Editorial

# Influence and mechanism of lung cavitation development on antiangiogenic therapy: is cavitation the new caveat?

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## Is cavitation the new caveat?

In the last two decades, the clinical application of different antiangiogenic drugs has improved the outcome of most solid tumors. In particular, gastrointestinal and lung cancers are commonly treated with antiangiogenic drugs, either alone or combined with standard chemotherapy. Since their introduction in clinical practice, the need for novel radiological patterns of response to antiangiogenics have early emerged, as a consequence of a distinctive mechanism of action (1).

Formation of tumor cavitation—defined as a change of the density of the tumor mass with appearance of air-filled cavity inside the lesion and concomitant decrease of the solid component—is a common phenomenon during antiangiogenic therapy for lung malignant lesions. Although tumor cavitation seems related to the activity of the antiangiogenic therapy, its appearance has no clear prognostic significance. Tumor cavitation appeared in 14–24 % of patients with primary lung cancer receiving bevacizumab in combination to a platinum-based chemotherapy (2-4). Because of limited significant differences in disease control rate or survival emerged between lung cancer patients who developed cavitation as response to therapy and patients who did not, the relationship between bevacizumab-induced cavitation and clinical benefit remains uncertain. Moreover, tumor cavitation has been linked to increased risks for infection and bleeding.

Among gastrointestinal cancers, regorafenib or bevacizumab may also produce cavitation of lung metastases. The orally available multikinase inhibitor regorafenib demonstrated improved progression-free survival (PFS) and overall survival (OS) in pre-treated patients with metastatic colorectal cancer (mCRC) in the CORRECT trial (5). After 8 weeks of full-dose therapy, the RadioCORRECT study (a post-hoc analysis of the pivotal trial) reported a rate of 34.3% of *de novo* lung metastasis cavitation in patients treated with regorafenib, together with a 66.7% of airspace increase in those who had pre-existing cavitations (6). The onset of tumor cavitation during treatment significantly associated with prolonged PFS on treatment (HR 0.58; 95% CI, 0.36–0.93). Moreover, the presence at baseline of cavitation involving lung metastasis and its increase within the treatment course associated with both PFS and OS. Less defined is the frequency and the significance of lung metastasis cavitation in patients with mCRC treated with bevacizumab and chemotherapy. A retrospective analysis that included 60 mCRC patients with lung metastasis treated with bevacizumab and chemotherapy in first- or second-line setting showed longer OS in patients who developed cavitation during first-line bevacizumab-based treatment.

We compliment Jiang and co-authors that in their original article entitled "*influence and mechanism of lung cavitation development on antiangiogenic therapy*" present the results of a large retrospective analysis of patients with primary or metastatic lung or gastric tumours receiving therapy with apatinib, a novel inhibitor of vascular endothelial growth factor (VEGF) signalling. Not only the Authors report on the occurrence of cavitation development

during therapy and its relation with outcomes, but also, they provide a smart translational analysis of the mechanisms of growth inhibitions in cell line.

## Apatinib for the treatment of solid tumors

Apatinib is a small tyrosine kinase inhibitor (TKI) that selectively inhibits the vascular endothelial growth factor receptor 2 (VEGFR-2) by binding its intracellular adenosine triphosphate site, thus determining decrease in endothelial cell migration, proliferation, and tumor microvascular density (7). More recently, it has been suggested that apatinib could directly promote tumor cell apoptosis by inhibiting the PI3K/Akt signalling pathway with a subsequent upregulation of proapoptotic genes Bax and caspase-9 and downregulation of the anti-apoptotic gene Bcl-2.

All these mechanisms provide anti-tumor activity inhibiting the formation of new blood vessels supplying the tumor and promoting concomitant apoptosis of tumor cells. Results is a change in the vascularisation and density of the tumor (8).

To date, data from clinical trial investigating the use of apatinib are available in gastric cancer, breast cancer, lung cancer, osteosarcoma and oesophageal squamous cell cancer.

In a phase II trial in gastric cancer apatinib improved OS and PFS in pre-treated patients with advanced or metastatic gastric carcinoma when compared with placebo (9). The subsequent phase III trials enrolled 267 heavily pre-treated mGC patients (10). A significant improvement for both OS and PFS was reported in patients receiving apatinib versus patients in the placebo arm. Based on these results, apatinib gained approval by the China General Administration of Food and Drug Administration in 2014 and recommended by the Chinese Society of Clinical Oncology as a third-line therapy for mGC. Nevertheless, the drug was not developed in European Countries (11).

Although no other large phase III trials have been conducted in major solid malignancies, consistent data suggesting antitumor activity of apatinib in a scope of different tumours have emerged from small phase II trial. In breast cancer, a small prospective phase II trials evaluated the effect of apatinib in pre-treated triple negative metastatic patients (12). An overall response rate (ORR) of 10.7% was reported among 56 patients suggesting anti-tumor activity in a poor prognosis cohort of patients. Further trials investigating apatinib in combination with chemotherapy are ongoing in the metastatic breast cancer setting.

In non-small cell lung cancer (NSCLC) apatinib was tested as a salvage therapy in 42 Asian patients without molecular selection (13), limiting the interpretation of the results for the clinical practice. An ORR of 9.5% and a disease control rate of 61.9% were reported. Another small trial conducted in 16 patients with metastatic NSCLC EGFR wild type pre-treated patients reported a response rate and a control rate of 18.8% and 68.8%, respectively (14). As these first data seem to suggest anti-tumor activity in post-second-line treatment for advanced lung cancer, larger trials investigating apatinib in third-line therapy and in combination with chemotherapy versus chemotherapy alone are ongoing. Furthermore, the potential role of the anti-angiogenic effect of apatinib in combination with EGFR targeting agents to prevent or delay EGFR-TKI resistance is a field of pre-clinical and clinical investigation, supported by strong biological rationale, as before mentioned. A recent phase II trial enrolled 37 pre-treated patients affected by advanced osteosarcoma (15). The results showed a high rate of objective response of 43% that was not so different from others TKIs approved in the treatment of this disease. Finally, in a phase II trial enrolling 62 patients with advanced oesophageal squamous cell cancer, apatinib produced ORR of 24.2% and a disease control rate of 74.2% (16).

To sum up, apatinib has shown promising consistent results in several malignancies and setting of treatment. Trials testing apatinib in combination with chemotherapy and immunotherapy are ongoing. An in-depth comprehension of the therapeutic mechanisms of apatinib and the consequent radiological patterns of response to therapy are required to shed light on clinical perspectives of the treatment and specific differential potentialities with respect to other known anti-angiogenic agents.

## Apatinib-induced tumor cavitation: is this a valuable predictive tool?

The report presented by Jiang and co-authors is the first published analysis focusing on the clinical outcome of a large cohort of patients developing cavitation in lung lesions following apatinib treatment. The analysis was restricted to heavily pre-treated lung and gastric cancer patients and this made the cohort of observed patients quite homogeneous. On the other hand, the reason of this selection is not clear from the biological point of view. The number of patients included in the analysis was 189, the highest ever

reported in an analysis to observe tumor cavitation of lung lesions during antiangiogenic therapy. Rate of tumor cavitation was 26% and occurred in all cohorts of patients regardless of whether patients had primary lung squamous carcinoma or adenocarcinoma or metastatic gastric cancer. This was consistent with the results from previous reports (9,10,13,14). Notably, local disease control, PFS and OS were all significantly improved in patients presenting tumor cavitation during therapy. Since similar results were not previously reported with any other antiangiogenic drug, it may suggest that the development of lung cavitation is a reliable biomarker of response during treatment with apatinib and it should be considered when reassessing the tumour during treatment. In the manuscript, data about potential clinical complications associated with tumor cavitation are not fully cleared, even though they are commonly observed in clinical practice and they even limit the use of antiangiogenic drugs when cavitation is present at baseline.

The authors also reported a translational analysis on human gastric cancer (SCG-7901) and human NSCLC (H1299) cell lines. Apatinib was able to inhibit tumor growth by both vascular proliferation suppression and direct cell proliferation inhibition.

Overall, the retrospective analysis shows an interesting model suggesting a key role of cavitation in the response to antiangiogenic drugs, even taking into account the limitations recognized by the authors themselves. In particular, the model might also renew interest in other drugs such as nintedanib for lung cancer and aflibercept for colon cancer.

On the other side, studies on the role of anti-VEGF treatment had proposed a different model in the balance between hypoxia and normoxia and potential impact of metabolic alterations induced by hypoxia. According to this model, the rapid development of necrosis following anti-VEGF treatment in *in-vivo* models was associated with rapid development of acquired resistance, probably related to the recruitment of inflammatory cells supporting tumor growth and metastatic potential (17,18).

The potential differential role of antibodies directly targeting VEGF and multi-target small molecules with multiple mechanisms of action needs to be further explored in preclinical models, to better understand how to exploit the potential of these drugs. In addition, specific analysis needs are eagerly awaited to understand the role of cavitation formation following combination treatment including anti-angiogenic agents and chemotherapy or immunotherapy, since the metabolic impact of the association could be differently associated with outcome.

## Conclusions

The occurrence of cavitation during antiangiogenic treatment deserves to be considered as potential factor affecting clinical outcome during treatment with antiangiogenic agents. It is a direct consequence both of the intratumoral vascular proliferation suppression and pro-apoptotic signalling mediated by multi-target antiangiogenic agents. Among these agents, apatinib seems the most promising. The study presented by Jiang and co-authors suggest that the occurrence of cavitation during therapy should be regarded as part of the antitumor activity and might be incorporated in the analysis and interpretation of future clinical trials to better understand potential application of apatinib.

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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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