the diagnosis of cancer) suggests a specific role of cancer itself and its management in facilitating thrombogenesis.

The investigators observed that irrespective of tumor site, tumor-specific mutations in *KRAS* and *STK11* were associated with increased risk for ATE (for *KRAS*, HR: 1.98 [95% CI: 1.34-2.94; $P = 0.015$]; for *STK11*, HR: 2.51 [95% CI: 1.44-4.38; $P = 0.015$]).[1] This group previously reported that the same genes were associated with VTE (for *KRAS*, HR: 1.34 [95% CI: 1.09-1.64; $P = 0.08$]; for *STK11*, HR: 2.12 [95% CI: 1.55-2.89; $P < 0.001$]).[2]

These genetic alterations have been previously associated with worse cancer outcomes. The *KRAS* gene is expressed ubiquitously in various cancers and

*Editorials published in *JACC: CardioOncology* reflect the views of the authors and do not necessarily represent the views of *JACC: CardioOncology* or the American College of Cardiology.

From [a]Université Paris Cité, Paris, France; [b]Assistance Publique des Hôpitaux de Paris, Hôpital Louis Mourier, Médecine Interne, Colombes, France; [c]Innovative Therapies in Haemostasis, INSERM UMR_S1140, Paris, France; [d]INNOVTE, FCRIN, France; [e]Gustave Roussy, Patient Pathway Department, Villejuif, France; [f]Hematology and Thrombosis Center, Hôpital Tenon, Hôpitaux Universitaires de l'Est Parisien, Assistance Publique Hôpitaux de Paris, Faculté de Médecine, Sorbonne Université, Paris, France; and the [g]Research Group "Cancer, Vessel Biology and Therapeutics," INSERM U938, Centre de Recherche Saint-Antoine, Institut Universitaire de Cancérologie, Faculty of Medicine, Sorbonne University, Paris, France.

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

ISSN 2666-0873 https://doi.org/10.1016/j.jaccao.2023.03.002

increases the adaptability of tumor cells under stress. The *KRAS* mutation has a prognostic impact on metastatic diseases, confers resistance to epidermal growth factor receptor inhibitors, and results in constitutive activation of the KRAS protein, which stimulates downstream signaling pathways, including cell proliferation, survival, and tumorigenesis.[7] Numerous studies have reported in patients with metastatic but also localized colorectal cancer that the $KRAS^{G12C}$ mutation is associated with worse overall survival or a higher rate of early relapse.[7-9] Mutation of *STK11*, a tumor suppressor gene, has been associated with sporadic cancers such as non-small cell lung cancer and with worse overall survival.[10] Thus, the risk for ATE could be related to the cancer genetic polymorphisms that are associated with worse tumor prognosis.

Of interest in the present study by Feldman et al,[1] patients with all types of cancer investigated were at increased risk for ATE, with lung and pancreas cancer conferring the highest risk in terms of cumulative 1-year incidence, as found for VTE.[2] Interestingly, cancer has even been reported as an independent risk factor for ATE in patients with VTE in several population-based studies and in a recent meta-analysis.[11] In the present study,[1] 9% of patients were on anticoagulant agents, and only 4% had atrial fibrillation; suggesting that the remaining 5% of patients without atrial fibrillation were being treated for VTE. Anticoagulant therapy was associated with reduced risk for both arterial and venous complications (HR: 0.57; 95% CI: 0.36-0.89); antiplatelet therapy was not protective. In addition, prior clinical trials have demonstrated that anticoagulant therapies (low-molecular weight heparin and direct oral anticoagulant agents) at prophylactic doses are effective at preventing VTE in patients with cancer, but they are associated with a risk for bleeding.[12,13]

Data on the risk factors and mechanisms of cancer-associated ATE and VTE are still lacking. However, these observations provide insights into the pathophysiology of ATE in patients with cancer and the role of cancer itself as a risk factor for thrombosis.[14] Oncogenes and tumor gene suppressor alterations are linked to hemostasis effectors such as platelet reactivity, serine-protease synthesis, neutrophil extracellular trap formation, tissue factor exposure, and exacerbated thrombin generation capacity.[15] This constitutive gene expression may promote hypercoagulability and lead to the possibility of tumor cells' being protected under a "bush-like clot" of fibrin, less accessible to chemotherapy or targeted therapies and therefore facilitating cancer resistance.[16] We must keep in mind the role of genetic and epigenetic consequences according to the site of cancer and its characteristics.[17] Cancer therapies are also indisputable factors contributing to the increased risk for thrombosis in patients with cancer.[18]

Some limitations of this study must be acknowledged. Common tumors, such as prostate and breast cancers, were underrepresented in the study, while cardiovascular complications are a leading cause of death in women who have survived breast cancer.[19] Moreover, these findings must be confirmed in well-designed large prospective cohorts.

Available risk stratification scores for VTE occurrence appear to be inadequate for many groups of patients with cancer,[20] and there are none available for ATE prediction. Genetic profiling is an attractive strategy to improve thrombotic risk stratification tools. The recently proposed clinical-genetic ONCOTHROMB risk score, combining genetic variants with 3 clinical variables (tumor site, TNM stage, and body mass index >25 kg/m^2) was found to be associated with VTE in outpatients with cancer and to provide better VTE prediction than the Khorana score.[21] A multidimensional evaluation to predict thrombotic risk in patients with cancer to establish an adapted thromboprophylaxis strategy in cases of high-risk status is an important priority for the fields of cardiology and oncology.

Thus, the identification and integration of tumor molecular genomics into clinical assessment and risk stratification would be a major advance in the management of patients with cancer. A more global approach integrating patient characteristics (age, comorbidities, medications, frailty, etc), biological data, and multidisciplinary genomic analysis could be considered in the future to evaluate the prognostic impact on cancer progression, comorbidity evolution, and occurrence of complications such as ATE.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

Prof Mahé has served on boards or received consulting fees from Leo Pharma, Pfizer, Bristol Myers Squibb, Bayer and Sanofi; and has

JACC: CARDIOONCOLOGY, VOL. 5, NO. 2, 2023
APRIL 2023:256–258

received research funding from Bristol Myers Squibb-Pfizer and Leo-Pharma. Dr Scotté has served on boards or received consulting fees from Leo Pharma, Pfizer, Bristol Myers Squibb, Bayer, Merck Sharp & Dohme, Amgen, Pierre Fabre Oncology, Gilead, Helsinn, GlaxoSmithKline, Sandoz, Pharmanovia, and Viatris. Prof Elalamy has served on boards or received consulting fees from Sanofi, Leo Pharma, Viatris, Pfizer, Bristol Myers Squibb, Gedeon Richter, Stago, Boehringer Ingelheim; and has received research funding from Sanofi, Leo Pharma, and Viatris.

ADDRESS FOR CORRESPONDENCE: Dr Isabelle Mahé, Université Paris Cité, APHP, Hôpital Louis Mourier, Service de Médecine Interne, Inserm UMR_S1140, Innovations thérapeutiques en hémostase, 178 rue des Renouillers, 92700 Colombes, France. E-mail: isabelle.mahe@aphp.fr. Twitter: @isabellemahe1.

REFERENCES

1. Feldman S, Gupta D, Navi BB, et al. Tumor genomic profile is associated with arterial thromboembolism risk in patients with solid cancer. *J Am Coll Cardiol CardioOnc*. 2023;5:246–255.

2. Dunbar A, Bolton KL, Devlin SM, et al. Genomic profiling identifies somatic mutations predicting thromboembolic risk in patients with solid tumors. *Blood*. 2021;137(15):2103–2113.

3. Mulder F, Horváth-Puhó E, van Es N, et al. Arterial thromboembolism in cancer patients. *J Am Coll Cardiol CardioOnc*. 2021;3(2):205–218.

4. Scotté F, Leroy P, Chastenet M, Aumont L, Benatar V, Elalamy I. Treatment and prevention of cancer-associated thrombosis in frail patients: tailored management. *Cancers (Basel)*. 2019;11(1):48.

5. Potere N, Barco S, Mahé I, et al. Awareness of venous thromboembolism among patients with cancer: preliminary findings from a global initiative for World Thrombosis Day. J. *Thromb Haemost*. 2022;20(12):2964–2971.

6. Siegel RL, Miller KD, Wagle NS, Jemal A. Cancer statistics, 2023. *CA Cancer J Clin*. 2023;73(1):17–48.

7. Modest DP, Ricard I, Heinemann V, et al. Outcome according to *KRAS*-, *NRAS*- and *BRAF*-mutation as well as *KRAS* mutation variants: pooled analysis of five randomized trials in metastatic colorectal cancer by the AIO Colorectal Cancer Study Group. *Ann Oncol*. 2016;27:1746–1753.

8. Chida Keigo, Kotani Daisuke, Masuishi Toshiki, et al. The prognostic impact of *KRAS* G12C mutation in patients with metastatic colorectal cancer: a multicenter retrospective observational study. *Oncologist*. 2021;26:845–853.

9. Taieb J, Tabernero J, Mini E, et al. for the PETACC-8 Study Investigators. Oxaliplatin, fluorouracil, and leucovorin with or without cetuximab in patients with resected stage III colon cancer (PETACC-8): an open-label, randomised phase 3 trial. *Lancet Oncol*. 2014;15(8):862–873.

10. Pécuchet N, Laurent-Puig P, Mansuet-Lupo A, et al. Different prognostic impact of *STK11* mutations in nonsquamous non-small-cell lung cancer. *Oncotarget*. 2017;8(14):23831–23840.

11. Noumegni SR, Didier R, Mansourati V, et al. Risk factors of arterial thrombotic events after unprovoked venous thromboembolism, and after cancer associated venous thromboembolism: a prospective cohort study. *Thromb Res*. 2022;214:93–105.

12. Liu M, Wang G, Li Y, et al. Efficacy and safety of thromboprophylaxis in cancer patients: a systematic review and meta-analysis. *Ther Adv Med Oncol*. 2020;12:1758835920907540.

13. Bosch FTM, Mulder FI, Kamphuisen PW, et al. Primary thromboprophylaxis in ambulatory cancer patients with a high Khorana score: a systematic review and meta-analysis. *Blood Adv*. 2020;4(20):5215–5225.

14. Khorana AA, Mackman N, Falanga A, et al. Cancer-associated venous thromboembolism. *Nat Rev Dis Primers*. 2022;8(1):11.

15. Buijs JT, Versteeg HH. Genes and proteins associated with the risk for cancer-associated thrombosis. *Thromb Res*. 2020;191(suppl 1):S43–S49.

16. Palacios-Acedo AL, Mège D, Crescence L, Dignat-George F, Dubois C, Panicot-Dubois L. Platelets, thrombo-inflammation, and cancer: collaborating with the enemy. *Front Immunol*. 2019;10:1805.

17. Mantha S, Rak J. Cancer genetic alterations and risk of venous thromboembolism. *Thromb Res*. 2022;213(suppl 1):S29–S34.

18. Grover SP, Hisada YM, Kasthuri RS, Reeves BN, Mackman N. Cancer therapy-associated thrombosis. *Arterioscler Thromb Vasc Biol*. 2021;41(4):1291–1305.

19. Mehta LS, Watson KE, Barac A, et al. for the American Heart Association Cardiovascular Disease in Women and Special Populations Committee of the Council on Clinical Cardiology; Council on Cardiovascular and Stroke Nursing; and Council on Quality of Care and Outcomes Research. Cardiovascular disease and breast cancer: where these entities intersect: a scientific statement from the American Heart Association. *Circulation*. 2018;137(8):e30–e66.

20. Moik F, Englisch C, Pabinger I, Ay C. Risk assessment models of cancer-associated thrombosis - Potentials and perspectives. *Thrombosis Update*. 2021;5:100075.

21. Muñoz A, Ay C, Grilz E, et al. A clinical-genetic risk score for predicting cancer-associated venous thromboembolism: a development and validation study involving two independent prospective cohorts. *J Clin Oncol*. Published online February 2, 2023. https://doi.org/10.1200/JCO.22.00255

KEY WORDS arterial thrombosis, cancer, gene, genetic, mutation, venous thrombosis