**Pharmacokinetic and pharmacodynamic end points with anti-VEGFR: the more it hurts, the more it works?**

For the past decade, an increasing number of publications and international meeting abstracts have suggested a relationship between the occurrence of specific toxicities and the anti-tumour activity of molecular targeted agents. Indeed, these agents are supposed to be targeted against specific kinases and signal transducers in cancer cells and their micro-environment, but their targets are also expressed in normal tissues, leading to a broad range of clinical and biological toxicities. In particular, hypertension has been suggested as a potential surrogate marker for the activity of anti-vascular endothelial growth factor (VEGF) agents bevacizumab, sunitinib, sorafenib and axitinib [1].

A majority of previously published studies found a relationship between blood pressure (BP) elevation (with various thresholds) and treatment activity (based on response rate, progression-free survival or overall survival) [2–8]. Theoretically, five hypotheses may account for these results, but also for the contradictory results of large cohort analyses [9):

- Patients with prolonged survival are more likely to develop hypertension because of length-bias (i.e. patients must live long enough to develop hypertension),
- Heterogeneity in the definition of hypertension, in the definition of activity, or in the study population,
- Hypertension and response to anti-VEGF agents are favoured by a common set of prognostic factors,
- Hypertension truly predicts the activity of anti-VEGF agents,
- Chance (which cannot be definitively ruled out, even in large phase III studies).

Strategies to manage the length-bias issue are the time-dependent covariate approach, which was used in only one study of bevacizumab in non-small-cell lung cancer patients [10], and the landmark method. Using the latter, patients who died or discontinued treatment before the landmark time point are excluded from analyses, while patients who develop hypertension after the landmark time point are included in the same group than patients who never developed hypertension. Different landmark time points were used in previous studies, and all of them were determined empirically. However, we should keep in mind that the earliest landmark points are probably the more helpful for treatment adjustments.

As far as the definition of hypertension is concerned, it should be borne in mind that toxicity was graded according to the NCI-CTC v2.0 or v3.0 in most previous studies, both classifications being based on therapeutic interventions but not specifically on BP levels. The methods used for BP monitoring were also poorly reported, and only two studies mentioned the use of a validated BP measurement device, and only one study mentioned twice daily assessments after a period of rest, in supine position, as recommended by international guidelines [11].

Regarding heterogeneity in patients’ populations, several studies included patients with metastatic renal cancer (mRCC) who previously underwent nephrectomy. Such patients with a unique kidney may be at higher risk for developing hypertension, due to either increased volemia or underlying renal diseases [1], and therefore should probably be analysed separately.

Another source of error are factors favouring both hypertension and tumour response. This issue was explored by Guiu et al. [12], who identified visceral fat area (VFA) as a predictor of response to bevacizumab in colorectal cancer patients. Indeed, patients with a high VFA had a worse response rate and shorter survival. Visceral fat is an endocrine tissue that generates a number of pro-angiogenic factors, including leptin. Interestingly, patients with a high VFA are more prone to develop primary hypertension [13].

Finally, a significant relationship between drug exposure and (i) diastolic BP elevation on one hand, and (ii) treatment outcomes on the other hand, was reported in patients receiving sunitinib [7].

In the present issue of *Annals of Oncology*, Rini et al. [14] report a comprehensive analysis taking into account all these factors, carried out in a phase II trial of axitinib dose titration in patients with mRCC. Notably, axitinib was the first anti-VEGF receptor tyrosine kinase inhibitor (VEGFR TKI) approved with a predefined dose titration schedule based on BP levels.

The authors should be congratulated for having used multimodal evaluation of BP variations, having included pharmacokinetic assessments, and the methodological validity of their analyses.

Their analysis showed that patients eligible for dose titration (i.e. with low BP levels) had lower plasma exposure at the starting dose. As expected, axitinib dose titration based on BP levels increased drug exposure, resulting in higher response rates, but no significant difference in progression-free survival. In patients with area under the curve ≥ 200 (n = 118) versus <200 ng h/ml (n = 49), response rates were 53% and 37%, respectively.

However, since the study was not powered to detect pharmacokinetic differences between treatment arms, only a weak correlation was found between axitinib exposure and diastolic BP elevation.

The authors conclude that neither treatment activity nor BP elevation is driven solely by drug exposure, and increased exposure alone will not guarantee improved outcomes.

Indeed, factors driving BP variations and anti-tumour activity are obviously more complex than a simplistic view of a pharmacokinetic/pharmacodynamic relationship between axitinib exposure and clinical outcomes.

From this perspective, BP monitoring in patients receiving axitinib is not ‘pharmacokinetics for the poor’, but rather a perfect tool for therapy optimization.

From a broader perspective, one could therefore hypothesize that the occurrence of hypertension might, in part, reflect the intensity of VEGF pathway inhibition rather than exposure to anti-VEGF agents. The knowledge that a vast majority (92%) of mRCC patients receiving bevacizumab and sunitinib in a phase
I study developed hypertension supports this hypothesis, leading to the concept of supra-additive toxicity [15].

The intensity of VEGF pathway inhibition might in part depend on pharmacokinetics, but also on host-related factors, including pro- and anti-angiogenic factors imbalance (for instance in patients with high visceral fat), and/or pharmacogenetic factors such as VEGFA or WNK1 polymorphisms [16, 17], the nitric oxide synthase and endothelin axis [17–19]. Such factors may be implemented in further studies aiming to identify predictors of response to axitinib, along with largely powered pharmacokinetic assessments.

With regards to other TKIs, recent data indicate the feasibility of dose titration of sunitinib based on pharmacokinetic data [20], with preliminary activity data in selected patients [21].

Optimizing the use of anti-VEGFR TKIs other than axitinib beyond the standard doses recommended in phase I trials should necessarily rely on the identification of predictive biomarkers of efficacy, within dedicated studies incorporating pharmacokinetic, pharmacodynamic and pharmacogenetic factors.

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disclosure
OM has acted as paid consultant for Amgen, Astra-Zeneca, Bayer, Glaxo Smith Kline, Novartis, Pfizer, Roche and Servier. All remaining authors have declared no conflicts of interest.

references