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EDITORIAL COMMENT

Ticagrelor in Patients With Cancer

2 Birds With 1 Stone*

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Atherothrombotic manifestations of cardiovascular disease are increasingly prevalent among patients with underlying malignancy, an epidemiology that reflects progressive gains in cancer survivorship and vascular effects of oncological therapeutics (1,2). As a result, the putative role of conventional cardiovascular drugs, including antiplatelet agents, may offer salutary benefits in such patients. Patients with active or recent malignancy, however, are usually excluded from large-scale clinical trials in cardiovascular medicine, rendering the safety and efficacy of commonly used therapeutics somewhat unclear. This evidence gap is particularly relevant as tumor-related thrombosis remains a leading cause of mortality among patients with cancer (3). It generally manifests as venous thromboembolism and reflects a high degree of disease progression, usually to a metastatic stage (4). The potential for arterial thrombosis is also enhanced, as tumor cells and tumor-derived secreted factors induce platelet activation and expression of adhesion molecules, among other effects (5,6). Beyond these considerations, experimental evidence has also shown that circulating platelets are implicated in the pathogenesis of malignant disease (7). Activated platelets are involved in the initiation, growth, and spread of tumor cells. Indeed, platelets may facilitate the establishment of metastatic lesions by guarding circulating tumor cells from the host immune system and promoting their adhesion to the endothelial wall (7). Moreover, tumor cells and platelets can create a positive feedback loop: tumor cells secrete adenosine diphosphate and activate platelets, which in turn secrete factors promoting tumor cell proliferation and epithelial-mesenchymal transition (8). Although some of these effects are mediated by different purinergic receptors, $P2Y_{12}$ receptors seem to be the most relevant for platelet activation.

Within this context Wright et al. (9) report findings from the TICONC (Ticagrelor Oncology) study in this issue of *JACC: CardioOncology*. In this multiphase study, the investigators examined the impact of ticagrelor, a direct-acting $P2Y_{12}$ inhibitor, and aspirin monotherapy, or a combination of both, on platelet activation and aggregation among patients with metastatic cancer. The study encompassed 2 distinct phases, the first being an in vitro phase evaluating human platelet-tumor cell interaction before and after the addition of antiplatelet agents and the second being an ex vivo phase with a similar

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aim but conducted among 22 healthy donors and 16 patients with metastatic breast (n = 10) or colorectal (n = 6) cancer randomized to treatment with aspirin or ticagrelor (at the commercially approved dose regimens) using a crossover design. The study results demonstrate that ticagrelor monotherapy significantly reduces in vitro platelet aggregation and activation induced by human breast and colorectal tumor cells as well as ex vivo spontaneous platelet aggregation in patients with metastatic cancer. In contrast, aspirin failed to show similar efficacy both in vitro and ex vivo and did not seem to confer any additive antiplatelet effect when coadministered with ticagrelor. Finally, the platelet-mediated effect on cancer metastatic capacity was evaluated in vitro by assessing tumor cell adhesion to cultured human umbilical vein endothelial cells. Both ticagrelor and aspirin monotherapy significantly reduced platelet-induced endothelial adhesion of colorectal, but not breast, tumor cells.

Besides the positive, albeit somewhat heterogeneous, results, an interesting finding from the TICONC study is the observation that different histological types of tumors are associated with different levels of platelet activity and thrombogenicity. In the in vitro phase, colorectal tumor cell lines induced higher overall levels of platelet activation and showed greater adhesion to endothelial wall. Similarly, ex vivo levels of spontaneous platelet aggregation and secretion were higher among patients with metastatic colorectal cancer, thereby suggesting that the efficacy of antiplatelet therapy in patients with cancer may vary according to the type of tumor being treated.

Compared with prior preclinical investigations on the role of $P2Y_{12}$ receptors in cancer progression, the present study by Wright et al. (9) is the first to specifically explore the effects of ticagrelor administration in patients with metastatic cancer. Preventing metastatic spread and cancer-related thrombosis by potent $P2Y_{12}$ inhibition is certainly an appealing treatment option, but it must be remembered that the therapeutic potential of any antiplatelet regimen must be weighed against its associated increase in bleeding risk. Careful evaluation of the risk-benefit trade-off associated with antiplatelet therapy is of primary clinical relevance in patients who are more susceptible to bleeding complications, such as those with active ongoing malignancy (10). To this end, a growing body of evidence supports ticagrelor monotherapy as a valid treatment strategy that maintains adequate antithrombotic efficacy while minimizing the risk for bleeding (11). Accordingly, the TICONC study showed that the addition of aspirin to ticagrelor did not result in an incremental reduction of platelet aggregation and activation. Although some of these findings could be anticipated in light of the existing evidence on ticagrelor and aspirin in patients with atherosclerosis (12,13), knowledge about the safety and efficacy of these drugs in an oncological setting is limited. Identification of the exact pathways mediating tumor cell-induced platelet activation is essential for defining the most appropriate antiplatelet regimen in patients with cancer. To date, however, several questions remain unanswered. One such question is whether platelets are activated at the systemic level or only locally at the primary or metastatic tumor site. Moreover, the adenosine diphosphate level necessary to maintain the positive feedback loop between platelet and tumor cells is unknown, although it could possibly serve as a biomarker for identifying patients who would benefit from $P2Y_{12}$ inhibitors.

In conclusion, the present data suggest that ticagrelor is effective in favorably modulating tumor cell-induced platelet activation and aggregation, with potential implications in terms of cancer progression and cancer-related thrombotic events. Therefore, large-scale trials evaluating clinical outcomes in patients with cancer treated with ticagrelor or other antiplatelet agents are warranted and should leverage the 10-year experience with these drugs in the setting of atherothrombosis. Of note, as patients with cancer are generally at increased risk for both thrombotic and bleeding complications, they represent an extremely complex and high-risk population. Just as in patients with coronary artery disease, a strategy of tailoring antiplatelet therapy according to individual risk features, including tumor type, tumor burden, and concomitant anticancer therapy may enable clinicians to optimize the trade-off between the beneficial and side effects of antiplatelet therapy even in patients with cancer.

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