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LETTER TO THE EDITOR

Is there association between clinically relevant toxicities of pazopanib and sunitinib with the use of weak CYP3A4 and P-gp inhibitors?

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Dear Editor,

We read with great interest the article entitled "Association between clinically relevant toxicities of pazopanib and sunitinib and the use of weak CYP3A4 and P-gp inhibitors" by Azam et al. [1]. Notably, they demonstrated that patients who received co-medications with potential pharmacokinetic drug-drug interaction (P-PK-DDI) were significantly more vulnerable to dose reduction during the first month of treatment and ultimate discontinuation of pazopanib or sunitinib. Given that the tyrosine kinase inhibitors (TKIs) are being considered for different malignancies, their toxicities and interactions are worth paying attention to. Therefore, we would like to discuss some points regarding the mentioned study.

The authors reported hypertension (HTN) as the second most prevalent toxicity and the leading cause of dose reduction during the first month after the initiation of TKIs. However, baseline prevalence of HTN was not similar in patients with and without P-PK-DDI (93% vs. 25%). Meanwhile, it was previously shown that patients receiving angiotensin system inhibitors were significantly more prone to develop pazopanib-induced HTN, and those with higher baseline systolic blood pressure showed a higher tendency towards this adverse effect [2]. We would like to emphasize that the association between P-PK-DDI and dose reduction due to toxicity should be interpreted cautiously. Since the difference in the baseline characteristics could have affected the incidence of medication-induced HTN and attributing the dose reduction to the P-PK-DDI might be misleading.

The study findings regarding the role of toxicities associated with P-PK-DDI and their consequent dose reduction during the first month of treatment are quite noteworthy. However, it is substantially important to pay attention to the differences between toxicities in terms of their dose-related nature as well. There are several adverse events with pazopanib, such as nausea, fatigue, vomiting, dysgeusia, and rash that are not exposure related [3]. It can be presumed that P-PK-DDI could not increase the risk of such toxicities. It was very informative if the authors described how such toxicities were considered in the study.

Additionally, in the article, it is not clear how the reported toxicities were managed in a stepwise approach before dose reduction. Different strategies were proposed for the management of some of the adverse events of TKIs before dose reduction [4]. These strategies are helpful to preserve dose reduction only for patients with either unsuccessful response or high-grade toxicities. It was very helpful if the authors elaborated this issue. It can be assumed that there might be differences among physicians' practice regarding this issue that probably affected the results.

To assess the adverse events of pazopanib, one of the major influential factor is the considerable inter-patient PK variability which can be associated with elevated exposure and increased toxicity [5]. Additionally, it was previously indicated that polymorphism of ABCB1 (ATP-binding cassette subfamily B member 1) was associated with increased sunitinib exposure and adverse events such as rash and mucositis [6]. Similar findings support the significant role of CYP3A4*22 and CYP3A5*1 in the lower clearance of sunitinib [7]. It seems that this issue is worth to be mentioned among the limitations of the study. The concern here is the possibility of different genetic polymorphism backgrounds of patients who experienced toxicities and dose reduction that might have been attributed to the presence of P-PK-DDI.

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Dietary factors are also valuable to be considered. There is evidence supporting the role of food as a reason for variation in the pharmacokinetics of pazopanib which might affect the interpretation of the results if patients did not follow the same instruction regarding fasting [8].

Moreover, one of the considerable points in the assessment of medication-related toxicities is the need for determining their causality. The importance is specially highlighted considering that some adverse events such as fatigue can be a manifestation of hypothyroidism, anemia [9], or underlying malignancy itself. This assessment by using one of the different available scales can provide valuable data.

Data availability Not applicable

Code availability Not applicable

Declarations

Ethics approval Not applicable

Consent to participate Not applicable

Consent for publication Not applicable

Conflict of interest The authors declare no competing interests.

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