Improving efficacy of the combination between antiangiogenic and chemotherapy: Time for mathematical modeling support

In their interesting paper published recently in PNAS (1), Heist et al. report the clinical benefits of combining antiangiogenic bevacizumab, with the doublet carboplatin plus nab-paclitaxel, in non-small cell lung cancer (NSCLC) patients. This regimen demonstrated promising efficacy. Interestingly, whereas functional imaging showed that bevacizumab exerts an antiangiogenic effect, better survival was achieved in patients displaying improved blood perfusion. In contrast, patients with the most bevacizumab-induced decreased median transit time or decreased permeability surface showed poor clinical outcome. These observations support the hypothesis that antiangiogenic effects of bevacizumab may limit the efficacy of concomitantly administered cytotoxics. Conversely, the transient normalization phase in the neovasculature quality and improved tumor blood flow repeatedly suggested with bevacizumab (2, 3) could explain the better efficacy reported in the subset of NSCLC patients with increased blood perfusion. The authors propose further exploration of various doses of bevacizumab so as to modulate this effect and to improve the efficacy of this combination.

In addition to changing the doses, we believe that reconsidering the very way this association is administered should bring substantial clinical benefit. In the Heist et al. study (1), after a 14-d induction phase bevacizumab was given concomitantly to the chemotherapy (although an uncertainty remains about the repeated dosing of nab-paclitaxel on day 8 and day 15, by reading figure S1 in ref. 1) with a cycle duration of 21 d. Our modeling and simulation group has developed a mathematical pharmacokinetics/pharmacodynamics model dedicated to describing the impact of bevacizumab on vasculature quality and resulting tumor blood flow (4). In silico simulations have suggested that a 5- to 10-d delay coincides with an increase in tumor perfusion, a time-window that could be used to administrate the chemotherapy so as to maximize the amount of cytotoxics reaching the tumor eventually, thus achieving better antitumor efficacy. In a nonclinical proof-of-concept study, rather than changing the doses, our group has tested a variety of sequences associating bevacizumab and paclitaxel in mice bearing triple-negative breast human MDA231 tumors. Our data confirmed model predictions and the superiority of the alternative schedule (i.e., sequential administration of bevacizumab given before the chemotherapy), in terms of survival, tumor growth, and metastatic spreading. Most interestingly, in our study some sequences or use of bevacizumab alone seemed to have deleterious effects by triggering metastasis acceleration (5).

Extensive pharmacokinetics/pharmacodynamics modeling of bevacizumab in patients is eagerly awaited as a support to better understand the importance of the interindividual variability in drug exposure and its subsequent effects among patients administered following standard dosing, and to identify the individual time-window during which tumor perfusion is increased. Based on the clinical data of Heist et al. (1) and the reported heterogeneity in median transit time observed among patients all treated with 15 mg/kg of bevacizumab, we can hypothesize that a 7-d delay between the administration of carboplatin + nab-paclitaxel and bevacizumab, associated with adaptive dosing strategy to smooth the interpatient variability in drug exposure levels, could achieve substantial improvements in the therapeutic benefits of this new and promising regimen in NSCLC patients.

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5 Mollard S, et al. (2014) Abstract 3677: Model-based optimization of combined antiangiogenic + cytotoxics modalities: Application to the bevacizumab-paclitaxel association in breast cancer models. *Cancer Res* 74:3677.

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The authors declare no conflict of interest.

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