Evaluation of utility of pharmacokinetic studies
in phase I trials of two oncology drugs

Kehua Wu¹, Larry House¹, Jacqueline Ramírez¹, Michael J. Seminerio¹,², Mark J. Ratain¹,²,³

¹Departments of Medicine, ²Committee on Clinical Pharmacology and Pharmacogenomics, ³Comprehensive Cancer Center, The University of Chicago, Chicago, IL

Running Title: Utility of pharmacokinetic drug-drug interaction studies

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Corresponding Author: Mark J. Ratain, The University of Chicago, 5841 South Maryland Avenue, MC 2115, Chicago, IL 60637, USA. Phone: 773-702-4400; Fax: 773-702-3969; E-mail: mratain@medicine.bsd.uchicago.edu

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Statement of translational relevance

Drug-drug interaction studies may help prevent adverse reactions. However, the utility of these studies may be low without a mechanistic basis. After conducting a literature review of pharmacokinetic drug-drug interaction studies embedded within phase I oncology trials over a 5-year period, we found that most studies reported negative findings. We demonstrated a strong association between lack of mechanistic preclinical rationale and lack of interaction. Pharmacokinetic drug-drug interaction studies should not be routinely performed in phase I trials with co-administered oncology drugs when there is no scientific justification.
Abstract

Purpose: There are many phase I trials of oncology drug combinations, very few of which report clinically significant pharmacokinetic interactions. We hypothesized that the utility of such pharmacokinetic drug-drug interaction (DDI) studies is low in the absence of a mechanistic hypothesis.

Experimental Design: We retrospectively reviewed 152 phase I (2 drug) combination studies published in 2007-2011.

Results: Only 28 (18%) studies had an implicit or explicit rationale, either inhibition/induction of a drug metabolizing enzyme or transporter, co-substrates for the same enzyme or transporter, potential for end-organ toxicity, or protein binding. Only 12 (8%) studies demonstrated a statistically significant DDI, based on change in clearance (or area under the curve) of parent drug and/or active metabolite. There was a strong association between a rationale and a demonstrable drug interaction, as only 2% of studies without a rationale demonstrated a DDI, compared to 32% of studies with a rationale (Fisher's exact test, p<10^{-6}).

Conclusion: DDI studies should not be routinely performed as part of phase I trials of oncology combinations.
Introduction

A drug-drug interaction (DDI) refers to the changes in response (increase or decrease) to an investigational drug due to the addition of another drug (1). Approximately 20-30% of all adverse reactions are caused by DDIs (2). DDIs in oncology may be anticipated due to the common use of multidrug regimens (3). Antineoplastics generally have narrow therapeutic windows, steep dose-toxicity profiles, and high interindividual (and potentially intraindividual) variability in pharmacokinetics and pharmacodynamics all increasing the risk of a DDI. Additionally, most cancer patients are elderly, which is another risk factor for DDIs (4). Finally, the development of new drug combinations has also led to an increase in the possibility for interactions (5). Thus, the potential for DDIs should be considered during the preclinical and early clinical development phase of a new anticancer agent, especially if both drugs are orally administered (given the potential for a DDI in the gut wall).

Pharmacokinetic interactions (one kind of DDI) occur when the concentration (drug exposure) of one drug is altered by the co-administration of another drug. DDIs can occur during absorption, distribution, metabolism and/or excretion with involvement of numerous metabolizing enzymes and/or drug transporters. A patient’s response to the administration of a drug is closely associated with concentration level at the site(s) of action and is usually related to the blood or tissue concentration (6). DDIs can lead to a change in concentration and/or...
systemic exposure, resulting in variations in drug response of the co-
administered drugs and may exacerbate the adverse events.

In order to better understand the importance of DDIs, we performed a study to
evaluate the utility of pharmacokinetic DDI studies, embedded within phase I oncology trials, over a recent five-year period (2007-2011). We hypothesized that a study would have a low probability of demonstrating a DDI when a mechanistic basis is absent. The following information was collected and analyzed: rationale, study design, number of patients, number of sampling points, data analysis methods, sponsor, and authors’ conclusions.

**Materials and Methods**

A literature search was performed in the PubMed library database using the search terms: "antineoplastic combination pharmacokinetics phase-i" OR "antineoplastic combined chemotherapy protocols/pharmacokinetics" (search date: April 6, 2012; subsequent cut off time of inclusion was the end of 2011). We narrowed down our search by focusing on phase I clinical trial manuscripts containing only two antineoplastic drugs. The exclusions in our search criteria included studies that lacked pharmacokinetic DDI evaluations, combinations between drug and other forms of therapy, or any clinical trial other than phase I. The following information was extracted: study design, preclinical rationale, number of patients and samples, results of pharmacokinetic DDI study (author’s interpretation), statistical method, pharmacokinetic data analysis (non-
compartmental vs. population method), and sponsor (data collected form is shown in Supplementary Table S1; data collected are shown in Supplementary Table S2). We defined a positive DDI as a change in area under the curve (AUC) (or clearance) with a specified statistical method. If the author(s) clearly stated a rationale based on previous studies, we defined this as positive author-stated rationale. If there was no mention of a rationale by the authors, regardless of whether there is known evidence, we have defined this as a negative author-stated rationale. To assess whether there was an objectively existing rationale (independent of the author’s assessment), we utilized the Metabolism and Transport Drug Interaction Database™ (DIDB) (http://www.druginteractioninfo.org/) from the University of Washington.

Concomitant ingestion of dietary supplements, fruit juices or therapeutic proteins was beyond the scope of this study. We used Fisher’s exact test to evaluate the associations between the information collected and the DDI results.

Three of the authors (K.W., L.H., J.R.) served as reviewers, with two assigned per article. If there was a discrepancy in interpretation between the two reviewers, a meeting was convened among all three reviewers to discuss and reach a conclusion about the article.

Results

We reviewed 152 papers specific to phase I combination (2 drug) trials in oncology. The distribution of pharmacokinetic DDI results according to rationale
is represented in Table 1A and 1B. We identified 9 papers reporting a positive clinically relevant DDI with a purported pharmacokinetic mechanism (Table 2). There was a strong association between author-stated rationale and a reported interaction, as only 2% of studies without a rationale demonstrated a DDI, compared to 32% of studies with a rationale (Fisher’s exact test, $p<10^{-6}$). A similar association was observed between the DDI results and objectively existing rationale (Fisher’s exact test, $p=0.0003$, Table 1). Of the 152 papers, 22 studies (44%) were retrospectively determined to have an objectively existing rationale not noted by the authors (Table 1, 50 vs. 28).

The statistical method used to evaluate the DDI was also noted, as shown in Figure 1. Most studies (81/152), did not include a specific statistical method in their paper. Twelve papers (8%) describe a change but failed to perform any formal statistical testing. Eighteen studies (12%) employed the analysis of variance, as approved by EMEA (7). Twelve studies (8%) were evaluated with a non-parametric method (Mann-Whitney or Wilcoxon signed rank test). Thirteen (9%) studies used the confidence interval test. Only 29 (19%) papers reported the 90% or 95% confidence interval, as recommended by FDA (6). There was no association of the type of statistical analysis used by the primary investigators and the presence or absence of a detectable DDI.

We considered four types of study design in DDI studies: randomized crossover, one-sequence crossover, parallel (6) and historically controlled studies. One-
sequence crossover design was the most common, accounting for 64% of the eligible papers. The second most common was a historically controlled design (27%), in which both drugs were given together and their pharmacokinetic parameters were compared with previous reported results of monotherapy. The average number of patients ranged from 20 to 27 for these 4 study designs. According to Fisher’s exact test, the DDI results were independent of study design.

We also analyzed the impact of funding source on the probability of detecting a DDI. Although there was a slightly lower probability of a reported DDI for industry-funded studies (4/64 versus 8/88), this difference was not statistically significant. Most (94%) of the studies employed non-compartmental pharmacokinetic analysis. Ten of these studies identified a DDI. Only nine studies used population analysis, identifying two DDIs. The DDI results were independent of data analysis methods.

Discussion
We reviewed 152 phase I combination (2 drug) studies published during 2007 - 2011 to evaluate the utility of pharmacokinetic DDI studies. Our results demonstrate a direct correlation between preclinical pharmacokinetic rationale and detection of a DDI, suggesting DDI studies should only be performed when there is a prespecified plausible hypothesis. When DDI studies were performed with a clear rationale, the probability of identifying a DDI increased from 8% to
32% (12/152 to 9/28, Table 1). Furthermore, we determined that statistical
methods, study designs and funding resources are unrelated to the DDI results.
The overall impact and application of these findings can potentially expedite the
new drug development process and reduce costs benefiting both the industry
and academic sectors. Moreover, patients will directly benefit from bypassing
needless and intensive blood draws.

Recently, the FDA released a draft regulation for industry regarding drug
interaction studies. FDA suggests using both in vitro and in vivo studies to
evaluate the plausibility of drug interactions. Results from in vitro studies are
suggested as a screening mechanism to determine if additional in vivo studies
are necessary (6). This draft guidance includes several decision trees to help
determine if an in vivo pharmacokinetic DDI study is indeed necessary.
According to the decision trees, the interacting drug should be selected based
upon the results of an in vitro experiment (pharmacokinetic mechanism-based
rationale). For example, if the investigational drug is a substrate of an enzyme
responsible for at least 25% of its systemic clearance, in vivo studies should be
performed with a strong inhibitor/inducer to evaluate the interactions. The
majority of papers included herein evaluated two drug combinations of
therapeutic interest, rather than combinations hypothesized to have a DDI.
Because of this issue, the vast majority (92%) did not identify a DDI. During our
evaluation, we found three studies reporting a DDI, despite no prespecified
rationale (Table 2). In particular, one study investigated the interaction between
nilotinib and imatinib in which a reduction in nilotinib clearance was observed (8).

This was likely attributed to an inhibition of CYP3A4-mediated metabolism of nilotinib by imatinib (9,10), an interaction that could really have been hypothesized as a rationale for the study.

We recommend following FDA Guidance, utilizing preclinical models to assess whether a DDI is plausible, and if so, incorporating appropriately designed pharmacokinetic studies into early clinical trials of the combination (6). For example, the FDA recommends the use of basic, mechanistic static, and physiological based pharmacokinetic models for predicting DDIs. Moreover, a Bayesian meta-analysis approach may improve efficiency by incorporating previously published pharmacokinetic and in vitro experimental data for both investigational and interacting drugs (11,12).

Only 19% of the studies evaluated herein employed confidence intervals to evaluate a change in pharmacokinetics. This is of concern, given that FDA recommends use of 90% confidence intervals for the geometric mean ratio of the observations before and after the addition of the interacting drug. An analysis of variance together with confidence interval is acceptable to EMEA (7).

There were 3,663 patients enrolled in these 152 studies from 2007-2011 and approximately 70,000 pharmacokinetic samples were analyzed for an estimated total expense of approximately seven million dollars (based on an estimated cost on May 3, 2017. © 2013 American Association for Cancer Research. clincancerres.aacrjournals.org Downloaded from
of $100 per sample for study initiation, sample collection, preanalytical processing and analysis). It was determined that more than 75% of this expense could have been avoided, as there was no plausible rationale for a pharmacokinetic DDI. Furthermore, only 28 studies (18%) had a prespecified author-stated rationale further suggesting that the majority of the expenses could have been bypassed.

As noted in the methods, only phase I clinical trials which investigated the pharmacokinetic interaction between two antineoplastic drugs were evaluated in this study. We recognize that most cancer patients take supplemental drugs, potentially altering the results of DDI studies. Additionally, food has been shown to interact with a myriad of drugs. We understand these variables could confound the results of DDI studies and represent a possible study limitation. Nevertheless, the importance and underlying finding of this study should not be overlooked. Since the number of two drug combinations is proportional to the square of the number of available drugs, there has been a very large increase in the number of two drug combinations tested in recent years. Although DDI studies are often performed in conjunction with such studies, these are often perfunctory studies without preclinical rationale. As shown by our results, the utility of these DDI studies is low, adding complexity and expense to early clinical trials without any meaningful results. Furthermore, such studies do not appear to be a regulatory requirement in the absence of scientific justification. This analysis
demonstrates the importance of understanding the mechanism behind a DDI and the value to which this translates clinically.

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Authors’ Contributions

Conception and design: M.J. Ratain

Development of methodology: K. Wu, L. House, J. Ramírez, M.J. Ratain

Acquisition of data: K. Wu, L. House, J. Ramírez, M.J. Ratain

Analysis and interpretation of data: K. Wu, L. House, J. Ramírez, M.J. Ratain

Writing, review and/or revision of the manuscript: K. Wu, L. House, J. Ramírez, M.J. Seminerio, M.J. Ratain

Study supervision: M.J. Ratain
References


Table 1. Distribution of pharmacokinetic DDI results (A) with or without specific author-stated rationale, and (B) with or without specific objectively existing rationale

<table>
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<th></th>
<th>DDI</th>
<th>No DDI</th>
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<td><strong>A.</strong></td>
<td></td>
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<tr>
<td>Specific author-stated rationale</td>
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<td>19</td>
<td>28</td>
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<td>No clear author-stated rationale</td>
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<td><strong>Total number of studies</strong></td>
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<td>152</td>
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<tr>
<td><strong>B.</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Specific objectively existing rationale</td>
<td>10</td>
<td>40</td>
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<tr>
<td>No clear objectively existing rationale</td>
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<td><strong>Total number of studies</strong></td>
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<td>Drugs</td>
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<td>17473200</td>
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</tr>
<tr>
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<td></td>
<td></td>
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<tr>
<td>2007</td>
<td>17095207</td>
<td>Mross</td>
<td>irinotecan / sorafenib</td>
</tr>
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<tr>
<td>2008</td>
<td>19047120</td>
<td>Molina</td>
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<td>18414469</td>
<td>Siegel-Lakhai</td>
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<td>2009</td>
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<td>Azad</td>
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<td>irinotecan / gefitinib</td>
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<tr>
<td>2010</td>
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</tr>
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<td>2011</td>
<td>21825263</td>
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<tr>
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<td></td>
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<tr>
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<td>18519774</td>
<td>Bekaii-Saab</td>
<td>oxaliplatin / paclitaxel</td>
</tr>
</tbody>
</table>

\(^a\) The change for SU12662 C_{trough} is not specified.

\(^b\) NA indicates that the drug was not specified in the publication.
<table>
<thead>
<tr>
<th>Year</th>
<th>ID</th>
<th>Study Author</th>
<th>Drug Combination</th>
<th>Drug 1</th>
<th>Drug 2</th>
<th>Change in Drug 1</th>
<th>Change in Drug 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>2008</td>
<td>17429623</td>
<td>Jimeno</td>
<td>irinotecan / UCN-01</td>
<td>NA</td>
<td>irinotecan</td>
<td>APC AUC; SN-38 AUC; SN-38/irinotecan AUC ratio</td>
<td>↓ up to 84%; ↓ up to 60%; ↓ 50%</td>
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<tr>
<td>2009</td>
<td>19723647</td>
<td>Demetri</td>
<td>nilotinib / imatinib</td>
<td>NA</td>
<td>nilotinib</td>
<td>CL</td>
<td>↓ 53%</td>
</tr>
</tbody>
</table>

1. The magnitude of the changes was not provided.
2. No clear rationale.

Abbreviations: CAI, carboxyamidotriazole; CL: clearance; AUC: $C_{\text{trough}}$: trough concentration; $C_{\text{max}}$: maximum concentration.
Figure Legends

Figure 1. Distribution of statistical methods.
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