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LETTER TO THE EDITOR

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Can thrombotic events be a major concern in hepatocellular carcinoma patients under systemic treatment during SARS-Cov-2?

To the Editor

We read with interest the editorial by Sharma and Pinato on the management of hepatocellular carcinoma (HCC) in the time of SARS-Cov-2.[1] The points raised by the authors will be of paramount importance to guide HCC groups worldwide.

Once there is no evidence suggesting that tyrosine kinase inhibitors (TKIs) increase the risk of COVID-19, the balance favours towards continuing TKIs for advanced-HCC patients who are likely to benefit from treatment. The approach to treat with a 50% dose reduction with a view to dose escalation can prevent early adverse events, what will reduce the frequency of outpatient visits and hospitalizations.

However, it deserves mention that SARS-Cov-2 infection in patients with HCC under TKIs can represent a more critical and intriguing scenario. In our tertiary academic center, Dolhnikoff *et al* performed minimally invasive autopsies in 10 fatal cases of COVID-19 (none of them with HCC) and observed a variable number of small fibrinous thrombi in pulmonary arterioles in 8 cases, endothelial tumefaction and a large number of pulmonary megakaryocytes in the pulmonary capillaries.[2] These findings suggest a strong activation of the coagulation cascade and support the concept of an hypercoagulative status as a mechanism of hypoxemia and, ultimately, multi-organ failure. This can be corroborated by the relation between D-dimer and mortality described in COVID-19.[3]

TKIs directed to vascular-endothelial growth factor (VEGF) receptor are the mainstay of systemic treatment in HCC (such as sorafenib, lenvatinib, cabozantinib and regorafenib). This class is associated with an increased risk of arterial and venous thromboembolic events.[4] It is hypothesized that TKIs disrupt the regenerative capacity of endothelial cells and cause vascular wall defects, exposing prothrombotic phospholips on the luminal membrane, leading to thrombosis. Also, reduction in nitrogen oxide and prostaglandin by VEGF inhibition can predispose to thrombosis.[5]

This picture highlights the importance of keeping a high level of suspicion for COVID-19 in patients under TKIs who are experiencing early symptoms or were potentially exposed to SARS-Cov-2. A decision to timely interrupt TKIs in suspected cases should be considered in order to avoid the harmful combination of the prothrombotic effects of both TKIs and SARS-COV2. While debates about the benefit of prophylactic or systemic anticoagulation take place in intensive care units (ICU), the experience of oncologists and hepatologists dedicated to HCC management can help ICU teams to assist this particular subgroup of HCC patients affected with COVID-19.

CONFLICT OF INTEREST

LGdF has received lectures fees from Bayer and Roche.

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