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Systems-level analysis of drug interactions in cancer patients supports the need for a broader analytical approach to personalized cancer medicine.

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BACKGROUND

The clinical response of cancer patients to drug interventions is influenced by three primary classes of molecular determinant: a) tumor intrinsic factors, b) patient intrinsic factors and c) patient extrinsic factors. Both tumor intrinsic and patient intrinsic factors derive from genomic diversity in the form of somatic aberrations and genetic polymorphisms, affecting drug pharmacodynamics and pharmacokinetics, respectively. While Next Generation Sequence (NGS) based diagnostics can provide invaluable insights into the effects of both of these factors on drug response, the strategy ignores the potentially important influence of extrinsic factors, in particular patient co-medications, on disease system behavior.

Patient co-medications are an extrinsic factor that act analogously to genomic mutations; by perturbing the function of genes that mediate cancer drug activity, co-medications have the potential to alter the directionality of cancer drug responsiveness and in particular, side effect and outcome profiles. Even in absence of such direct effects on cancer drug activity, co-medications have the potential to interact with each other to cause adverse events (AE's) that can exacerbate or cause other patient co-morbidities. In other instances such AE's may be falsely attributed to the anti-cancer medication. These clinical scenarios can potentially mask the true therapeutic effects of an otherwise effective anti-cancer medication and thereby negatively affect patient compliance.

In this study, we sought to characterize the potential influence of co-medications on the prevalence of adverse drug responses and negative clinical outcomes in cancer patients. Our goal was to ascertain the relevance of such extrinsic perturbations to precision medicine at several levels of the patient system – drug labels, targets, metabolizing enzymes and pathways.

METHODS

To characterize the potential influence of patient co-medications on cancer drug mode of action, toxicity profile and patient outcomes, we employed a proprietary analytical platform - Molecular Analysis of Side Effects (MASE™). The system uses a drug-centric data integration approach to map the publicly available AE data from the FDA Adverse Event Reporting System (FAERS) to chemical and biological data sources. Using this approach, data for over 2.3 million patient case reports were mapped to molecular knowledge for 1935 drugs (including known drug:drug interactions), 515 drug classes (ATC level 4), 1095 targets, 282 metabolizing enzymes/transporters and 931 pathways.

Each case report was analyzed for potential drug interactions as contraindicated in drug labels and with respect to interactions that can occur at the level of targets, metabolizing enzymes, transporters and pathways. Results were grouped according to cancer indications and cancer drugs and then compared against background drug interaction rates and associated patient outcomes across the entire dataset.

Fig. 1

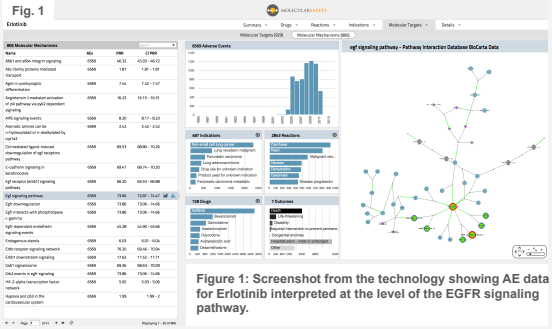


Figure 1: Screenshot from the technology showing AE data for Erlotinib interpreted at the level of the EGFR signaling pathway.

RESULTS

Generation and analysis of >250 million data points about the prevalence and mechanisms behind cancer patient AE's and seven classes of negative clinical outcome (death, life threatening, hospitalization, disability, congenital and other), revealed a broad prevalence of drug:drug interactions (DDI's) at all levels of the patient system, including labels, targets, metabolizing enzymes, transporters and pathways. The profile of cancer cases differs significantly from others in the FAERS database

For the complete FAERS data set, drug interactions that are contraindicated in drug labels were identified 11.9% of the cases whereas for cancer cases this number rises to 17.6% of cases and up to 33.2% in lung cancer patients. System level drug interactions are also significantly more common in cancer patients and are associated with a significantly higher rate of death, hospitalization and life threatening events. A synopsis of the results for top cancer types and targeted therapies is provided in Table 1.

Fig. 2

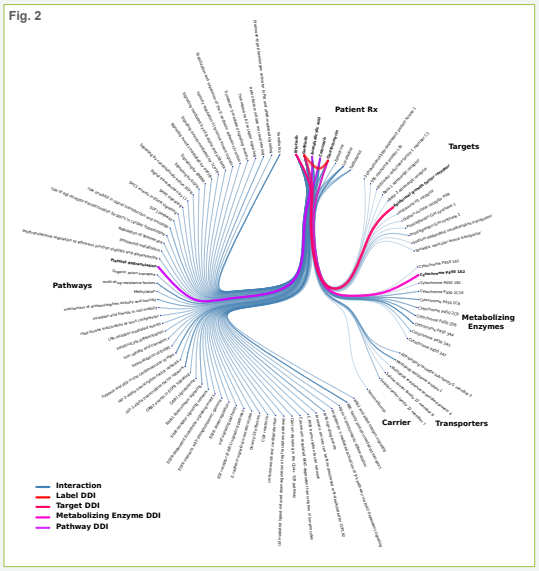


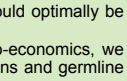
Figure 2: Systems pharmacology model of a lung cancer patient (FAERS case #: 5844187), highlighting a co-occurrence of label based drug interactions, target level drug interactions, metabolizing enzyme level interactions and pathway level interactions in this single patient.

Table 1:

		Cases	Label	Target	Enzyme	Pathway	Death	Life threatening	Hospitalization
	Overall	2,391,440	11.9%	19.6%	17.0%	37.6%	11.2%	4.5%	29.0%
Indications	Cancer	208,545	17.6%	35.4%	20.2%	57.0%	26.9%	7.7%	46.4%
	Breast cancer	27,880	15.6%	30.5%	25.1%	56.3%	11.8%	5.8%	40.1%
	Colorectal cancer	7,600	11.5%	58.5%	10.8%	69.8%	22.5%	9.3%	56.1%
	Lung cancer	11,546	33.2%	48.8%	21.3%	77.1%	28.5%	9.2%	62.8%
	Prostate cancer	8,657	16.1%	22.5%	30.6%	52.9%	24.9%	6.2%	45.9%
Drugs	Cetuximab	10,273	17.9%	36.2%	14.3%	56.7%	12.6%	9.3%	55.4%
	Erlotinib	6,569	18.2%	68.4%	17.7%	91.9%	29.3%	5.6%	57.1%
	Gefitinib	6,963	17.1%	58.7%	18.8%	78.0%	22.1%	7.3%	44.3%
	Imatinib	9,611	14.9%	17.5%	18.1%	35.9%	34.7%	5.5%	33.5%
	Lapatinib	5,541	12.4%	18.1%	26.2%	46.1%	11.9%	3.8%	35.1%
	Panitumumab	1,896	17.6%	48.8%	11.3%	65.3%	20.8%	8.1%	59.7%

Rates of Drug Interaction | Outcomes

Table 1: Synopsis of the rates of label and system-level drug interactions and clinical outcomes detected in FAERS case reports. Percentages refer to the percentage of cases in which a drug interaction was detected in that context.



CONCLUSIONS

- Our results highlight the prevalence and potential impact of extrinsic co-medications on cancer patient toxicities and negative clinical outcomes.
- Both label and system-based drug interactions were found to be significantly more common in cancer patients and associated with higher rates of morbidity, hospitalization and life threatening adverse events.
- We conclude that more must be done to protect the therapeutic fidelity of both anti-cancer drugs and other patient co-medication's.
- We propose that systems-level analysis of both biomarker and pharmacological information should optimally be performed immediately following predictive NGS testing.
- Because of the important implications for patient compliance, clinical outcomes and pharmaco-economics, we have integrated the analysis of patient co-medications together with analysis of somatic mutations and germline polymorphisms, as part of our predictive NGS (TreatmentMAP™) service offering.