

Is Bodyweight-Based Dosing Truly Better Than Flat Dosing for Panitumumab? [Letter]

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Dear editor

With great interest we read the paper by Liao et al in which they compared a 2-weekly bodyweight-based (6 mg/kg) and fixed (480 mg) administration of panitumumab, a monoclonal antibody (Mab) binding the EGFR receptor.¹ The authors used a population pharmacokinetics model to simulate pharmacokinetics of 1200 virtual individuals for each strategy. The observed interpatient variability in mean simulated AUC ($CV_{AUC\text{mean}}$) was compared and was 34% (fixed dosing) versus 29% (bodyweight-based dosing). Based on this, the authors concluded for panitumumab that “body weight-based approach is the recommended patient dosing strategy”.

Previously, we assessed feasibility of fixed dosing as an alternative strategy for thirteen Mabs including panitumumab.² We concluded that fixed dosing is a more rational approach as pharmacodynamics (efficacy and toxicity) of antagonistic Mabs are not concentration-related at concentrations exceeding the minimum target inhibitory concentration (IC_{min}).² For panitumumab, the estimated threshold is 3.83 $\mu\text{g/mL}$.¹ The authors compared the $CV_{AUC\text{mean}}$ of both dosing strategies.¹ However, because of the IC_{min} , trough levels (C_{min}) would be a better parameter for assessing efficacy of panitumumab. Although the observed C_{min} after bodyweight-based dosing is reported (Figure 1 and Discussion)¹, we miss report of simulated C_{min} of the fixed dosing schedule. As the lowest interquartile AUC after fixed and bodyweight-based dosing of panitumumab is comparable (987 versus 908 $\mu\text{g}\cdot\text{d/mL}$, respectively, in Table 2)¹, it is likely that C_{min} of the both strategies is comparable ($\sim 20\text{--}30 \mu\text{g/mL}$ and $\gg IC_{\text{min}}$) and, therefore, both strategies have equivalent efficacy.

The reported difference in $CV_{AUC\text{mean}}$ for both dosing strategies is mainly caused by the higher exposure of panitumumab in patients with a low bodyweight after fixed dosing (Figure 2)¹. This results in a difference between the highest interquartile AUC after fixed and bodyweight-based dosing (1582 versus 1254 $\mu\text{g}\cdot\text{d/mL}$, respectively in Table 2)¹. However, this is clinically irrelevant as for panitumumab (like most Mabs in oncology), an exposure-toxicity relationship is absent.^{2,3} Although increased incidence of skin toxicity has been reported with increasing doses, this is related to the EGFR inhibition and reaches a plateau at doses of $\geq 2.5 \text{ mg/kg}$.^{3,4} As onset of \geq grade 2 toxicity is related to better survival and is a result of target inhibition, it even may be evaluated as biomarker for efficacy.³ In fact, the manufacturer reports that doses up to 12 mg/kg have been used and that the safety profile was consistent with the recommended dose.⁴ Since

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an exposure-toxicity relationship is absent in the tested dose range, the interpatient variability of Mabs is of less concern as long as C_{\min} stays above IC_{\min} .

In conclusion, both fixed and bodyweight-based dosing give an exposure that is far above IC_{\min} and therefore give similar clinical benefit and risks. Therefore, we argue that for panitumumab – as for most Mabs in oncology – no dosing strategy is to be preferred over the other. If one should be preferred, it should be the fixed dosing strategy for several reasons.^{2,5} This is in accordance with the recently FDA and EMA approved fixed doses of nivolumab and pembrolizumab.

Disclosure

The authors declare no conflicts of interest in this communication.

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