Evaluation of Utility of Pharmacokinetic Studies in Phase I Trials of Two Oncology Drugs

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

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 (two drug) combination studies published between 2007 and 2011.

**Results:** Only 28 (18%) studies had an implicit or explicit rationale, either inhibition/induction of a drug-metabolizing enzyme or transporter, cosubstrates for the same enzyme or transporter, potential for end-organ toxicity, or protein binding. Only 12 (8%) studies demonstrated a statistically significant DDI, on the basis of 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 with 32% of studies with a rationale (Fisher exact test; \( P < 10^{-6} \)).

**Conclusion:** DDI studies should not be routinely performed as part of phase I trials of oncology combinations. Clin Cancer Res; 19(21): 6039–43. ©2013 AACR.

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% to 30% of all adverse reactions are caused by DDIs (2). DDIs in oncology may be anticipated because of 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. In addition, most patients with cancer 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 coadministration 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 sites 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 coadministered drugs and may exacerbate the adverse events.

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 5-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 cutoff time of inclusion was the end of 2011). We narrowed down our search by focusing on phase I clinical trial articles containing only two antineoplastic drugs. The exclusions in our search criteria...
Translational Relevance

Drug–drug interaction (DDI) studies may help in preventing adverse reactions. However, the utility of these studies may be low without a mechanistic basis. After conducting a literature review of pharmacokinetic DDI 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 DDI studies should not be routinely performed in phase I trials with coadministered oncology drugs when there is no scientific justification.

Results

We reviewed 152 articles specific to phase I combination (two drug) trials in oncology. The distribution of pharmacokinetic DDI results according to rationale is represented in Table 1A and B. We identified nine articles 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 with 32% of studies with a rationale (Fisher exact test; \( P < 10^{-6} \)). A similar association was observed between the DDI results and objectively existing rationale (Fisher exact test; \( P = 0.0003 \); Table 1).

Of the 152 articles, 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 Fig. 1. Most studies (81 of 152) did not include a specific statistical method in their article. Twelve articles (8%) describe a change but failed to perform any formal statistical testing. Eighteen studies (12%) used the ANOVA, as approved by the European Medicines Agency (EMEA) (7). Twelve studies (8%) were evaluated with a nonparametric method (Mann–Whitney or Wilcoxon signed rank test). Thirteen (9%) studies used the confidence interval (CI) test. Only 29 (19%) articles reported the 90% or 95% CI, as recommended by the U.S. Food and Drug Administration (FDA; ref. 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 designs 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 articles. 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 four study designs. According to the Fisher 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

<p>| Table 1. Distribution of pharmacokinetic DDI results (A) with or without specific author-stated rationale and (B) with or without specific objectively existing rationale |
|-----------------|-------|-------|-------|
|                  | DDI   | No DDI| Total number of studies |
| Specific author-stated rationale | 9     | 19    | 28 |
| No clear author-stated rationale | 3     | 121   | 124 |
| Total number of studies | 12    | 140   | 152 |
| Specific objectively existing rationale | 10    | 40    | 50 |
| No clear objectively existing rationale | 2     | 100   | 102 |
| Total number of studies | 12    | 140   | 152 |</p>
<table>
<thead>
<tr>
<th>Year published</th>
<th>PMID</th>
<th>First author</th>
<th>Drugs</th>
<th>Enzyme or transporter involved in the pharmacokinetic DDI (rationale)</th>
<th>Affected drug</th>
<th>Affected parameter</th>
<th>Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>2007</td>
<td>17473200</td>
<td>Adjei</td>
<td>sorafenib/gefitinib</td>
<td>CYP3A4</td>
<td>gefitinib</td>
<td>C&lt;sub&gt;max&lt;/sub&gt; and AUC</td>
<td>26% and 38%</td>
</tr>
<tr>
<td>2007</td>
<td>17095207</td>
<td>Moss</td>
<td>irinotecan/sorafenib</td>
<td>CYP3A4</td>
<td>irinotecan</td>
<td>irinotecan AUC; SN-38 AUC</td>
<td>up to 42%; up to 120%</td>
</tr>
<tr>
<td>2008</td>
<td>19047120</td>
<td>Molina</td>
<td>lapatanib/topotecan</td>
<td>BCRP and Pgp</td>
<td>topotecan</td>
<td>AUC</td>
<td>18%</td>
</tr>
<tr>
<td>2008</td>
<td>18414469</td>
<td>Siegel-Lakhai</td>
<td>indisulam/capecitabine</td>
<td>CYP2C9</td>
<td>indisulam</td>
<td>exposure</td>
<td>up to 300%</td>
</tr>
<tr>
<td>2009</td>
<td>19738417</td>
<td>Azad</td>
<td>CAI/paclitaxel</td>
<td>CYP3A4</td>
<td>CAI</td>
<td>C&lt;sub&gt;trough&lt;/sub&gt;</td>
<td>115%</td>
</tr>
<tr>
<td>2009</td>
<td>19687340</td>
<td>Furman</td>
<td>irinotecan/gefitinib</td>
<td>ABCG2</td>
<td>irinotecan</td>
<td>irinotecan CL; SN-38 CL</td>
<td>37% and 38%</td>
</tr>
<tr>
<td>2010</td>
<td>20091169</td>
<td>Chiorean</td>
<td>paclitaxel/vatalanib</td>
<td>CYP3A4 and CYP2C8</td>
<td>paclitaxel</td>
<td>CL</td>
<td>38%</td>
</tr>
<tr>
<td>2010</td>
<td>20485286</td>
<td>Hamberg</td>
<td>sunitinib/fosfamide</td>
<td>CYP3A</td>
<td>sunitinib</td>
<td>SU12662 C&lt;sub&gt;trough&lt;/sub&gt;</td>
<td>9%</td>
</tr>
<tr>
<td>2011</td>
<td>21825263</td>
<td>Hofmeister</td>
<td>lenalidomide/CCI-779</td>
<td>Pgwp</td>
<td>lenalidomide</td>
<td>CL</td>
<td>49%</td>
</tr>
<tr>
<td>2008</td>
<td>18519774</td>
<td>Bekai-Saab</td>
<td>oxaliplatin/paclitaxel</td>
<td>NA&lt;sup&gt;b&lt;/sup&gt;</td>
<td>oxaliplatin</td>
<td>CL</td>
<td>~50%</td>
</tr>
<tr>
<td>2008</td>
<td>17429623</td>
<td>Jimeno</td>
<td>irinotecan/UCN-01</td>
<td>NA&lt;sup&gt;b&lt;/sup&gt;</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>
</tr>
<tr>
<td>2009</td>
<td>19736647</td>
<td>Demetri</td>
<td>nilotinib/matinib</td>
<td>NA&lt;sup&gt;b&lt;/sup&gt;</td>
<td>nilotinib</td>
<td>CL</td>
<td>53%</td>
</tr>
</tbody>
</table>

Abbreviations: CAI, carboxamidotriazole; CL, clearance; AUC, area under curve; C<sub>trough</sub>, trough concentration; C<sub>max</sub>, maximum concentration.

<sup>a</sup>The magnitude of the changes was not provided.

<sup>b</sup>No clear rationale.
studies (4 of 64 vs. 8 of 88), this difference was not statistically significant. Most (94%) of the studies used noncompartmental 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 (two drug) studies published from 2007 to 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 that 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 can 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 about 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 in determining if an in vivo pharmacokinetic DDI study is indeed necessary. According to the decision trees, the interacting drug should be selected on the basis of 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 articles 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, using 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 physiologic 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 used CIs to evaluate a change in pharmacokinetics. This is of concern, given that FDA recommends use of 90% CIs for the geometric mean ratio of the observations before and after the addition of the interacting drug. ANOVA, together with CI, is acceptable to EMEA (7).

There were 3,663 patients enrolled in these 152 studies from 2007 to 2011 and approximately 70,000 pharmacokinetic samples were analyzed for an estimated total expense of approximately seven million dollars (on the basis of an estimated cost of $100 per sample for study
initiation, sample collection, preanalytic 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 Materials and Methods, only phase I clinical trials that investigated the pharmacokinetic interaction between two antineoplastic drugs were evaluated in this study. We recognize that most patients with cancer take supplemental drugs, potentially altering the results of DDI studies. In addition, food has been shown to interact with a myriad of drugs. We understand that 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. Because 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 seem 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.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

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Conception and design: M.J. Ratain
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Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): K. Wu, L. House, J. Ramirez
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): K. Wu, L. House, J. Ramirez
Writing, review, and/or revision of the manuscript: K. Wu, L. House, J. Ramirez, M.J. Seminerio, M.J. Ratain
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): M.J. Seminerio
Study supervision: M.J. Ratain

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