Clinical Pharmacology: Advances and Applications

Dovepress

open access to scientific and medical research

Open Access Full Text Article

LETTER

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

This article was published in the following Dove Press journal:
Clinical Pharmacology: Advances and Applications

Jeroen JMA Hendrikx[1–3]
Jos H Beijnen[1]
Alwin DR Huitema[1–3]

[1]Department of Pharmacy & Pharmacology, The Netherlands Cancer Institute, Amsterdam, The Netherlands; [2]Department of Nuclear Medicine, The Netherlands Cancer Institute, Amsterdam, The Netherlands; [3]Department of Clinical Pharmacy, University Medical Center Utrecht, Utrecht University, Utrecht, The Netherlands

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 ($CV_{AUCmean}$) 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 µg/mL.[1] The authors compared the $CV_{AUCmean}$ 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 µg*d/mL, respectively, in Table 2)[1], it is likely that C_{min} of the both strategies is comparable (~20–30 µg/mL and »IC_{min}) and, therefore, both strategies have equivalent efficacy.

The reported difference in $CV_{AUCmean}$ 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 µg*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 ≥2.5 mg/kg.[3,4] As onset of ≥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

Correspondence: Jeroen JMA Hendrikx
Department of Pharmacy & Pharmacology, The Netherlands Cancer Institute, Plesmanlaan 121, Amsterdam 1006 BE, The Netherlands
Tel +31 205 127 948
Email J.Hendrikx@nki.nl

submit your manuscript | www.dovepress.com
DovePress
http://doi.org/10.2147/CPAA.S282866

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.

References

1. Liao MZ, Berkhout M, Prenen H, Dutta S, Upreti VV. Dose regimen rationale for panitumumab in cancer patients: to be based on body weight or not. *Clinical Pharmacology*. 2020;12:109–114.
2. Hendrikx JJMA, Haanen JBAG, Voest EE, Schellens JHM, Huitema ADR, Beijnen JH. Fixed dosing of monoclonal antibodies in oncology. *Oncologist*. 2017;22(10):1212–1221. doi:10.1634/theoncologist.2017-0167
3. Ketzer S, Schimmel K, Koopman M, Guchelaar HJ. Clinical pharmacokinetics and pharmacodynamics of the epidermal growth factor receptor inhibitor panitumumab in the treatment of colorectal cancer. *Clin Pharmacokinet*. 2017;57(4):455–473.
4. European Medicines Agency (EMA). Vectibix - EPAR scientific discussion, dated 2007 and EPAR product information; 2020. Available from: http://www.ema.europa.eu. Accessed September 3, 2020.
5. Heinhuis KM, Barkman HJ, Beijnen JH, Hendrikx JJMA. A cost analysis study of the implementation of fixed-dosing of monoclonal antibodies in the Netherlands Cancer Institute. *Int J Clin Pharm*. 2020. doi:10.1007/s11096-020-01131-z