Reply to the letter to the editor 'Potential clinical relevant drug-drug interactions

van Leeuwen, R. W. F.; Mathijssen, R. H. J.; Jansman, F. G. A.; van Gelder, T.

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Potential clinical relevant drug–drug interactions: comparison between different compendia, do we have a validated method?

Recently, it was published a prospective study on drug–drug interactions (DDIs) [1]. Several considerations must be discussed about this issue.

The authors defined 'potentially clinical relevant DDIs' as those leading to clinical interventions [1]. A recent expert consensus workgroup defined 'clinically relevant potential' DDI as a potential DDI with safety concerns related to either toxicity or loss of efficacy that warrants the attention of health care professionals and/or systems involved in the medication therapy process [2]. Defining the clinical relevance of a DDI is extremely important because of thousands of theoretical, but not clinically relevant, interactions. High-quality evidence to support the existence of many DDIs is lacking, there are few controlled clinical studies conducted in relevant populations, and individual case reports are underreported and often lack information [2]. Furthermore, this expert workgroup recommended a validated systematic approach to assess a potential DDI [2].

There are no guidelines or standards for determining clinical relevance of interactions via consistent systematic evaluation or classification [2]. One possible approach is to check medication for DDI by using DDI compendia. Nowadays, several commercial DDI compendia are available. It is advisable to consult more than just one DDI information reference source to ensure that is safe to use certain drugs concomitantly [2]. Two different compendia (Micromedex and www.drugs.com) were employed by van Leeuwen et al. to 'maximize accuracy' of the medication review [1]. However, a recent systematic review on interactions between oral antineoplastic agents and concomitant medication was carried out by using Micromedex and LexiComp Handbook [3]. Moreover, studies have shown that major conflicts exist among drug compendia on DDI information such as severity and evidence ratings [4]. So, which compendia are more advisable? Currently there are no evidence supporting any of them respect the others. To illustrate disparities between drug information resources, we evaluate the DDI identified by van Leeuwen et al by making a comparative assessment of the level of severity between different DDI compendia (supplementary Table S1, available at *Annals of Oncology* online). The DDIs were rated as category A (no known interaction), B (minor/no action needed), C (moderate/monitor therapy), D (major/therapy modification), and X (contraindicated/avoid combination). This classification was based on the same used by some compendia. Several discrepancies were observed between the different compendia, some of them remarkable. Compendia use differing approaches to identify and evaluate evidence on DDI. It has been reported that the main factors that contributed to the observed discrepancies could be related to different sources of information and the different assumptions to extrapolated DDI of one drug to other drugs within the same class [4].

As mentioned above, more research is warranted to provide more evidence for clinical meaningful DDI. Further studies should be conducted to create a standard evaluation tool or selection criteria to standardize the definitions and classifications of DDIs among databases commonly used to identify DDIs. One solution could be the Drug Interaction eVidence Evaluation (DRIVE) instrument when formally validated [2]. Additionally, research is needed to examine how frequently these combinations are being prescribed and whether the DDIs actually cause harm to patients. We think that this issue could be a matter of deeper discussion.

D. Conde-Estévez[1,2*], D. Echeverría-Esnal[1], I. Tusquets[2,3,4] & J. Albanell[2,3,5]

[1]Department of Pharmacy, Hospital del Mar. Barcelona;
[2]Hospital del Mar Medical Research Institute (IMIM), Barcelona;
[3]Department of Medical Oncology, Hospital del Mar. Barcelona;
[4]Medical Oncology Department, Universitat Autònoma de Barcelona, Barcelona;
[5]Medical Oncology Department, Pompeu Fabra University, Barcelona, Spain
(*E-mail: dconde@hospitaldelmar.cat)

disclosure

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Reply to the letter to the editor 'Potential clinical relevant drug–drug interactions: comparison between different compendia, do we have a validated method?' by Conde-Estévez et al.

We appreciate the opportunity to respond to the letter to the editor by Conde-Estévez et al. [1], concerning our prospective study on drug–drug interactions (DDIs) in cancer patients [2]. With the increasing numbers of new (oral) anticancer agents, the risk for DDIs is a relevant concern for clinical oncology practice [2–5]. An important outcome of our most recent study is that oncologists often do not have a complete overview

of all co-medication, and that, without a systematic review of the given medication, some important DDIs will remain unnoticed.

Conde-Estévez et al. present the outcomes of several software tools for the identification of DDIs. In their informative table, they show that the application of several of these tools may result in different classifications of DDIs. This is somehow remarkable, as all programs are based on the same scientific literature. And all DDIs software try to answer the same questions: (i) is there a DDI? (ii) what is the clinical relevance of this DDI? and (iii) how can I manage this DDI? However, the interpretation of the available data on DDIs in the literature is open for discussion. We therefore agree with Conde-Estévez et al. that it would be good if future programs would aim for a better standardization of definitions and classifications of DDIs in these programs.

In our work, we have chosen 'Intervention Yes/No' as the primary end point for clinical relevance, since this end point is highly consistent, easy to score, and therefore reproducible. The expert team consisting of three clinical pharmacologists sent out a recommendation on a DDI to the treating physician, and only when the treating physician decided to intervene, the DDI was classified as 'clinically relevant'. With this procedure, an additional assessment of the clinical relevance was applied, i.e. acceptance by the treating physician.

However, the ultimate proof for clinical relevance would be to demonstrate that in a population with medication review and DDI interventions, clinical outcome (i.e. progression-free survival) and number/severity of adverse events, would be favorable compared with a group of patients in whom medication review is not carried out. However, such a controlled study design would require a very large sample size. In addition, with the current knowledge in mind it might also be unethical to perform such a study.

R. W. F. van Leeuwen[1,2*], R. H. J. Mathijssen[2], F. G. A. Jansman[3] & T. van Gelder[1,4]

[1]Department of Hospital Pharmacy, Erasmus University Medical Center, Rotterdam;
[2]Department of Medical Oncology, Erasmus MC Cancer Institute, Rotterdam;
[3]Department of Clinical Pharmacy, Deventer Hospital, Deventer, and University Groningen, Groningen;
[4]Department of Internal Medicine, Erasmus University Medical Center, Rotterdam, The Netherlands
(*E-mail: r.w.f.vanleeuwen@erasmusmc.nl)

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