Metformin in Combination with Immune Checkpoint Inhibitors: Myocardial FDG Uptake Can Predict Prognosis?

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Short Editorial related to the article: Variations in Myocardial FDG Uptake and Metformin Use: Implications for Survival During Immunotherapy

In Brazil, the estimate for 2023-2025 indicates that there will be 704,000 new cancer cases in the country, 221,000 of which will be non-melanoma skin cancers, cited as the most common type. After this type of cancer, breast cancer has the highest incidence, with 74,000 cases, followed by prostate cancer, with 72,000 cases, colorectum cancer, with 46,000 cases, and lung cancer, with 32,000 new cases.[1] The cancer epidemiological profile in Brazil is like countries with a high income; however, it differs when analyzed by region, indicating significant regional inequalities. While in the country's more developed regions (South and Southeast), the age-adjusted incidence rates range between 180 and 190 cases per 100,000 inhabitants, in less developed regions (North and Northeast), these rates vary from 157 to 164 cases per 100,000 inhabitants.[1] The highest cancer mortality in Brazil is due to lung cancer (13.7% of cancer deaths), followed by colorectum cancer (10.4% of cancer deaths), and then breast cancer (8% of cancer deaths).[2]

Immune checkpoints, like PD-1, PD-L1, and CTLA-4, regulate the immune system and help to equilibrate immune activation and suppression. They act by avoiding a strong immune response that could attack normal cells. Tumor cells can use these mechanisms to elude the immune system, decreasing its response.[3] The mechanisms used for immune system evasion in lung cancer are linked to PD-1 inhibition, which reduces the activity of tumor immunity cells.[4] Additionally, there is a decrease in T-lymphocyte proliferation and cytokine production (IL-2 and IFN-γ), allowing neoplastic cells to proliferate.

Immune Checkpoint Inhibitors (ICIs) are drugs that block checkpoint proteins and increase immunological defenses against cancer, by permitting a larger response.[5] This block permits T-cells to recognize and destroy neoplastic cells effectively. A few examples of ICI are nivolumab, pembrolizumab, and ipilimumab, which inhibit PD-1 and CTLA-4, respectively. These drugs have been used to treat non-small cell lung cancer, melanoma, renal cell carcinoma, lymphoma, and other types of cancer with success, even in metastatic and chemotherapy-resistant cancer.[5]

One of the most typical Adverse Effects (AE) of the ICIs are the Immune-related Adverse Events (irAEs), that occur due to the suppression of immune inhibitory functions. It is uncommon but there is the potential for a higher grade of severity in 10–15% of cases and clinical manifestations usually start within the first few weeks to months after the onset of treatment. ICI myocarditis is reported at an incidence rate of 0.06% to 1.14%. The cardiovascular system can be affected by irAEs also as takotsubo syndrome, pericardial disease, acute coronary syndromes, thromboembolic events, and arrhythmias.[6]

Metformin has become a research target in oncology due to its properties in improving prognosis and promoting tumor growth regression.[2-4,7,8] In addition to its use in the treatment of type II diabetes, studies have reported evidence of metformin's action in tumors by reducing neoplastic cell proliferation.[8,9] One of the treatment strategies for cancer cells with mutations in the Epidermal Growth Factor Receptor (EGFR) involves the use of an EGFR Tyrosine Kinase Inhibitor (TKI). The combination of metformin with TKI shows a synergistic effect, delaying tumor resistance.[10] The transmembrane tyrosine-protein kinase receptor (IGF-1R) is expressed in various cells with mitogenic potential.[10,11] In this context, metformin acts by restoring the sensitivity of EGFR-TKI-resistant cells, inhibiting the IGF-1R pathway and the expression of IGFBP3, a gene that encodes the growth factor protein.[12] This regulation negatively impacts synergistic antitumor effects mediated by BIM, one of the apoptotic regulatory proteins involved in the control of tumorigenesis.[13]

An 18F-fluorodeoxyglucose positron emission tomography/computed tomography (18F-FDG PET/CT) is commonly used in the assessment of cancer therapy responses. Some studies are suggesting that 18F-FDG PET/CT may also be used as a tool for detecting irAEs.[14]

In this issue of the ABC Imaging, Torres *et al.*, evaluated the role of metformin as an adjuvant therapy with ICIs on the prognosis of advanced lung cancer patients and assessed the associated changes in myocardial FDG uptake rate (MGU).[15] Interestingly the authors found that metformin users presented a significant increase in Overall Survival (OS). Also, patients with a positive variation in myocardial

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SUV (a quantitative measure of tissue glucose uptake) had an increase in progression-free survival (PFS). The authors concluded that metformin has the potential to be an important adjuvant treatment option for patients undergoing ICI therapy. Also, they hypothesize that an increase in myocardial SUV could be a potential marker for ICI beneficial effects.[15] These findings are interesting and draw attention to the complex interactions between the immune system and cancer treatment, in which activation of immune cells can bring benefits but there is also a risk that overactivation can cause significant complications. PET/CT with 18F-FDG can identify patients at higher risk of cardiac complications from cancer treatment, as demonstrated by Dourado *et al* in ABC Cardiol, identifying a phenotype of patients with cardiotoxicity.[16,17] Could the inflammation observed in these patients be considered a prognostic predictor of response? Could this uptake in the myocardium be an indication of systemic activation of the immune system? Could metformin protect the heart from the AEs of therapy given the absence of clinically relevant cases of myocarditis in the sample? There are limitations to the study, such as the absence of a formal control group, the absence of serial troponin measurements, or monitoring of left ventricular function with speckle-tracking echocardiography. This information would provide additional data to understand the findings. In any case, the authors should be congratulated for this hypothesis-generating study, and we suggest that studies of ICIs that include metformin as an adjuvant should perform serial monitoring of cardiac parameters, including measurement of FDG uptake in the myocardium, as a way of understanding whether these parameters can contribute to the management of cancer patients receiving immunotherapy.

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