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SHORT COMMUNICATION

Hyperhydration with cisplatin does not influence pemetrexed exposure

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Pemetrexed is a cytotoxic drug for first-line treatment of lung cancer. It is often combined with other anticancer drugs such as cisplatin or carboplatin. In clinical practice, hyperhydration regimens are applied to overcome cisplatin-related nephrotoxicity. As pemetrexed is almost completely eliminated from the body by the kidneys, hyperhydration can result in augmented clearance. Furthermore, administration of large quantities of fluid may increase the volume of distribution of pemetrexed. Pharmacokinetics and, thus, efficacy and toxicity may be influenced by hyperhydration. This has not yet been properly studied. We performed a population pharmacokinetic analysis to assess hyperhydration as a covariate for pemetrexed clearance and for volume of distribution A relevant change was defined as >25% increase in clearance or volume of distribution. In our extensive dataset of 133 individuals, we found that hyperhydration did not significantly or relevantly explain variability in pemetrexed clearance (unchanged, $P = .196$) or volume of distribution (+7% change, $P = .002$), despite a power of >99% to detect a relevant change. Therefore, dose adjustments of pemetrexed are not required during hyperhydration with cisplatin.

KEYWORDS

hyperhydration, pemetrexed, pharmacokinetics

The authors confirm that the PI for this paper is Rob ter Heine and that he had direct clinical responsibility for patients.

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1 | INTRODUCTION

Pemetrexed is a multitargeted folate antagonist, used for first-line treatment of advanced nonsmall cell lung cancer and mesothelioma. During induction treatment, pemetrexed is administered in combination with either carboplatin or cisplatin and, often, also immune checkpoint inhibition.[1,2] Both pemetrexed and platinum clearance, and thus exposure, is highly dependent on renal function.[3,4] Earlier, we described a case of a patient who tolerated combination therapy of pemetrexed with cisplatin and hyperhydration very well, but experienced severe side effects during all cycles of pemetrexed monotherapy.[5] Hyperhydration is routinely used to ensure adequate diuresis and clearance during treatment with cisplatin to avoid nephrotoxicity.[3] One of the proposed mechanisms is that forced diuresis enhances cisplatin excretion by enhancing renal blood flow and filtration, and decreasing the contact time of cisplatin and renal tubules.[3] Moreover, one could hypothesize that hyperhydration can affect central volume of distribution, thereby decreasing pemetrexed peak plasma concentrations. For example, for high-dose methotrexate a 1.4-fold higher peak plasma level was measured with a low hydration regimen compared to a high hydration regimen, supporting the hypothesis of increased apparent volume of distribution.[6] Altogether, although literature is scarce on this matter, it may be postulated that hyperhydration can influence the pharmacokinetics (PK) of renally cleared drugs, such as pemetrexed.[7]

As systemic exposure to pemetrexed may impact both toxicity and efficacy of pemetrexed,[8] it is paramount to elucidate the effect of comedication and hydration on its PK. Early and small phase-I studies investigated the PK of pemetrexed in combination with cisplatin only as a secondary objective with unknown power.[9,10] As it stands, there is no conclusive evidence regarding the effect of cisplatin hyperhydration schedules on the PK of pemetrexed. Therefore, the objective of this comprehensive PK analysis was to investigate the impact of hyperhydration on pemetrexed exposure.

What is already known about this subject

- Pemetrexed is a cytotoxic agent that is mainly eliminated from the body by the kidneys.
- Pemetrexed is often combined with cisplatin and hyperhydration regimens, which may influence clearance and distribution volume and, thus, efficacy or toxicity of pemetrexed.

What this study adds

- Pemetrexed pharmacokinetics are not relevantly altered when combined with cisplatin and hyperhydration regimens.

2 | METHODS

2.1 | Data

To obtain a rich PK dataset of pemetrexed data from different sources were combined (phase-I data from the manufacturer and PK data from NL6889,[11] NCT03655821 and NCT03656549,[12,13] and the PERSONAL cohort[14]). For each subject, the following information was incorporated in the dataset: dose, infusion duration, sampling times and plasma concentrations of pemetrexed, sex, age, weight, height, body surface area, serum creatinine and estimated glomerular filtration rate (eGFR), calculated with the Chronic Kidney Disease–Epidemiology Collaboration (CKD-EPI) equation.[15] For all patients that received cisplatin and hyperhydration, information regarding the hyperhydration regimen used was collected.

2.2 | PK analysis

A compartmental PK analysis was performed by means of nonlinear mixed-effect modelling using the software package NONMEM V7.4 (Icon, Dublin, Ireland). A previously developed model for pemetrexed[4] was fitted to the data. In the model, eGFR at baseline (thus unaffected by hyperhydration) was a covariate for clearance of pemetrexed. After the base model was fitted, hyperhydration was investigated as a binary covariate on clearance and on central volume of distribution, using $P < .05$ as a level of significance. We defined + 25% as a clinically relevant change in clearance or volume of distribution. This was based on a previously proposed efficacy target range AUC of 164 mg h/L ± 25% by Latz *et al.* (2006)[8] and on what is deemed relevant in clinical practice: dose reductions of cytotoxic agents are often done in 25% decrements, resulting in the same fraction of difference in exposure. A *posthoc* power calculation was performed in case of nonsignificant result, to assess the power to detect a clinically relevant difference (+25%) with the final dataset at a significance level of 0.05, by means of stochastic simulation and re-estimation, using 1000 replicates of our dataset.

3 | RESULTS

3.1 | Data

The final dataset consisted of PK data of 133 individuals with 140 dose events with a total of 981 paired observations of time and pemetrexed plasma concentrations. Study subjects had a median age of 65 years (range 25–82) and baseline eGFR of 87.9 mL/min/1.73m^2 (range 7.5–197.3). Of the 140 pemetrexed dose events, 36 were in combination with cisplatin and hyperhydration. The remaining pemetrexed dosing events were administered without hyperhydration, either as monotherapy or in combination with carboplatin.

Hyperhydration regimens were part of standard care and differed per hospital. Schedules consisted of 2000–4000 mL of fluids administered over a range of 4–18 hours. Fluids consisted of either sodium chloride (NaCl) 0.9% or glucose 2.5%-NaCl 0.45% with or without added electrolytes. See Table 1 for subject characteristics per dataset.

3.2 | PK analysis

The previously used 3-compartment model with eGFR (calculated with the CKD-EPI equation) as a linear covariate on renal pemetrexed clearance fitted well to the data. Nonrenal clearance and renal clearance of pemetrexed were estimated at 0.79 L/h (24% relative standard error) and 3.32 L/h (6% relative standard error), respectively. See Table S1 and Figures S1 and S2 for detailed results of the PK analysis. Addition of hyperhydration as a binary covariate on clearance of pemetrexed did not result in a better model fit ($P = .196$) nor a decrease in inter-individual variability in clearance. Figure 1 shows the empirical Bayes estimates for clearance of pemetrexed in the subjects with and without hyperhydration regimens (normalized to an eGFR of 90 mL/min). Our *posthoc* power calculation showed that, with our dataset, we had a power of >99% to detect a 25% increase in

TABLE 1 Characteristics of study subjects presented as median [range] unless otherwise specified

	NL6889	NCT03655821 NCT03656549	PERSONAL	Manufacturer	Total
Subjects	4	67	15	47	133
Dose events	5	68	19	48	140
Age (y)	61 [58–67]	65 [29–82]	67 [43–77]	62 [25–79]	65 [25–82]
CKD-EPI baseline (mL/min/1.73m^2)	102.5 [90.0–111.0]	90.1 [7.5–197.3]	99.7 [53.9–134.2]	68.2 [12.2–128.1]	87.9 [7.5–197.3]
Pemetrexed dose (mg/m^2)	502 [493–506]	498 [130–590]	500 [463–519]	500 [149–610]	500 [130–610]
Hydration[a]					
Yes *n* (%)	4 (80.0)	13 (19.1)	15 (100.0)	0	36 (25.7)
No *n* (%)	1 (20.0)	55 (80.9)	0	48 (100.0)	104 (74.3)
Administered hydration regimens (mL) [b]	4 × 1000	4 × 1000 2 × 1000 3 × 1000 6 × 1000	4 × 1000	-	-
Hydration time (h)[b]	16	16 4 14 18	12	-	-

[a]Relative to amount of dose events.

[b]Hydration regimens differed between hospitals. NCT03655821 and NCT03656549 included multiple study sites.

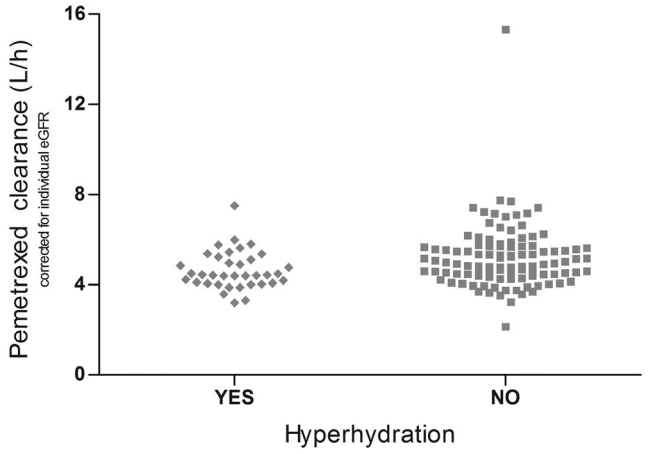

FIGURE 1 Hydration *vs*. empirical Bayes estimates for systemic pemetrexed clearance. Each square represents an individual estimate for clearance normalized to an estimated glomerular filtration rate (eGFR) of 90 mL/min to account for effect of renal function on clearance

clearance due to hyperhydration. Hyperhydration was not included in the model as covariate on central volume of distribution, as it resulted in a clinically irrelevant 7% increase in central volume of distribution ($P = .002$) with no decrease in interindividual variability.

4 | DISCUSSION

Our study describes a comprehensive PK analysis of pemetrexed in which the effect of hyperhydration on clearance and volume of distribution was investigated. We could not identify a significant or relevant increase in systemic pemetrexed clearance or volume of distribution in patients with hyperhydration. Our hypothesis was that forced diuresis could increase renal excretion of pemetrexed, possibly compromising exposure. Renal clearance of pemetrexed consists of both glomerular filtration and active transport.[7] Mita *et al*. (2006) reported tubular secretion to be the predominant mechanism of pemetrexed clearance in case of adequate renal function. Interestingly, with decreasing renal function, glomerular filtration becomes the primary mechanism of pemetrexed elimination.[7] We identified a population pemetrexed clearance (4.1 L/h) to be lower than the median eGFR (5.7 L/h) in our dataset. Only the unbound fraction (~20%) can be cleared from plasma, which might explain these findings. Also, hyperhydration can influence glomerular filtration rate.[3] Since pemetrexed is predominantly actively secreted in patients with adequate renal function, this might be a limiting step in clearance. On a side note, it should be mentioned that eGFR remains to be an estimate of glomerular filtration rate, which is very sensitive to factors such as muscle mass; thus, this comparison must be interpreted with caution.

In a phase-I dose escalation study ($n = 21$), Dickgreber *et al*. (2009) performed a PK analysis of pemetrexed in combination with cisplatin (75 mg/m^2). They reported that PK parameters of pemetrexed were comparable to those found when pemetrexed was administered as single agent in other studies.[9,16] Furthermore, Thödtmann *et al*. performed an explorative noncompartmental PK analysis in their phase-I study of pemetrexed in 2 small cohorts ($n = 4$ and $n = 11$, respectively). In cohort 1, patients received pemetrexed, 3000 mL hydration and cisplatin on day 1, in cohort 2 they received pemetrexed on day 1, and 3000 mL hydration and cisplatin on day 2. They did not find changes in pemetrexed PK between both groups.[10] Both phase-I studies were small and only investigated pemetrexed PK as a secondary objective with unknown power. We additionally investigated the effect of hyperhydration on volume of distribution, as peak plasma concentrations could be a determinant for efficacy (which also applies to pemetrexed's structural analogue methotrexate[17]). A significant increase of 7%, however, was not considered relevant. For other renally excreted drugs coadministered with cisplatin and hyperhydration, some small PK studies have been performed. No effects have been reported of hyperhydration on topotecan and (medium dose) methotrexate PK.[18,19]

There are a few limitations to our study. The first is that the effect of cisplatin or hyperhydration cannot be distinguished. Theoretically, with the acute nephrotoxic potential of cisplatin,[3] exposure to pemetrexed could also increase. This was not observed in our data. Moreover, there was a substantial variety in the used hyperhydration regimens with relatively long duration. One may argue that intensifying the hyperhydration schedule by shortening the duration, could affect pemetrexed PK. If so, this could be used as an advantage in case of expected toxicity. Lastly, this retrospective analysis included more patients than previous studies but is a relatively small sample size considering the current treatment population. Nonetheless, in a *posthoc* analysis, we showed that we had a high power (>99%) to detect a relevant change in clearance.

Altogether, in our elaborative dataset we could not show increased clearance of pemetrexed in patients receiving hyperhydration with cisplatin treatment. Although absence of evidence is not evidence of absence, it is highly unlikely that hyperhydration as used with cisplatin results in increased clearance of volume of distribution of pemetrexed, considering the high power of our study to detect a relevant difference. Exposure of pemetrexed does not seem influenced when combined with cisplatin and hyperhydration regimens.

4.1 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, and are permanently archived in the Concise Guide to PHARMACOLOGY 2019/20 (Alexander *et al*., 2019 a,b).

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COMPETING INTERESTS

See also COI forms. N.d.R., H.D., R.B., S.C., A.H., D.B., S.K., L.H., M.v.d.H., B.B., R.t.H.: Nothing to disclose. B.P.: Dr Piet reports other from Takeda, other from Bristol Meyer Squibb, other from Astra Zeneca, other from Pfizer, outside the submitted work. J.B.: Dr Burgers reports other from MSD, other from Roche, other from AstraZeneca, outside the submitted work. J.A.: Dr Aerts reports personal fees and nonfinancial support from MSD, personal fees from BMS, personal fees from Boehringer Ingelheim, personal fees from Amphera, personal fees from Eli Lilly, personal fees from Takeda, personal fees from Bayer, personal fees from Roche, personal fees from Astra Zeneca outside the submitted work. In addition, Dr Aerts has a patent allogenic tumour cell lysate licensed to Amphera, a patent combination immunotherapy in cancer pending, and a patent biomarker for immunotherapy pending. A.D.: Consulting/advisory role for Roche, Eli Lilly, Boegringer Ingelheim, Astra Zeneca, Pfizer, BMS, Amgen, Novartis, MSD, Takeda, Pharmamar, Sanofi, outside the submitted work. L.H.: Dr Hendriks reports other from boehringer ingelheim, other from BMS, other from Roche Genentech, grants from Roche Genentech, grants from Boehringer Ingelheim, other from AstraZeneca, personal fees from Quadia, grants from Astra Zeneca, other from Eli Lilly, other from Roche Genentech, other from Pfizer, other from MSD, other from Takeda, nonfinancial support from AstraZeneca, nonfinancial support from Novartis, nonfinancial support from BMS, nonfinancial support from MSD/Merck, nonfinancial support from GSK, nonfinancial support from Takeda, nonfinancial support from Blueprint Medicines, nonfinancial support from Roche Genentech, other from Amgen, nonfinancial support from Janssen Pharmaceuticals, outside the submitted work. A.M.: Dr Mathijssen reports grants from Astellas, grants from Bayer, grants from Boehringer-Ingelheim, grants from Cristal Therapeutics, grants from Pamgene, grants from Pfizer, grants from Novartis, grants from Roche, grants from Sanofi, grants from Servier, outside the submitted work; In addition, Dr Mathijssen has a patent Pamgene pending.

CONTRIBUTORS

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ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Protocols were approved by local medical ethics committees at each institution and if applicable for the study, consent was obtained from the participants.

The manufacturer shared the data through Clinical Study Data Request.

Studies were performed in accordance with the Declaration of Helsinki.

DATA AVAILABILITY STATEMENT

Part of the data is available on request from the authors. Part of the data was made available from Eli Lilly. Restrictions apply to the availability of these data, which were used under license for this study. Data were requested via www.ClinicalStudyDataRequest.com with the permission of Eli Lilly.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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