Drug-Drug Interactions in elderly patients with cancer

Fabienne Divanon
General introduction

Cancer patients are at particularly high risk of drug-drug interactions (DDIs) because they commonly receive multiple medications:

- Conventional cytotoxic drugs, hormonal agents, targeted therapies, immunotherapy and supportive care drugs

In addition, the majority of cancer patients are elderly and require concomitant medications for co-morbid conditions:

- Cardiovascular, gastrointestinal, rheumatological diseases...

Furthermore, the age-related decline in hepatic and renal function reduces their ability to metabolize and clear drugs and increases the potential for toxicity.
General introduction

As elderly patients with cancer often take many comedication, they are particularly at risk for DDIs

DDIs seem to be responsible for 20-30% of all adverse drug reactions and may be the cause of death in 4% of all cancer patients, where others may be deprived from optimal anticancer therapy through reduced pharmacologic effects.\(^1,2\)

Polypharmacy is defined:

By the co-prescription of 3 drugs\(^3\) but most authors agree « set the threshold » of polymedication to the use of at least 5 different drugs\(^4,5\)

- Advanced age, number of physicians, number of diseases and/or symptoms diagnoses are the main sources of polypharmacy in the elderly

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\(^3\)Elderly and drugs. Report of the National Pharmacy Academy, June 2005.
New challenge(s)

Paradigm shift

1950-2000

• Conventional cytotoxic drugs were predominantly administered intravenously on a discontinuous bases (every 2,3 ou 4 weeks)

> 2000

• Targeted therapies are predominately administered orally and continued over much longer periods of time. TKIs have become an established factor in daily oncology practice (~ 25 TKIs approved by the EMA)

• TKIs are generally characterized by a poor and variable bioavailability, are metabolized predominantly by CYP enzymes

Risk for DDIs
Not all DDIs can be predicted* and those that are predictable are not always avoidable!

*This is not an exhaustive review, it is intented that the information provided will enable physicians to reduce the risk of some interactions choosing appropriate drugs and monitoring for DDIs
The prevalence and impact of polypharmacy in patients of geriatric oncology is a little-explored area

There are more published data on the elderly, but little on the elderly patient with cancer

DDIs are defined:

- As a modification of the effect of a drug when administered with another drug in a given patient.

- Can be divided into 2 main groups:
  - Pharmacodynamic DDIs
  - Pharmacokinetic DDIs
Pharmacodynamic DDIs

Positive effect
Combination regimen of anticancer drugs. Pharmacodynamic DDIs are used, intentionally to reduce resistance and improve antitumor activity of the anticancer drug in an additive or even synergistic manner.

Negative effect
Many anticancer (AC) drugs prolong the QTc interval (e.g. anthracyclines). Concomitant use of medication that prolong the QTc interval may further increase the risk of TdP and sudden heart death during AC therapy.

Possible outcomes of pharmacodynamic DDIs: increased or decreased therapeutic and/or adverse effects.
Pharmacokinetic DDIs

Subdivided according to the pharmacokinetic properties ADME*

If a parameter is modified by comedication, systemic exposure of the anticancer drug might be affected and the patient may be deprived from optimal therapy.

*Abbreviations: ADME (Absorption, Distribution, Metabolism, Elimination)

Pharmacokinetic DDIs

Absorption
GI absorption of an AC drug depends on its chemical characteristics and can be influenced by DDIs.

Factors influencing drug absorption:
1- changes in stomach pH (e.g. due to coadministration of acid suppressive agents)
2- inhibition or induction of drug transporters (P-glycoprotein) and intestinal enzymes (CYPs)
   - DDIs between PPIs and TKIs

Distribution
Competition for plasma protein (PP) binding (e.g. albumin) can alter distribution of drugs. If two highly PP bound drugs are used concomitantly, one drug can displace the other from its protein binding site, thereby increasing the fraction of unbound and pharmacologically active drug.

- Many AC drugs are highly PP bound (>90%)
  - DDIs between TKIs and vitamin K antagonists

Metabolism
Altered metabolism is among the most complex of the mechanisms by which DDIs can occur.

Inhibition or induction of hepatic enzymes (CYPs) by drugs or foods are often implicated.

- Most AC drugs are entirely or partly metabolized by CYPs
  - The cytochrome P450 system is an important site of DDIs

Elimination
DDIs occur due to renal impairment during the use of nephrotoxic comedication. Although, some AC drugs are highly dependent on renal elimination (platina compounds, MTX). Most AC drugs are eliminated through liver metabolism and subsequent excreted into the feces.

- Because AC drugs are predominately excreted through hepatic metabolism, DDIs concerning elimination seem to be of minor significance
## DDIs with tyrosine-kinase inhibitors

### Summary of the most significant DDIs in TKI therapy

<table>
<thead>
<tr>
<th>TKIs prone to significantly interact with:</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acid suppressive agents (PPIs*, H2As*, antiacids) Bosutinib, crizotinib, dasatinib, erlotinib, gefitinib, ibutinib, lapatinib, pazopanib, regorafenib</td>
<td>Concomitant use of acid suppressive agents can significantly affect the drug absorption of these TKIs. If possible, the combination must be avoided or the time of drug intake must be split by at least several hours</td>
</tr>
<tr>
<td>Strong CYP3A4 inhibitors**/inducers*** Axitinib, crizotinib, dasatinib, erlotinib, gefitinib, imatinib, lapatinib, nilotinib, pazopanib, regorafenib, ruxolitinib, sunitinib, vemurafenib</td>
<td>Concomitant use of strong CYP3A4 inhibitors/inducers can significantly influence the exposure to these TKIs. Dose adjustments are highly recommended</td>
</tr>
<tr>
<td>Other QTc-interval prolonging drugs Crizotinib, gefitinib, lapatinib, nilotinib, pazopanib, sorafenib, sunitinib, vandetanib, vemurafenib</td>
<td>Concomitant use of other QTc-interval prolonging drugs along with these TKIs can significantly prolong the QTc-interval. If indicated, it is strongly recommended that an ECG is obtained 24-48 hours before and one week after initiating the concomitant therapy</td>
</tr>
</tbody>
</table>

*PPIs : proton pump inhibitors, H2As : H2-antagonists ; **ketoconazole ; ***rifampicin, phenytoin, carbamazepine

TKIs and PPIs really incompatible?

- PPIs are frequently used in cancer patients to gastroprotection or treating gastrointestinal symptoms (NSAIDs, corticosteroids...)

- The major determinant in TKIs absorption is the pH-dependent solubility

  - Balance between the ionized and non-ionized form depends on the gastric pH and the pKa of the TKI

  - Normal acidic intragastric pH (pH range 1 to 2): ionized form ++++, solubility +++, optimized TKI absorption at low intragastric pH

  - If intragastric pH elevated by concurrent PPI use: non-ionized form ++++, solubility and bioavailability

  - TKIs with a pKa near the pH range of stomach (pH 1-4) (erlotinib) are usually more affected by intragastric pH than TKIs with a higher pKa near 4 to 5 (imatinib)
TKIs and PPIs really incompatible?

For most PPIs, the acid-inhibitory effects ($pH > 4$) will only be reached 1 to 4h after intake

- This delayed onset of action is caused by the use of enteric coated forms. PPIs are protected against degradation in the stomach and arrive intact in the duodenum where absorption takes place.

- The intragastric pH starts to decrease and drops to pH values < 4 within 12-14 hours after PPI administration.

**Conclusion:** no clear recommendations on how to manage DDIs between TKIs and PPIs!

Concomitant use of TKI and PPI? TKI administered in the morning 2 to 3 hours before PPI intake?
### Effects of acid-suppressive agents on the bioavailability of TKIs\(^ {11}\)

<table>
<thead>
<tr>
<th>TKI</th>
<th>Acid suppressive agent (ASA)</th>
<th>Effect on TKI exposure</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Axitinib</td>
<td>Rabeprazol 20mg q.d.</td>
<td>42% □ 15% □</td>
<td>H2As, antiacids, PPIs can be used concomitantly with A</td>
</tr>
<tr>
<td>Crizotinib</td>
<td>-</td>
<td>-</td>
<td>The solubility of crizotinib is pH dependent, decreases as pH increases.</td>
</tr>
<tr>
<td>Dasatinib</td>
<td>Famotidine 40mg, 10h before D Maalox 30ml, 2h before D Maalox 30ml concomitantly with D</td>
<td>63% □ 61% □</td>
<td>H2As can be used 2h after D Antiacids can be used 2h before or after D</td>
</tr>
<tr>
<td></td>
<td>Famotidine 40mg, 2h after D</td>
<td>-</td>
<td>PPIs should not be used concomitantly with D</td>
</tr>
<tr>
<td></td>
<td>Maalox 30ml, 2h before D</td>
<td>26% □ -</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Maalox 30ml concomitantly with D</td>
<td>58% □ 54% □</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Omeprazole 40mg q.d. concomitantly with D</td>
<td>42% □ 43% □</td>
<td></td>
</tr>
<tr>
<td>Erlotinib</td>
<td>Omeprazole 40mg q.d. concomitantly with E Ranitidine 300mg q.d. concomitantly with E</td>
<td>61% □ 46% □</td>
<td>H2As can be used 2h after E. Ranitidine should be given to 150mg daily twice</td>
</tr>
<tr>
<td></td>
<td>Ranitidine 150mg b.i.d. (E 2h before and 10h after R)</td>
<td>54% □ 33% □</td>
<td>Antiacids can be used 4h before or 2h after E</td>
</tr>
<tr>
<td></td>
<td></td>
<td>15% □ 15% □</td>
<td>PPIs should not be used concomitantly with E</td>
</tr>
</tbody>
</table>

**Effects of acid-suppressive agents on the bioavailability of TKIs**

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<tr>
<td>Gefitinib</td>
<td>Two oral doses of ranitidine (13h and 1h before G)</td>
<td>71% □ 47% □</td>
<td><strong>H2As et PPIs</strong> should not be used concomitantly with G. <strong>Antiacids</strong> can be used 2h before or after G.</td>
</tr>
<tr>
<td>Imatinib</td>
<td>Omeprazole 40mg q.d. concomitantly with I Maalox 20ml 15 minutes before I</td>
<td>- -</td>
<td><strong>H2As, antiacids, PPIs</strong> can be used concomitantly with I.</td>
</tr>
<tr>
<td>Lapatinib</td>
<td>Esomeprazole 40mg q.d. 12h prior to L</td>
<td>- 27% □</td>
<td><strong>H2As et PPIs</strong> should not be used concomitantly with L. <strong>Antiacids</strong> can be used 2h before or after L.</td>
</tr>
<tr>
<td>Nilotinib</td>
<td>Esomeprazole 40mg q.d. concomitantly with N Famotidine 20mg b.i.d. 2h after N</td>
<td>27% □ 34% □</td>
<td><strong>H2As</strong> can be used 10h before ou 2h after N. <strong>Antiacids</strong> can be used 2h before or after N <strong>PPIs</strong> can be used concomitantly with N.</td>
</tr>
</tbody>
</table>

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Effects of acid-suppressive agents on the bioavailability of TKIs\textsuperscript{11}

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<thead>
<tr>
<th>TKI</th>
<th>Acid suppressive agent (ASA)</th>
<th>Effect on TKI exposure $C_{\text{max}}$</th>
<th>Recommendations</th>
</tr>
</thead>
</table>
| Pazopanib  | Esomeprazole (evening) concomitantly with P (morning) | 42% □                                  | H2As can be used 10h before or 2h after P  
Antacids can be used 4h before or 2h after P  
PPIs can be used concomitantly with P (evening) |
| Regorafenib| -                                               | -                                      | No study data available yet                                                      |
| Ruxolitinib| -                                               | -                                      | H2As, antacids, PPIs can be used concomitantly with R                           |
| Sorafenib  | Esomeprazole concomitantly with S                | -                                      | H2As, antacids, PPIs can be used concomitantly with S                           |
| Sunitinib  | -                                               | -                                      | Due to the high solubility, no effect on S would be expected during H2A, antacid or PPI concomitantly used |
| Vandetanib | -                                               | -                                      | H2As, antacids, PPIs can be used concomitantly with V                           |
| Vemurafenib| -                                               | -                                      | H2As, antacids, PPIs can be used concomitantly with V                           |

Interest of the acidic beverage cola in patients treated with erlotinib

When erlotinib (ERLO) is taken concurrently with a PPI, stomach pH will increase, resulting in a clinically relevant decrease of erlotinib bioavailability.

Randomized cross-over pharmacokinetic study in patients taking ERLO for NSCLC

Results: in the patients taking ERLO + esomeprazole + cola (group B), the mean $AUC_{0-12h}$ increased with 39% ($p=0.004$) whereas in patients without a PPI (group A), the mean $AUC_{0-12h}$ was only slightly higher (9%, $p=0.03$) after ERLO intake with cola.

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DDIs with tyrosine-kinase inhibitors

Others recommendations for clinical practice

- P-glycoprotein substrates with a narrow therapeutic window (e.g. digoxin, ciclosporin and tacrolimus) should be extensively monitored during the use of TKIs that inhibit P-glycoprotein.

- The combination of grapefruit juice and sunitinib or nilotinib should be avoided. Others products labels discourage intake of grapefruit juice only on theoretical assumptions (e.g. pazopanib, lapatinib).

- To improve the safe use of TKIs in clinical oncology, a profound assessment of co-prescribed drugs, herbal supplements, lifestyle food and drinks, cardiac risk factors, and physical examination is needed.

## DDIs with conventional cytotoxic drugs

### Potential DDIs involving CCD

<table>
<thead>
<tr>
<th>Type of DDi</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antiarythmics (amiodarone, digoxine, sotalol) / Antibiotics (clarithromycin, levofloxacin)</strong></td>
<td>Drug combination can prolong QT-interval</td>
</tr>
<tr>
<td>Doxorubicin</td>
<td></td>
</tr>
<tr>
<td><strong>Antibiotics</strong></td>
<td></td>
</tr>
<tr>
<td>1-Penicillins&lt;sup&gt;13&lt;/sup&gt; : methotrexate</td>
<td>Penicillins may decrease the total clearance of methotrexate</td>
</tr>
<tr>
<td>2-Quinolones&lt;sup&gt;14,15&lt;/sup&gt; : carboplatin, cisplatine, cyclophosphamide, doxorubicin, etoposide, mitoxantrone, vincristine</td>
<td>Absorption of quinolones may be decreased due to damaged gastrointestinal mucosa</td>
</tr>
</tbody>
</table>

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### DDIs with conventional cytotoxic drugs

#### Potential DDIs involving CCD

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<tr>
<th>Type of DDi</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anticoagulants</strong></td>
<td>Chemotherapy-induced protein displacement and inhibition of warfarin metabolism with higher risk of bleeding. Patients should have frequent monitoring of INR</td>
</tr>
</tbody>
</table>
| Fluorouracil, capecitabine, carboplatin, cyclophosphamide, etoposide, ifosfamide, paclitaxel | Anticoagulants  

**Anticonvulsants**

1. Phenytoin: doxorubicin, cisplatin, cyclophosphamide, etoposide, vincristine
2. Valproic acid: doxorubicin, cisplatin, bleomycin

Plasma concentration and therapeutic effect of phenytoin/valproic acid or CCD may be altered

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## Potential DDIs involving CCD

<table>
<thead>
<tr>
<th>Type of DDi</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>CCD metabolized by CYP3A4: cyclophosphamide, docetaxel, paclitaxel, etoposide, irinotecan, vinblastine, vinorelbine, vincristine...</td>
<td>CYP3A4 inhibition (induction) may increase (decrease) the plasma concentrations of CDD</td>
</tr>
<tr>
<td>1-Inducers (phenytoin, rifampicin, HIV protease inhibitors, carbamazepine, St. John’s wort...)</td>
<td></td>
</tr>
<tr>
<td>2-Inhibitors (amiodarone, diltiazem, ciclosporin, clarithromycin, erythromycin, ketoconazole, cimetidine, reverse transcriptase inhibitors, grapefruit juice...)</td>
<td></td>
</tr>
<tr>
<td>CCD P-gp substrates</td>
<td>P-gp inhibition (induction) may increase (decrease) the plasma concentrations of CDD</td>
</tr>
<tr>
<td>Doxorubicin, etoposide, paclitaxel, vinblastine, vincristine, trabectedin</td>
<td></td>
</tr>
</tbody>
</table>

## Potential DDIs involving supportive care drugs

<table>
<thead>
<tr>
<th>Type of DDi</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antiemetics</strong></td>
<td></td>
</tr>
<tr>
<td>1-Ondansetron[^8^]: anthracyclines, trastuzumab, tamoxifen, antiarrythmics, levofloxacine, clarithromycine, droperidol, haloperidol</td>
<td>Drug combination can prolong QT-interval</td>
</tr>
<tr>
<td>2-Metoclopramide[^30^]: SSRI’s (sertraline, venlafaxine)</td>
<td>Serotonin syndrome with extrapyramidal movements may occur</td>
</tr>
<tr>
<td><strong>CNS-interactions</strong></td>
<td></td>
</tr>
<tr>
<td>Ondansétron + tramadol, gabapentin + opioids/depressants of CNS</td>
<td>Impaired consciousness, may increase sedation and the risk of falling</td>
</tr>
</tbody>
</table>


Summary of pharmacokinetic DDIs

Absorption

Distribution

Metabolism

Elimination

pH dependent solubility, insoluble complexes, drug sequestration, modification of gastric emptying

Space the drug intake

P-glycoprotéin

Change in plasma protein binding

Rarely significant clinical consequences

Cytochrome P450

3A4, 2C9, 2D19, 2D6, 2E1, 1A2 (genetic variability)

Inhibition

Induction

Significant changes in plasma concentrations

Change in the glomerular filtration, tubular secretion, tubular reabsorption

Interdependence

Pharmacokinetic
To guarantee the safe use of medication, a drug review for each patient is needed

**Recommendations**

- **Select patients with medication at high risk of DDIs**: vitamin K antagonists, NOA, antiepileptics, antihypertensive agents, ASA...
- **Take into account the physiological (liver and kidney function, comorbidities) and environmental factors** (nutrition, food supplements, herbal medicine, alcohol consumption...)
- **Scan for potentially inappropriate medications** (Beers criteria, adapted by Laroche), redundancies, drugs number

**Screening for potentially relevant DDIs**

Before starting **AND** during anticancer treatment

High probability to detect clinically irrelevant DDIs
Thank you for your attention!