Editorial

Lung cavitation in lung metastases of gastric and non-small-cell lung cancer patients treated with apatinib

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In one of the latest issues of *Translational Lung Cancer Research* (*TLCR*), Jiang *et al.* have reported on the frequent cavitation of lung metastases in metastatic lung and gastric cancer patients following treatment with apatinib. It has been recognized that anti-angiogenic compounds surface among the anti-cancer therapies, inducing lung cavitation. Although lung cavitation was not found to influence PFS and OS in previous studies (1), the study of Man Jiang, directed by Xiaochun Zhang, has shown that apatinib induces cavitation of lung metastases in a significant number of patients treated with apatinib. Detection of cavitation of lung metastases was associated with longer PFS and OS. What is lung cavitation? Cavitary lung diseases have, for a long time, been an object of study and have broad differential diagnoses. The study of Jiang *et al.* opens the gates for further clarification of this subject. A cavity is defined as a gas-filled space, seen as a lucency or low attenuation area, between a nodule, mass or area of parenchymal consolidation. It also has a clearly defined wall, 4 mm thick (2). Multiple peripheral nodules in variant stages of cavitations could indicate septic emboli, pulmonary Langerhans cell histiocytosis, possible infarction or tumors with hemorrhage. True cavities should be differentiated from cystic disease, emphysema, infected bullae and cystic bronchiectasis. Cavities are relatively frequent in lung cancer, with an incidence of up to 20% in chest CT scans. Pulmonary metastases can also cavitate. In the current study, the lung cavitation was clearly associated with apatinib treatment, since it occurred in a short period of time, less than 12 weeks, according to prior imaging. What is apatinib? Apatinib is a multi-receptor tyrosine kinase (RTK) inhibitor that was originally studied in patients with non-small cell lung cancer and gastric cancer in China (3). Apatinib has been approved to treat advanced or metastatic chemo-resistant gastric cancer in China. Apatinib is an orally administered RTK inhibitor that targets the vascular endothelial growth factor receptor-2 (VEGFR-2), RET, platelet-derived growth factor-β (PDGFR-β), c-Src and stem cell factor receptor (c-Kit) (4). Apatinib has been used in combination with pemetrexed and carboplatin in non-squamous non-small-cell lung cancer (5) and in combination with docetaxel in lung adenocarcinoma (6). Although apatinib has significant side effects, like hypertension, hand foot syndrome, fatigue and others, at lower doses of 250 mg per day it is well tolerated (6).

Apatinib as a multi-RTK, as well as inhibiting Src, could become a very important anticancer drug if used correctly in combination, not only with chemotherapy, but also with other targeted therapy inhibitors that can abrogate important cancer signaling pathways. For example, regorafenib (approved for the treatment of colon cancer) in combination with neratinib, an irreversible inhibitor of ERBB1/2/4, and sildenafil, a phosphodiesterase 5 inhibitor, has demonstrated significant efficacy in mouse cancer models (7). Moreover, apatinib, as other drugs, reverts multidrug resistance by inhibiting the efflux dynamics of ATP- binding cassette transporters. Therefore, apatinib could be useful in combination with chemotherapeutic drugs that are exposed to this mechanism of resistance (3). Admittedly, the mechanism of cavitation is not fully understood and, recently, cavitation has been noted following pembrolizumab therapy (8). Respiratory, fungal

infections in patients with compromised immune functions and inflammatory cytokine production in lung epithelial cells can function to modulate the immune defense signaling through pattern recognition receptors, including toll like receptors and cytokine receptors, such as IL-IR, TNFR or IFNR. Such cytokines are fully recognized to be involved in the mechanisms of immune resistance and sensitivity to immune checkpoint PD-1 and PD-L1 inhibitors. Moreover, we propose that autophagy also plays an important role in the mechanisms of immune resistance and disturbances in key autophagy molecules, such as Rubicon, can participate in the process of cavitation, as can be seen from the compelling evidence of lung fungal infections (9). Another important player is interleukin-33 (IL33) that stimulates NETosis (formation of Neutrophil Extracellular Traps). Recruited neutrophils release genomic DNA, as well as neutrophil proteases (10). Intriguingly, interferon-ϒ from natural killer cells induces NETosis and deep vein thrombosis in mice (11). Jiang *et al.*, *TLCR* 2019 gives insights on the mechanisms of cavitation by looking at the expression of VEGFR and HIF-1α in normal or hypoxic conditions. Apatinib in hypoxic conditions increases the expression of HIF-1α.

In conclusion, lung cavitation is an intriguing phenomenon in lung metastases that requires a differential diagnosis. It can be related to cytokine release and, therefore, components of autophagy, such as Rubicon, should be kept in mind. As the authors commented in their article, further studies with apatinib are warranted.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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