Drug-Drug Interactions and Practical Lessons for Cancer Therapy

David J Kerr
Professor of Cancer Medicine
Universities of Oxford and Cornell

What do we mean by DDI?

- A clinically relevant drug-drug interaction (DDI) occurs when the effectiveness or toxicity of one medication is altered by the administration of another medicine (herbal remedy??)
- Adverse DDIs may result from either diminished therapeutic effect or increased toxicity.
- Among the various types of medical errors, the occurrence of adverse DDIs is one that is usually preventable.
- It is therefore essential that health professionals be able to evaluate the potential for DDIs and appropriate prevention or management strategies.

Categories of DDI

- pharmacokinetic, pharmacodynamic and pharmaceutic interactions.
- Pharmacokinetic interactions involve one drug altering the absorption, distribution, metabolism, or excretion of another drug.
- Interpatient variability in the pharmacokinetic profile of many anticancer agents complicates the predictability of the antitumor response and toxicities.
- drug interactions involving hepatic metabolism via Cyt P 450 is probably the most common and important mechanism responsible for oncologic drug interactions.

CYP450 subtypes and anticancer drugs

- Cyclophosphamide 2B6, 2D6 and 3A4 ;Cytarabine 3A4 Docetaxel 3A4
- Doxorubicin 3A4 ; Erlotinib 1A2 and 3A4;Etoposide 3A4 Exemestane 3A4
- Gefitinib 2C19 and 2D6 3A4;Idarubicin 2D6 2C9 and 2D6;Ifosphamide 3A4
- Imatinib mesylate* 2C9, 2D6 and 3A4;Irinotecan 3A4
- Ketoconazole* 3A4 and 2C9;Letrozole* 2A6 and 2C19 2A6 and 3A4;
- Paclitaxel 2C8 and 3A4;Tamoxifen* 3A4 1A2, 2A6, 2B6, 2D6, 2E1 and 3A4
- Teniposide 3A4 ;Tretinoin* 2C8 and 3A4;Vinblastine 2D6 3A4
- Vincristine 2D6 3A4 ;Vinorelbine 2D6 3A4

Why is CYP3A4 so important and why do we avoid grapefruit juice?

- CYP3A4, mainly found in the liver, is also present in the gut wall.
- It is involved in reducing the absorption of many drugs and is subject to both induction and inhibition
- Grapefruit juice inhibits the action of CYP3A4 in the bowel (and liver with repeated consumption) and can lead to significant increases in bioavailability of several drugs, e.g. the bioavailability of rapamycin is increased by 350% by coingestion of grapefruit juice.
- This interaction can occur even after consuming just 200mL of grapefruit juice and inhibition can persist for up to 72 hours
- An interaction may occur, whatever the source, e.g. fresh grapefruit and grapefruit juices including fresh, frozen, or diluted from concentrate.

Effect of Food on Anticancer Agents

- Busulfan,fluorouracil,methotrexate and topotecan - Delayed absorption
- Altretamine, capecitabine,chlorambucil, estramustine, gefitinib,melphalan and thioguanine - Decreased absorption
- Erlotinib and tretinoin - Increased absorption
- Etoposide, imatinib, mercaptopurine and temozolomide - Unaffected absorption

DDIs are more common when:

- Drug elimination occurs through a single metabolic pathway.
- Drug is a potent inhibitor or inducer of a drug-metabolizing enzyme.
- Interacting drugs have steep dose-response curves.
- Interacting drugs have narrow therapeutic ranges.
- Inhibition of the primary metabolic enzyme diverts the drug into an alternative pathway, which generates a metabolite that has toxic or modified pharmacodynamic activity.
- Drug has nonlinear pharmacokinetics, or the interaction results in a conversion from linear to nonlinear pharmacokinetics.
- The drug is metabolized through, or inhibits, a polymorphic drug-metabolizing enzyme

Factors that predispose a patient to drug interactions

- Advancing age
- Multiple medications
- Compromised renal/hepatic function
- More than one prescriber
- Comorbidity

Can we predict DDIs?

- While it is possible to predict the likelihood of a drug interaction, it is often difficult to predict the clinical relevance.
- Elderly patients or those with impaired renal and/or hepatic function are more at risk.
- Drug interactions may be overlooked and explained as poor compliance, or even progressive disease.
- Knowledge of drug interaction processes can aid in the diagnosis of unexplained or unexpected response to drug therapy.

Class of medication that interacts with chemotherapy

- Antacids that contain aluminium and magnesium can increase the bioavailability of capecitabine
- Antibiotics: Penicillins block the renal elimination of MTX
- Altered coagulation has been reported in patients who have taken warfarin concurrently with capecitabine
- Anticonvulsants : Carbamazepine increases systemic clearance of teniposide
- Anti-emetics : Co-administration of ondansetron withcisplatin and cyclophosphamide can result in a decrease in systemic exposure to both drugs
- Antifungal agents: Ketoconazole inhibits the metabolism of irinotecan, which leads to an increase in exposure to SN-38
- Anti-retroviral agents : Co-administration of delvairdine and saquinavir with paclitaxel has resulted in severe paclitaxel toxicity (CYP3A inhibition?)
- Corticosteroids : decrease the anti-tumour efficacy of aldesleukin
- Herbal supplements: St John's wort decreases the plasma concentration of imatinib and SN-38
- Analgesics: NSAIDs block the elimination of MTX through renal tubular secretion, which results in elevated MTX levels

Possible mechanisms of DD interaction: irinotecan

- Carbamazepine Induction of CYP3A4 Decreased exposure to irinotecan and its active metabolite SN-38
- Cyclosporine Inhibition of ABCB1-mediated biliary excretion of SN-38 increases its AUC by 25-60%
- Ketoconazole Inhibition of CYP3A4; inhibition of UGT1A1 Relative APC formation was reduced by 87%; relative exposure to SN-38 was increased by 109%
- Phenobarbital Induction of CYP3A4- Irinotecan clearance increased by 27%; AUC of SN-38 decreased by 75%
- Phenytoin Induction of CYP3A4 - AUCs of irinotecan, SN-38 and SN-38G were approximately 40%, 25% and 25%, respectively, of those previously determined in patients who did not receive phenytoin
- St John's wort Induction of CYP3A4 -AUC of SN-38 decreased by 42%

Can modern genetics help to avoid drug toxicity?

- *Pharmacogenetics* is the study of how variation in an individual gene affects the response to drugs
- *Pharmacogenomics* is the study of how variation in the human genome can be used in the development of pharmaceuticals.
- *Polymorphisms* refer to commonly occurring genetic variants. A polymorphism in a critical coding or non-coding region can lead to altered protein synthesis or function with clinical implications such as abnormal drug responses.

Pharmacogenetic tests worth considering for your patients

- Capecitabine / 5-FU – DYPD; toxicity
- Irinotecan - UGTA1; toxicity
- Tamoxifen – CYP2D6 ; efficacy

DDI Summary

- An important component of safety
- Increasingly common with polypharmacy
- Elderly patients with hepato-renal impairment are more vulnerable
- Clinical pharmacology and pharmacogenetics give mechanistic insights
- Available information services are poor and there is room for a dedicated web-service