Development and evaluation of a predictive model of hyperphosphatemia induced by inhibition of FGFR by extending an existing multiscale systems pharmacology approach

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Abstract

OBJECTIVES: Fibroblast growth factor receptor (FGFR) inhibition has been investigated as a potential target for treating cancer. Hyperphosphatemia (HP) has been observed clinically following FGFR inhibition due to its role in regulating phosphate (P) balance through FGF23, which regulates urinary P excretion and indirectly impacts dietary P absorption and calcitriol (C) production. 

An existing systems pharmacology model was leveraged to explore the role of HP circumvention by extending an existing andropharmacologically based model to evaluate the impact of FGFR inhibition on phosphate balance.

METHODS: A systems pharmacology model (Bone. 2010) was extended to describe changes in serum P, parathyroid hormone (PTH), and FGF23 following oral ASPPS878 administration. The model evaluated concomitant P binder and impact of varied dosing regimens on exposure-related P changes. Analyses were conducted in R; simulation and estimation included mgno1 and minqa. QD and BID ASPPS878 dosing, total daily dose, and intermittent, 5 days on / 2 off, and 4 days on / 3 off, regimens were considered.

RESULTS: ASPPS878 PK followed a 1 compartment model (typical t1/2 = 2.63h). Added mathematical descriptions included: FGF23 control urinary P, PTH and C production, with feedback on FGF23 production from P and C. P binder was estimated to decrease its dietary bioavailability by up to 32%. The extended model described the time-course and magnitude of dose-related increases observed for P, C, FGF23 and PTH, including P > 6 mg/dl at doses ≥ 32 mg/day. P binder was predicted to mildly alleviate the increase at targeted doses. Efficacious response was not obtained by any simulated regimen that minimized to acceptable P.

CONCLUSIONS: Results from the extended systems model supported program termination.

Methods

1. Systems pharmacology model [1] extension with population PK for exposure-response on serum phosphate, calcium, parathyroid hormone (PTH), and FGF23 following oral ASPPS878 administration. See QR code for further details.
2. Evaluated concomitant P binder and impact of varied dosing regimens on exposure-related P changes.
3. Population PK model development in NONMEM®. All other analyses were conducted in R [2]; simulation and estimation included mgno1 and minqa [4].
4. Simulations:
   • Can dose-adjustments, with or without P binder, avoid hyperphosphatemia? (See QR code)
   • Simulation scenarios: QD and BID ASPPS878 dosing, total daily dose, and intermittent, 5 days on / 2 off, and 4 days on / 3 off, with and without P binder. Figure 5

Conclusion

• Extension of systems pharmacology model allowed for characterization of FGFR inhibition on multiple physiologically-based homeostatic mechanisms for phosphate balance.
• The impact of phosphate binder concomitant treatment could also be integrated into the systems model.
• Serum phosphate response to FGFR inhibitor therapy was associated with drug exposure and the magnitude and time-course of these changes was predicted to be influenced by the dosing regimen.

Results from the extended systems model supported program termination.

References


Model Code and Additional Supporting Information

Figure 1: Multiscale physiologic model, reproduced from Peterson and Riggs [1] with proposed modifications and extensions noted.

Figure 2: Extensions to describe FGFR/FGF23 control of phosphate homeostasis.

Figure 3: Phosphate by regimen; reference lines at 5.5, 6 and 7 mg/dl.

Figure 4: Calcitriol by regimen

Figure 5: Simulated phosphate response for candidate regimens with and without phosphate binder effect

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