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Commentary

An Interpretation of Pharmacologic Endpoints for Anti-VEGFR

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DESCRIPTION

Over the last decade, an increasing number of specific toxicities and the anti-tumor activity of molecular targeted agents have been discussed. These agents are intended to target specific kinases and signal transducers in cancer cells and their microenvironment, but their targets are also expressed in normal tissues, resulting in a wide range of clinical and biological toxicity. In particular, hypertension has been proposed as a potential surrogate marker for the activity of anti-VEGF agents such as bevacizumab, sunitinib, sorafenib, and axitinib. In theory, five hypotheses could account for these findings, as well as the contradictory findings of large cohort analyses.

Patients with longer survival are more likely to develop hypertension due to length bias (patients must live long enough to develop hypertension).

Heterogeneity in the definition of hypertension. A common set of prognostic factors favours hypertension and response to anti-VEGF agent Hypertension accurately predicts anti-VEGF agent activity. The time-dependent covariate approach, which was used in only one study of bevacizumab in non-small-cell lung cancer patients and the Predetermined period of time approach are two strategies for dealing with length bias.

Patients who died or stopped taking their medication before the predetermined period of time are excluded from the analyses, whereas patients who develop hypertension after the predetermined period of time are included in the same group as patients who never developed hypertension. Previous studies used various predetermined period of times were all determined empirically.

However, note that the earliest end points are likely to be the most useful for treatment adjustments. In terms of hypertension definition, it should be noted that in most previous studies, toxicity was graded using the NCI-CTC v2.0 or v3.0, with both classifications based on therapeutic interventions but not specifically on BP levels. 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. In terms of patient population heterogeneity, several studies included patients with metastatic renal cancer (mRCC) who had previously undergone nephrectomy. Such patients with a distinct kidney may be at a higher risk of developing hypertension due to increased volemia or underlying renal diseases and should therefore be evaluated separately. Their findings revealed that patients who were eligible for dose titration (i.e., had low blood pressure levels) had lower plasma exposure at the starting dose. As expected, titration of axitinib dose based on blood pressure levels increased drug exposure, resulting in higher response rates but no significant difference in progression-free survival. Response rates were 53%and 37%, respectively, in patients with an area under the curve of 200 (n=118) *versus* 200 ng h/ml (n=49).

However, because the study was not powered to detect pharmacokinetic differences between treatment arms, only a weak correlation between axitinib exposure and diastolic blood pressure elevation was discovered. The authors conclude that neither treatment activity nor blood pressure elevation are solely driven by drug exposure, and that increased exposure does not guarantee improved outcomes. Indeed, the factors influencing blood pressure variations and anti-tumor activity are clearly more complex than a simplistic view of an axitinib pharmacokinetic/pharmacodynamic relationship.

The intensity of VEGF pathway inhibition may be influenced by pharmacokinetics as well as host-related factors such as pro- and anti-angiogenic factor imbalance (for example, in patients with high visceral fat) and/or pharmacogenetic factors such as VEGFA or WNK1 polymorphisms, the nitric oxide synthase and endothelin axis. Such factors, along with highly powered pharmacokinetic assessments, could be used in future studies aimed at identifying predictors of response to axitinib. In terms of other TKIs, recent data show that sunitinib dose titration based on pharmacokinetic data is feasible, with preliminary activity data in selected patients. Beyond the standard doses recommended in phase I trials, optimizing the use of anti-VEGFR TKIs other than axitinib must rely on the identification of predictive biomarkers of efficacy within dedicated studies incorporating pharmacokinetic, pharmacodynamic, and pharmacogenetic factors.

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