Comparative Analysis of Pharmacokinetics of Oncology Drugs between Health Subjects and Patients with Cancer

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Introduction

There has been an increased use of healthy subjects (HS) in early oncology drug development (e.g., rBA, food effect). The results of dedicated pharmacokinetic (PK) studies in HS can provide insight into drug characteristics and facilitate optimized clinical studies in patients with cancer (PC).

Higher observed PK variability is reported in PC compared to HS for targeted oncology drugs[1]. The altered CYP expression caused by tumor-associated inflammation has been considered as one of the physiological differences between HS and PC, contributing to the PK difference between PC and HS[2].

Here, we investigate orally administered small molecule oncology drugs that have been tested in both PC and HS to compare and quantify the PK differences (e.g., AUC, CL) and identify physiological and mechanistic reasons to account for the PK differences between the two populations

Methods

Small molecule oral oncology drugs were compiled based on new drug applications approved from 1999 to 2022. PK parameter data, specifically drug clearance (CL), for PC were primarily obtained from US prescribing information, while PK data for HS were obtained from clinical studies reviewed in FDA new drug applications. When information on clinical studies was unavailable, other health authority documents, such as the EMA assessment report, and published literature were used.

The PK parameters were collected taking various study design factors into account, including food effects, dose linearity, and formulation effect, to ensure valid comparisons between HS and PC. We included drugs for which CL data were available for both HS and PC. For drugs without directly reported CL data, CL is derived by calculating from available AUC and dose data.

A meaningful numerical difference was determined when the CL of the HS to PC ratio exhibited a greater than 25% difference (i.e., the ratio was outside the range of 0.8-1.25).

Drug characteristics and properties (i.e., $f_{u,p}$, $f_{m,CYP3A4}$) were also obtained primary from the University of Washington Drug Interaction Database (UW DIDB) to understand the mechanistic and physiological reasons to account for the PK difference between HS and PC.

Results

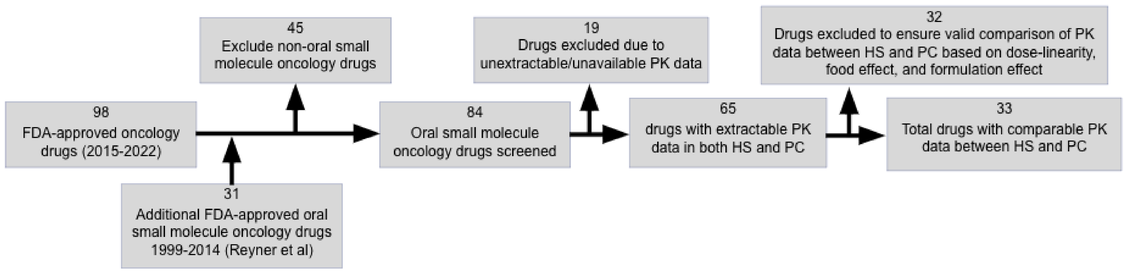

Fig 1. Flow diagram for inclusion and exclusion of oral small-molecule drugs in oncology

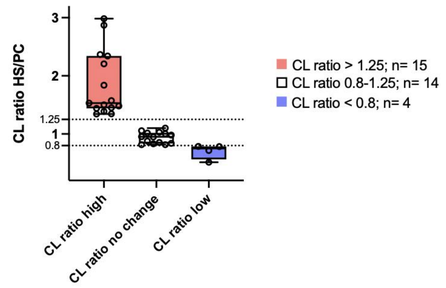

Fig 2. Identified 33 orally dosed small molecule oncology drugs out of 129 drugs approved by the FDA from 1999 to 2022, with high-quality extractable PK data. Among these, 15, 14, and 4 drugs show higher, comparable, and lower CL ratios between HS and PC, respectively.

Factors that are important to PK difference between HS and PC

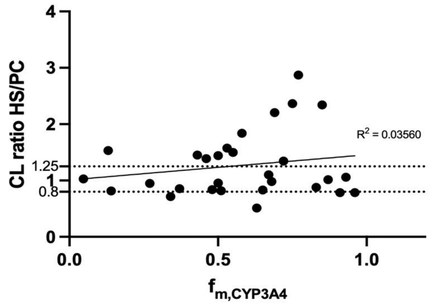

Fig 3. Impact of fraction metabolized by CYP3A4 ($f_{m,\ CYP3A4}$) on CL ratio (HS/PC): Of the 33 orally dosed small molecule oncology drugs identified, 31 are CYP3A4 substrates, and 29 drugs have available dedicated clinical DDI studies with strong CYP3A4 inhibitor. Drugs with greater $f_{m,\ CYP3A4}$ show a trend of lower CL in PC compared to HS.

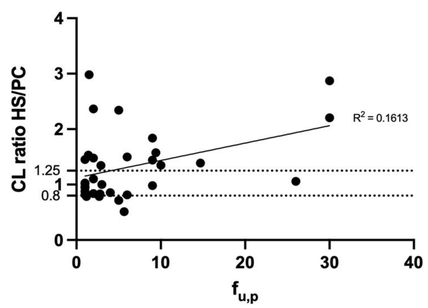

Fig 4. Impact of unbound fraction in plasma ($f_{u,p}$) on CL ratio (HS/PC): Of the 33 drugs identified, drugs with the greater $f_{u,p}$ show a trend of lower CL in PC compared to HS.

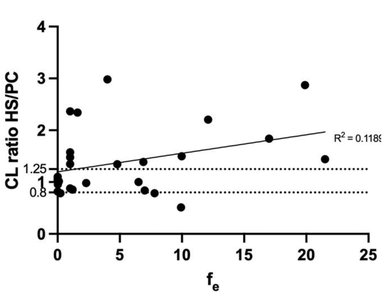

Fig 5. Impact of fraction excreted unchanged in urine (f_e) on CL ratio (HS/PC): f_e is available for 27 of the 33 drugs identified. Drugs with greater f_e show a trend of lower CL in PC compared to HS.

Factors that are less important

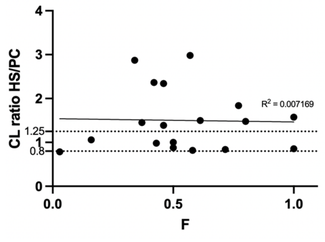

Fig 6. Impact of absolute bioavailability (F) on CL ratio (HS/PC): F is available for 18 of the 33 drugs identified. The absence of a clear trend in the data indicates that F may not explain the PK difference between PC and HS.

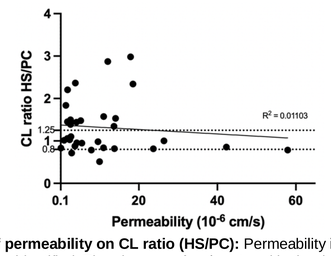

Fig 7. Impact of permeability on CL ratio (HS/PC): Permeability is available for 32 of the 33 drugs identified. The absence of a clear trend in the data indicates that permeability may not explain the PK difference between PC and HS.

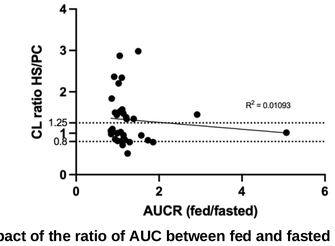

Fig 8. Impact of the ratio of AUC between fed and fasted state (AUCR) on CL ratio (HS/PC): AUCR of fed and fasted is available for all 33 drugs identified. The absence of a clear trend in the data indicates that food effect may not explain the PK difference between PC and HS.

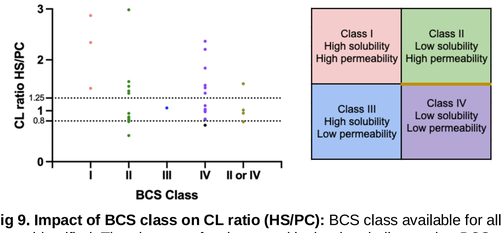

Fig 9. Impact of BCS class on CL ratio (HS/PC): BCS class available for all 33 drugs identified. The absence of a clear trend in the data indicates that BCS class may not explain the PK difference between PC and HS.

Conclusions

- CL ratio (HS/PC) was used to identify drugs that appear to show the difference between HS and PCs. Of the 33 drugs identified oral small-molecule oncology drugs, 15, 14, and 4 drugs show higher, comparable, and lower CL ratios between HS and PC, demonstrating an overall decrease in CL in PC compared to HS.
- Factors that could matter
  - Drugs with higher $f_{m,\ CYP3A4}$ show a trend of lower CL in PC relative to HS, suggesting reduced CYP3A4 enzymatic activity observed due to cancer.
  - Drugs with greater $f_{u,p}$ (less binding) show a trend of lower CL in PC relative to HS, which may be due to the changes in plasma protein levels (higher AGG and lower albumin) observed in PC. This $f_{u,p}$ effect may be influenced by drug's affinity for specific plasma protein, drug, and protein concentrations.
  - Drugs with greater f_e show a trend of lower CL in PC relative to HS, likely due to the decreased renal function commonly observed in PC.
  - While the positive trends are evident, the low R^2 value may suggest that other factors beyond $f_{m,\ CYP3A4}$, $f_{u,p}$, and f_e are also influencing the PK difference between HS and PC.
- Factors that may matter less
  - The differences in drug CL between HS and PC do not seem to be explained by absolute bioavailability (F), permeability, BCS class, or food effect, indicating drug absorption may not be the main mechanism for PK difference between HS and PC.

References

1. Reyner E, et al. Intrinsic and Extrinsic Pharmacokinetic Variability of Small Molecule Targeted Cancer Therapy. Clin Transl Sci. 2020

2. Schwenger E, Reddy VP, Moorthy G, et al. Harnessing Meta-analysis to Refine an Oncology Patient Population for Physiology-Based Pharmacokinetic Modeling of Drugs. Clin Pharmacol Ther. 2018;103(2):271-280. doi:10.1002/cpt.917