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Evidence- and consensus-based guidelines for drug-drug interactions with anticancer drugs; A practical and universal tool for management

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ABSTRACT

Drug-drug interactions (DDIs) with anticancer drugs are common and can significantly affect efficacy and toxicity of treatment. Therefore, a Dutch Multidisciplinary Expert group is assessing the clinical significance of DDIs in oncology and provides recommendations for the management of these DDIs. We present an overview of methodology and outcome of an evidence- and consensus-based assessment of DDIs between anticancer drugs and non-anticancer drugs.

A literature search was performed through PubMed and EMA and FDA assessment reports, to identify potential DDI's involving anticancer drugs. For each potential DDI a concept report for risk analysis and practical advice for management was created. Subsequently, this risk analysis and the corresponding advice were assessed and weighed.

A total of 290 potential DDIs have been identified in the literature thus far. Of these 290 potential DDIs, the Expert Group has identified 94 (32%) DDIs as clinically relevant, with a need for an automated alert and a suggested intervention. Furthermore, 110 DDIs have been identified as clinically not relevant. For 86 potential DDIs evidence supporting a relevant DDI was insufficient and in these cases neither an alert nor advice regarding a suggested intervention were formulated.

A transparent risk analysis is presented for identification of clinically relevant DDIs with anticancer drugs. Integration of DDI guidelines into the national electronic prescribing system is essential to achieve optimal efficacy and minimal toxicity in patients receiving anticancer therapy. A clear overview of clinically relevant DDIs with anticancer therapy provides clinicians with a structured, evidence-based and consensus-built tool for anticancer therapy surveillance.

Introduction

Over the past decades the incidence of cancer has rapidly increased making cancer the leading cause of death worldwide [1]. Cancer occurs primarily in older age groups, with over two third of the patients with cancer 65 years or older at the time of diagnosis [2]. Furthermore, comorbidities and polypharmacy defined as the use of ≥5 medications concomitantly, are common in elderly patients [3,4]. As a consequence, patients with cancer are at significant higher risk for drug related problems, such as drug-drug interactions (DDIs) [5,6]. Additionally, many anticancer drugs are potent and have narrow therapeutic windows with the result that (minor) changes in pharmacodynamic or pharmacokinetic

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parameters caused by DDIs may profoundly affect efficacy or toxicity. In this case, the anticancer drug is regarded as a victim. At the same time, an anticancer drug can act as the causative agent, that is, perpetrator, and compromise the efficacy or toxicity of other concomitantly used drugs.

Until a decade ago, cancer patients were predominately treated in a hospital setting with intravenously administered anticancer agents. Although anticancer therapy often involves highly potent and potentially toxic agents, medication surveillance on DDIs with anticancer agents was usually not standard of care. However, with the increased life expectancy and shifting paradigm towards personalized medicine, the need for monitoring and management of DDIs by healthcare professionals to optimize anticancer therapy became more apparent [5,6]. Furthermore, many novel orally administered anticancer drugs, often administered for prolonged periods of time have been introduced in the past decades (eg, tyrosine kinase inhibitors) [7]. Although in many cases these novel oral agents have significantly improved life expectancy, patient comfort and quality of life, many new challenges have emerged since these drugs are highly prone to DDIs that include amongst others impact on absorption or metabolism by cytochrome P450 (CYP)-enzymes as well as additional effects on QT_c-interval [8,9].

To obtain a solid medication surveillance in (hemato)oncology a novel approach was chosen by our Multidisciplinary Expert Group consisting of (hospital)pharmacists, medical oncologists, hematologists, internists and clinical pharmacologists, originally constituted in 2006 [10]. The Expert Group identified potential DDIs between anticancer drugs and non-anticancer drugs, assessed their clinical significance and provided practical recommendations for the management of these DDIs. The results of these assessments and the practical recommendation for the management of these DDIs were subsequently made available for healthcare professionals through integration into the national computerized medication surveillance system. In this system, alerts regarding DDIs pop-up during the prescribing process. The aim was to improve medication safety and optimize the efficacy-toxicity balance during anticancer therapy.

The first results of the Multidisciplinary Expert Group were published in 2011 [10]. This article represents an updated overview of the assessed DDIs, including novel insights in the evidence-based and consensus-based practical guidelines on the management of DDIs involving anticancer drugs. This article may function as a practical, universal tool to further optimize medication surveillance of DDIs in cancer care.

Methods

The Multidisciplinary Expert Group was established by the Royal Dutch Pharmacists Association and meets on a regular basis. The members represent their scientific organizations, and include the Dutch Association of Hospital Pharmacists, the Royal Dutch Pharmacists Association, the Dutch Society for Medical Oncology, the Haemato Oncology Foundation for Adults in the Netherlands, and the Dutch Society for Clinical Pharmacology & Biopharmacy. Data on potential DDIs were primarily derived from a database search in PubMed with the following RSS-Feed: ((drug-drug interaction[MeSH Terms] AND ((Clinical Trial[ptyp] OR Case Reports[ptyp] OR Controlled Clinical Trial[ptyp] OR Letter[ptyp] OR Multicenter Study[ptyp]) AND Humans[Mesh] AND English[lang]) AND ((Clinical Trial[ptyp] OR Case Reports[ptyp] OR Controlled Clinical Trial[ptyp] OR Letter[ptyp] OR Multicenter Study[ptyp]) AND Humans[Mesh] AND English[lang])) until January 1st 2022, and assessment reports provided by the EMA and FDA registration authorities [11,12]. The search was limited to DDIs between anticancer drugs and non-anticancer drugs. This only concerns authorized drugs since these are included in the electronic medication surveillance system. In addition, some Over-The-Counter (OTC)- and herbal drugs often used by patients on their own initiative that may jeopardize effective and safe anticancer therapy were considered for drug-drug interacting potential. For instance, St. John's Wort (hypericum) can significantly lower irinotecan exposure [13]. Therefore, some of the OTC- and herbal drugs have been included in the structural assessment of DDIs, for instance hypericum as an inducer of drug metabolizing enzymes, and supplements with calcium or magnesium for potential effects on drug absorption. Special attention was given to the extrapolation of a certain DDI to other drugs (also called the "group effect"). An example concerns the DDIs with CYP3A4 inhibitors and inducers. When an anticancer drug shows a DDI with a certain strong CYP3A4 inhibitor (eg, ketoconazole), this DDI generally also applies to other strong CYP3A4 inhibitors (eg, other azoles) [14]. As a consequence, the DDI-information and advice for management is extrapolated to these other CYP3A4 inhibitors. However, this extrapolation is more complicated when moderate CYP3A4 inhibitors (eg, fluconazole) are involved since data on DDIs with moderate CYP3A4 inhibitors are often not available. In such cases a thorough assessment by the Expert Group is needed. DDIs between anticancer drugs were not considered since anticancer drugs are frequently prescribed deliberately in combination in accordance with current guidelines. All data on potential DDIs were evaluated and categorized, with regard to quality, level of evidence and clinical significance as presented in Table 1 and Table 2 [15]. For each potential DDI a standardized data sheet for risk analysis and concise advice was predefined by a pharmacist and presented to the Multidisciplinary Expert Group. Subsequently, the Expert Group assessed, weighed and (if needed) adjusted the provided risk analyses to assess a final advice for management of the potential DDIs. After assessment, the results were grouped into 3 categories (Table 3). Thereafter, the risk analysis and the results of the as-

Table 1
Categories for quality of scientific evidence for DDIs[15]

Level	Quality of Scientific Evidence
-	No evidence
0	Pharmacodynamic animal studies; in vitro studies with a limited predictive value for the human in vivo situation; data on file
1	Incomplete, published case reports
2	Well-documented, published case reports; retrospective analyses of case series; case control studies
3	Controlled, published interaction studies in patients or healthy volunteers, surrogate end points.
4	Controlled, published interaction studies in patients or healthy volunteers, clinically relevant end points

Table 2
Categories for clinical effects of DDI with example[15]

Severity level and examples of clinical effects per category
A: Clinically irrelevant effect
Increase or decrease in drug level without direct clinical consequences: tyrosine kinase inhibitors, endoxifen (active metabolite of tamoxifen)
B: Temporarily adverse effect
Decrease simvastatin/zolpidem level (by induction enzalutamide)
C: Longer-lasting adverse effect
Increase of everolimus level (by CYP3A4-inhibitors)
Increase of phenytoin plasma concentration (by capecitabine/5FU)
D: Long-lasting or permanent adverse effect
Increased toxicity capecitabine/5FU (by folic acid/metronidazole)
Decrease of plasma concentration of carbamazepine/phenytoin/valproic acid by certain anticancer agents
E: Severe adverse effect:
Increased toxicity mercaptopurine (by allopurinol/febuxostat)
Neuromuscular toxicity vinblastine/vincristine (by CYP3A4-inhibitors)
Hepatic veno-occlusive disease by busulfan (by itraconazole/ketoconazole)
F: Potentially fatal effect
Multi-organ failure (by combination of busulfan and metronidazole)
Death (by combination of methotrexate and trimethoprim or co-trimoxazole)

Table 3
Categories for potential DDIs and advice for managing DDIs

Category	Advice
Drug-drug interaction (DDI) has been established, and the effect is clinically relevant.	Intervention is required, alert is generated
DDI has been established, but the effect is not clinically relevant	No intervention is required, no alert is generated
DDI has not been established	No intervention is required, no alert is generated

sessments are made available for healthcare professionals by integration into the national drug database for clinical decision support and is incorporated in all national electronic prescribing systems alerting medical doctors and pharmacists on clinically relevant DDIs. To optimize anticancer therapy, a clear and practical advice on the management of DDIs was given and, by this, solid medication surveillance for DDIs during prescribing of anticancer agents was guaranteed. The workflow as described above is summarized in Fig. 1, in which DDIs are distinguished between (1) 2 single drugs, (2) between 2 groups of drugs or (3) between a single drug and a group of drugs.

Results

A total of 290 potential DDIs were identified in the literature and presented to the Expert Group. By assessment, 94 DDIs (32%) were considered as clinically relevant and a practical advice for management was given (eg, dose modification, discontinuation of treatment or additional monitoring). Table 4 Among these, 12 DDIs with OTC- and herbal drugs, that is, antacids, folic acid and hypericum as a CYP3A4-inducer, were identified and assessed as clinically relevant. In contrast, 110 potential DDIs (38%) were identified as not clinically relevant, and consequently not requiring an alert nor advice regarding an intervention. These DDIs mostly concerned minor alterations in pharmacokinetics and/or additional toxicities. For the remaining 86 potential DDIs (39%) that were mentioned in literature, the Expert Group considered the evidence for a DDI insufficient and not relevant, so neither alert nor advice was generated.

The clinically relevant interactions requiring interventions mainly concern pharmaceutical interactions regarding decreased drug absorption in from the gastrointestinal tract, pharmacokinetic interactions with CYP450 metabolizing enzymes influencing efficacy or toxicity, and pharmacodynamic interactions leading to additional toxicities. Furthermore, several DDIs with specific underlying mechanisms were established and assessed as in need interventions. All results of the structured assessment of DDIs with anticancer drugs are presented in Supplementary Tables 5, 6, 7.

Discussion

Since the start of the Multidisciplinary Expert Group, 290 potential DDIs have been identified with almost half assessed as clinically relevant. The DDI assessments and management guidelines are integrated in all national electronic prescribing systems, thereby providing a practical tool for clinicians and (hospital)pharmacists for the management of DDIs involving anticancer therapies. More importantly, solid medication surveillance on DDIs is facilitated and guaranteed and patient safety improved.

With the increasing complexity of anticancer therapy and aging of the population, an adequate medication surveillance of DDIs in this population is increasingly important. Multiple studies show that DDIs are often not recognized as such by prescribers and that the prevalence of (clinically relevant) DDIs in cancer patients is high [5,16]. Although most DDIs are mild, some can be severe or even life threatening and an intervention is needed [10,16,17]. This can also apply to OTC- an herbal drugs, for which more research is warranted into their effects on the efficacy and toxicity of anticancer drugs.

The assessment of DDIs in anticancer therapy is an ongoing process since new insights in (the management of) DDIs are continuously presented in literature. Therefore, new information is continuously discussed and reassessed by the Expert Group and may lead to updates in the recommendations for management of a DDI. For instance, regarding the management of the DDI between tyrosine kinase inhibitors (TKIs) and proton pump inhibitors (PPIs), the use of the acidic beverage cola was added to the advice [18].

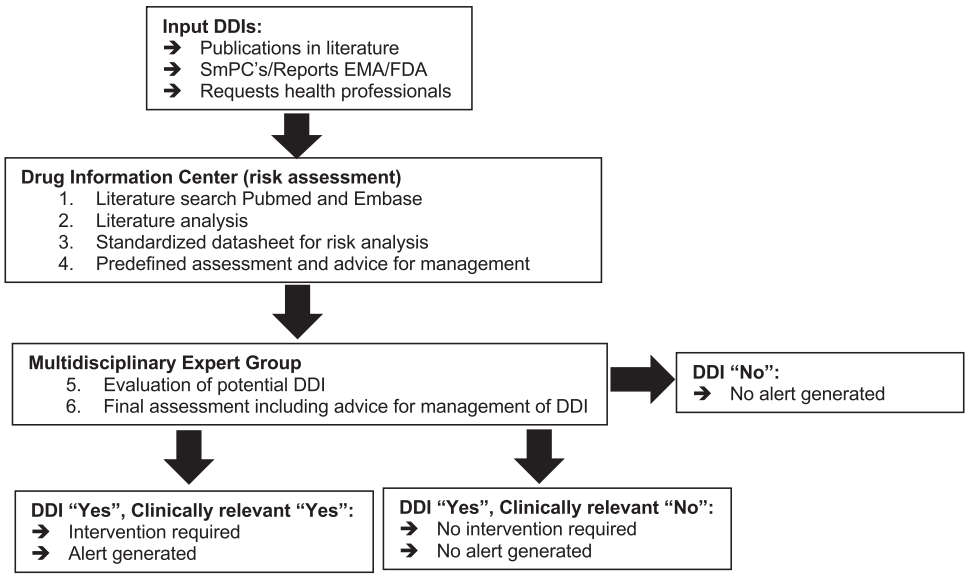

Fig. 1. Workflow Multidisciplinary Expert Group

Table 4
Clinically relevant drug-drug interactions, intervention required [See bottom of table for abbreviations and lists of drugs]

Anticancer agent	Interacting agent	Potential Effect	Management
• Abemaciclib • Palbociclib • Ribociclib	• CYP3A4-inducers	• Therapeutic failure of abemaciclib, palbociclib or ribociclib	• Avoid combination, or • Monitor effect of abemaciclib, palbociclib or ribociclib
• Abemaciclib • Palbociclib • Ribociclib	• CYP3A4-inhibitors	• ↑ toxicity of abemaciclib, palbociclib or ribociclib	• Avoid combination, or • ↓ abemaclib, palbociclib or ribociclib dose
• Abiraterone	• CYP3A4-inducers	• ↓ serum level of abiraterone	• Use alternative for the CYP3A4-inducer, or • ↑ abiraterone dose
• Afatinib	• Ritonavir • Lopinavir • Cobicistat	• ↑ serum level of afatinib	• Administer afatinib at least 1 hour before administration of HIV-medication
• Anagrelide • Arsenic trioxide • Oxaliplatin • Vandetanib	• QTDrug List	• ↑ QTc interval	• Avoid combination, or monitor ECG
• Anthracyclines	• Cyclosporine	• ↑ anthracycline serum levels	• Avoid combination, or monitor serum level of anthracycline
• Anti-androgens	• Androgens (androstanolone, nandrolone, prasterone, testosterone)	• Counteracting effect	• Avoid combination
• Anti-estrogens • Aromatase inhibitors	• Estrogens	• Counteracting effect	• Avoid combination
• Azathioprine • Mercaptopurine • Thioguanine	• Allopurinol • Febuxostat	• Myelosuppression	• Use alternative for allopurinol or febuxostat or • Reduce mercaptopurine/azathioprine dose • Monitor hematological parameters and liver function
• Azathioprine • Mercaptopurine • Thioguanine	• Ribavirin	• Reversible myelosuppression	• Monitor adverse effects (myelosuppression and pancytopenia) and hematological parameters
• Bendamustine	• Allopurinol	• ↑ toxicity (Stevens-Johnson syndrome and toxic epidermal necrolysis)	• Avoid allopurinol, or consider rasburicase in tumor lysis syndrome/rapid tumor lysis
• Bleomycin	• Oxygen	• ↑ bleomycin lung toxicity	• Inform the anesthesiologist about current or past bleomycin administration
• Busulfan	• Itraconazole • Ketoconazole	• ↑ busulfsan serum level	• Avoid combination • Interrupt itraconazole or ketoconazole
• Busulfan	• Metronidazole	• ↑ busulfsan serum level	• Avoid combination • Interrupt metronidazole
• Capecitabine • Fluorouracil	• Folic acid (5 mg)	• Capecitabine or fluorouracil toxicity	• Avoid concomitant folic acid
• Capecitabine • Fluorouracil • Tegafur	• Phenytoin	• ↑ serum level of phenytoin	• Avoid combination • Monitor phenytoin serum level
• Capecitabine • Fluorouracil • Tegafur	• Metronidazole	• Capecitabine or fluorouracil or tegafur toxicity	• Avoid combination • Interrupt capecitabine, fluorouracil or tegafur • Use alternative for metronidazole
• Certain cytostatic agents (bleomycin, carboplatin, carmustine, cisplatin, cyclophosphamide, dacarbazine, doxorubicin, mercaptopurine, vinblastine, vincristine)	• Phenytoin	• Therapeutic failure of phenytoin	• Monitor serum level of phenytoin, adjust dose accordingly

(*continued on next page*)

Table 4 (*continued*)

Anticancer agent	Interacting agent	Potential Effect	Management
• Certain cytostatic agents (bleomycin, cisplatin, cyclophosphamide, cytarabine, doxorubicin, etoposide, ifosfamide, methotrexate, paclitaxel)	• Valproic acid	• Therapeutic failure of valproic acid	• Monitor serum level of valproic acid, adjust dose accordingly
• Certain cytostatic agents (cisplatin, cyclophosphamide, cytarabine, daunorubicin, doxorubicin, hydroxycarbamide, thioguanine, vincristine)	• Carbamazepine	• Therapeutic failure of carbamazepine	• Monitor serum level of carbamazepine, adjust dose accordingly
• Cisplatin	• Aminoglycosides/ • amphotericin-B	• Nephrotoxicity	• Monitor adverse effects (nephrotoxicity)
• Cisplatin	• Loop diuretics	• Nephrotoxicity	• Avoid administration of loop diuretics up to a month after discontinuation of cisplatin. • Short term loop diuretic use during cisplatin infusion is allowed.
• Cladribine	• Lamivudine • Emtricitabine	• Therapeutic failure of cladribine	• Avoid lamivudine or emtricitabine use
• Cyclophosphamide	• Cyclosporine	• ↑ cyclosporine serum level	• Monitor serum level of cyclosporine
• Cytostatic agents	• VKA's	• Stronger fluctuation of coagulation time	• Monitor INR • Alert anticoagulation clinic
• Dabrafenib	• Gemfibrozil	• ↑ dabrafenib serum level	• Avoid gemfibrozil
• Dabrafenib • Lorlatinib • Apalutamide	• Midazolam	• ↓ midazolam serum level	• Use alternative for midazolam (temazepam, flurazepam or oxazepam)
• Dacomitinib	• Dextromethorphan	• ↑ dextromethorphan serum level	• Avoid combination
• Darolutamide	• CYP3A4-inducers	• ↓ darolutamide serum level	• Avoid combination
• Dexamethasone (≥ 5 mg/day) • Methylprednisolone			
• (≥ 100 mg/day)	• Voriconazole	• ↓ voriconazole serum level	• Avoid combination, or • Monitor for symptoms of therapeutic failure of voriconazole and monitor voriconazole Cmin
• Doxorubicin	• HIV protease inhibitors	• Doxorubicin toxicity	• Monitor doxorubicin toxicity
• Duvelisib • Idelalisib • Olaparib	• CYP3A4-inducers	• ↓ serum level of duvelisib, idelasib or olaparib	• Avoid combination, or • Monitor effect of duvelisib, idelalisib or olaparib
• Duvelisib	• CYP3A4-inhibitors	• ↑ duvelisib serum level	• Consider dose reduction of duvelisib • Monitor for symptoms of toxicity (e.g. infections, diarree, colitis)
• Duvelisib • Fedratinib • Idelalisib • Ribociclib • Enzalutamide	• Midazolam	• ↑ midazolam serum level	• Use alternative for midazolam, or • Monitor adverse effects (↑ sedation)
• Mitotane	• Non-anticancer CYP3A4 substrates: Antipsychotics, antiarrhythmic drugs, DOACs, contraceptives, HCV drugs, HIV drugs, immunosuppressants, opioids, other drugs	• ↓ serum level of non anticancer CYP3A4 substrate	• Avoid combination or • Monitor effect of the non anticancer CYP3A4 substrate and adjust dose accordingly

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Table 4 (*continued*)

Anticancer agent	Interacting agent	Potential Effect	Management
• Enzalutamide	• Gemfibrozil	• ↑ enzalutamide serum level	• Avoid gemfibrozil, or • Consider ↓ enzalutamide dose
• Enzalutamide			
• Apalutamide	• VKA's	• ↓ effect of VKA	• Alert anticoagulation clinic
• Enzalutamide • Apalutamide	• Omeprazole • Esomeprazole	• ↓ (es)omeprazole effect	• ↑ (es)omeprazole dose
• Etoposide	• Cyclosporine	• ↑ etoposide serum level	• ↓ etoposide dose
• Everolimus	• Cyclosporine	• ↑ everolimus serum level	• Avoid combination, or • Consider ↓ everolimus dose
• Everolimus	• CYP3A4-inducers • Dabrafenib	• ↓ serum level of everolimus	• Avoid combination, or • Consider ↑ everolimus dose
• Everolimus	• CYP3A4-inhibitors • Fluconazole • Imatinib • Verapamil	• ↑ everolimus serum level	• Avoid combination, or • Consider ↓ everolimus dose • No action needed if using 150 mg single dose or 150 mg once a week fluconazole
• Everolimus	• Flucloxacilline	• ↓ everolimus serum level	• Avoid combination, or monitor everolimus
• Ibrutinib	• CYP3A4-inhibitors	• ↑ ibrutinib serum level	• Avoid combination (ketoconazole) or • Consider decreasing dose ibrutinib (other CYP3A4-inhibitors)
• Ibrutinib • Acalabrutinib	• DOACs • TAIs • Heparins • NSAID's • SSRIś	• ↑ bleeding tendency	• Consultation with hematologist
• Ibrutinib • Acalabrutinib	• VKA's	• ↑ bleeding tendency, without affecting INR	• Alert anticoagulation clinic
• Imatinib • Ribociclib	• Simvastatin	• ↑ statin serum level	• Imatinib: Use alternative for simvastatin • Ribociclib: Stop simvastatin (patient is in palliative phase)
• Imatinib	• Cyclosporine	• ↑ cyclosporine serum level	• Monitor serum level of cyclosporine and renal function
• Immunomodulatory monoclonal antibodies	• Live attenuated vaccines	• Generalized infection or ↓ effect of vaccine	• Avoid combination
• Immuno-suppressant oncolytics • TKIs (immunosuppressive) • Monoclonal antibodies (immunosuppressant)	• Inactivated vaccines	• ↓ effect of vaccine	• Consider repeated administration
• Immuno-suppressant oncolytics • TKIs (immunosuppressive) • Monoclonal antibodies (immunosuppressant)	• Live attenuated vaccines	• Generalized infection or ↓ effect of vaccine	• Avoid combination
• Irinotecan	• CYP3A4-inhibitors	• ↑ serum level of active irinotecan metabolite, SN-38	• Use alternative for CYP3A4-inhibitor, or • Monitor AUC of SN-38
• Irinotecan	• Enzalutamide • Mitotane	• ↓ serum level of irinotecan and active irinotecan metabolite, SN-38	• Use alternative for CYP3A4-inhibitor, or • Donsider dose increase for irinotecan
• Ixazomib • Sonidegib	• Rifampicin	• ↓ serum level of ixazomib or sonidegib	• Avoid combination or • Monitor effect of ixazomib or sonidegib
• Lapatinib • Vemurafenib	• Digoxin	• ↑ digoxin serum level of	• Monitor serum level of digoxin and adverse effects

(*continued on next page*)

Table 4 (*continued*)

Anticancer agent	Interacting agent	Potential Effect	Management
• Methotrexate • Etoposide • Teniposide	• Carbamazepine • Phenytoin • Phenobarbital	• ↓ serum levels of carbamazepine, phenytoin, or phenobarbital	• Monitor serum level of antiepileptic drug
• Methotrexate	• Cotrimoxazole • Trimethoprim	• Methotrexate toxicity	• Avoid combination, except in acute lymphoblastic leukaemia (ALL) • Prophylaxis with low dose cotrimoxazole
• Methotrexate	• Cyclosporine	• ↑ serum level of both methotrexate and cyclosporine	• Monitor adverse effects of methotrexate • Monitor serum levels of methotrexate, and cyclosporine, hematological parameters, and renal function.
• Methotrexate	• Immunocyanin	• ↓ immunocyanin effect	• Avoid combination
• Methotrexate	• NSAID's	• ↑ methotrexate serum level	• Avoid combination, or • Monitor methotrexate serum level and adverse effects and renal function
• Methotrexate	• Probenecid	• ↑ methotrexate serum level	• Avoid combination, or • Monitor adverse effects of methotrexate and monitor renal function
• Methotrexate	• Tenofovir disoproxil	• ↑ risk of tenofovir disoproxil (nephro)toxicity	• Monitor renal function • Consider replacing tenofovir disoproxil by tenofovir alafenamide as part of combination antiretroviral therapy
• Methotrexate, high dose	• Levetiracetam	• ↑ methotrexate serum level	• Monitor adverse effects of methotrexate and renal function
• Methotrexate, high dose	• PPI's	• ↑ methotrexate serum level	• Interrupt PPI use
• Methotrexate, high dose	• Voriconazole	• ↑ risk of phototoxicity	• Monitor for symptoms of phototoxicity • Instruct patient to avoid sun exposure
• Mitotane	• Spironolactone	• ↓ mitotane effect	• Avoid combination, or • Monitor serum level of mitotane
• Olaparib	• CYP3A4-inhibitors	• Olaparib toxicity	• Avoid combination, or • ↓ olaparib dose
• Panobinostat	• CYP3A4-inducers	• ↓ panobinostat serum level	• Use alternative for panobinostat, or • Monitor effect of panobinostat
• Panobinostat	• CYP3A4-inhibitors	• ↑ panobinostat serum level	• Use alternative for panobinostat, or • Consider decreasing panobinostat dose
• Regorafenib Darolutamide	• Rosuvastatin	• Rosuvastatin toxicity (myopathy)	• Instruct patient on possible symptoms of rosuvastatin toxicity
• Regorafenib • Vandetanib	• Rifampicin	• Alteration of regorafenib or vandetanib effect	• Use alternative for regorafenib or vandetanib, or • Monitor effect regorafenib or vandetanib
• Rolapitant	• Rifampicin	• ↓ rolapitant serum level	• Monitor effect of rolapitant
• Ruxolitinib	• Fluconazole	• ↑ ruxolitinib serum level	• Avoid combination or • Consider reduction of ruxolitinib dose • No action needed with fluconazole dosages of 150 mg single dose or 150 mg once a week

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Table 4 (*continued*)

Anticancer agent	Interacting agent	Potential Effect	Management
• Talazoparib	• Itraconazole	• ↑ talazoparib toxicity	• Avoid combination or • Consider dose reduction of talazoparib
• Tamoxifen	• VKA's	• ↑ effect of VKA	• Monitor INR • Alert anticoagulation clinic
• Tamoxifen	• CYP2D6-inhibitors	• ↓ formation of active endoxifen metabolite	• Avoid combination
• Tamoxifen	• CYP3A4-inducers	• ↓ serum level of tamoxifen and active metabolite endoxifen	• Avoid combination, or • Monitor serum level of tamoxifen and endoxifen and consider dose-adjustment
• Tamoxifen	• Hydroxychloroquine • Chloroquine	• ↑ tamoxifen toxicity (irreversible retinopathy)	• Avoid combination or • Monitor toxicity (retinopathy)
• Temsirolimus	• CYP3A4-inducers	• ↓ (tem)sirolimus serum level	• Use alternative for CYP3A4-inducer, or • Consider increasing temsirolimus dose
• Temsirolimus	• CYP3A4-inhibitors	• ↑ (tem)sirolimus serum level	• Use alternative for CYP3A4-inhibitor, or • Consider reducing temsirolimus dose
• Temsirolimus	• Disulfiram • Metronidazole	• Torisel© solution for injection contains alcohol, resulting in ↑ alcohol toxicity when combined with metronidazole or disulfiram	• Avoid combination
• Tivozanib • Vemurafenib	• Rifampicin	• ↓ serum level of tivozanib or vemurafenib	• Avoid combination, or • Monitor effects of tivozanib or vemurafenib
• Trabectedin	• CYP3A4-inhibitors	• ↑ trabectedin serum level	• Avoid combination, or • Monitor adverse effects
• Trabectedin	• Rifampicin	• ↓ trabectedin serum level	• Avoid combination
• TKIs (all exept acalabrutinib, ibrutinib (separate DDI)	• VKA's	• Stronger fluctuation of coagulation time	• Monitor INR • Alert the anticoagulation clinic
• TKIs (acalabrutinib, afatinib, avapritinib, axitinib, bosutinib, brigatinib, cabozantinib, ceritinib, cobimetinib, crizotinib, dabrafenib, dasatinib, entrectinib, erlotinib, gefitinib, gilteritinib, ibrutinib, imatinib, lapatinib, larotrectinib, lorlatinib, midostaurine, neratinib, nilotinib, nintedanib, osimertinib, pazopanib, ponatinib, ruxolitinib, sorafenib, sunitinib)	• CYP3A4-inducers	• ↓ TKI serum level	• Avoid combination, or • Monitor effect of TKI, or • ↑ dose of TKI • Therapeutic drug monitoring of certain TKIs is an option
• TKIs (acalabrutinib, avapritinib, axitinib, bosutinib, brigatinib, ceritinib, cobimetinib, crizotinib, dabrafenib, dasatinib, encorafenib, entrectinib, erlotinib, fedratinib, gefitinib, gilteritinib, lapatinib, larotrectinib, lorlatinib, midostaurine, neratinib, nilotinib, pazopanib, regorafenib, ruxolitinib, sunitinib)	• CYP3A4-inhibitors	• ↑ TKI serum level	• Avoid combination, or • Reduce dose of tyrosine kinase inhibitor • Therapeutic drug monitoring of certain TKIs is an option.
• TKIs, various (acalabrutinib, bosutinib, ceritinib, dacomitinib, dasatinib, erlotinib, gefitinib, lapatinib, neratinib, pazopanib)	• Antacids	• ↓ absorption of TKI	• Separate the dose: TKI at least 2 hours before or 4 hours after the antacid
	• PPIs • H2-receptor antagonists	• ↓ availability of TKI	• Consider temporarily stop of the PPI or H2-recept antagonist, or separate the dose: TKI, 2 hours before PPI or H2-receptor antagonist; if this is not possible, TKI directly followed by PPI or H2-recept antagonist, or TKI concomitantly with Coca-Cola

(*continued on next page*)

Table 4 (*continued*)

Anticancer agent	Interacting agent	Potential Effect	Management
• Vandetanib	• Metformin	• ↑ metformin serum level	• Adjust metformin dose • Instruct patient on possible symptoms
• Venetoclax	• CYP3A4-inducers	• Therapeutic failure of venetoclax	• Avoid combination
• Venetoclax	• CYP3A4-inhibitors • Diltiazem • Fluconazole • Verapamil	• ↑ venetoclax serum level	• Avoid combination or decrease venetoclax dose • No action needed with fluconazole dosages of 150 mg single dose or 150 mg once a week
• Vinblastine	• CYP3A4-inhibitors	• Vinblastine (neuro)toxicity	• Avoid combination, or • Monitor toxicity of vinblastine
• Vincristine	• CYP3A4-inhibitors	• Vincristine (neuro)toxicity	• Avoid combination, or • Monitor toxicity of vincristine • No action needed with fluconazole dosages of 150 mg single dose or 150 mg once a week

Abbreviations: DOAC, direct oral anticoagulant; NSAID, non-steroidal anti-inflammatory drug; PPI, proton pump inhibitor; SSRI, selective serotonin reuptake inhibitor; TAI, thrombocyte aggregation inhibitor; TKI, tyrosine kinase inhibitor; VKA, vitamin K antagonist
Anthracyclines: Daunorubicin, doxorubicin, epirubicin, idarubicin, mitoxantrone, pixantrone
Anti-androgens: Abiraterone, apalutamide, bicalutamide, darolutamide, enzalutamide, nilutamide
Aromatase inhibitors: Anastrozole, exemestane, letrozole
CDK4/6 inhibitors: Abemaciclib, palbociclib, ribociclib
CYP3A4-inducers: Carbamazepine, efavirenz, enzalutamide, phenobarbital, phenytoin, hypericum, mitotane, nevirapine, primidone, rifabutin, rifampicin
CYP3A4-inhibitors: Clarithromycin, cobicistat, erythromycin, itraconazole, ketoconazole, posaconazole, voriconazole, voriconazole, ritonavir
CYP2D6-inhibitors: Bupropion, cinacalcet, fluoxetine, quinidine, paroxetine, terbinafine
DOACs - Direct oral anticoagulants: Apixaban, dabigatran, edoxaban, rivaroxaban
HIV protease inhibitors: Atazanavir, darunavir, fosamprenavir, indinavir, lopinavir/ritonavir, nelfinavir, ritonavir, saquinavir, tipranavir
Histamine H2-repceptor antagonists: Cimetidine, famotidine, nizatidine
Immunomodulatory monoclonal antibodies: Atezolizumab, avelumab, blinatumomab, cemiplimab, dinutuximab, dinutuximab beta, durvalumab, ipilimumab, nivolumab, pembrolizumab
Immmunosuppressant oncolytics: Cytostatics, alpelisib, bortezomib, carfilzomib, CDK4/CDK6-inhibitors, duvelisib, ixazomib, idelalisib, panobinostat, PARP-inhibitors pomalidomide, CAR-T-celtherapy, talimogene laherparepvec (T-VEC)
NSAIDs - Non-steroidal anti-inflammatory drugs: Celecoxib, diclofenac, etoricoxib, ibuprofen, indomethacin, mefenamic acid, naproxen
PPIs - Proton pump inhibitors: Dexlansoprazole, esomeprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole, omeprazole/sodium bicarbonate (Zegerid®)
QTDrug List: Amiodarone, azithromycin, chloorpromazine, chloorprotixeen, chloroquine, (es)citalopram, claritromycine, disopyramide, donepezil, droperidol, erytromycin, flecainid, fluconazole, haloperidol, hydroxychloroquine, ibutilide, ketanserine, kinidine, levofloxacine, levomepromazine, methadone, moxifloxacine, ondansetrone, papaverine, pentamidine, pimozide, procainamide, roxitromycine, sertindol, sotalol, sulpiride
Source: Arizona Center for Education and Research on Therapeutics (AZCERT): QTDrug List – Drugs with potential to prolong the QT interval and known risk of torsadse de pointes (TdP)
SSRIs - Selective serotonin reuptake inhibitors:
• Citalopram, dapoxetine, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline
• Duloxetin, milnacipram, venlafaxine (noradrenaline and serotonin reuptake inhibitors [SNRI]
• Trazodone (serotonin antagonist and reuptake inhibitor [SARI]
TAIs - Thrombocyte aggregation inhibitors: Acetylsalicylic acid, clopidogrel, dipyridamole, eptifibatide, prasugrel, ticagrelor, tirofiban
VKAs - Vit K antagonists: Acenocoumarol, phenprocoumon, warfarin

In addition, the extrapolation of the DDI between TKIs and PPIs must be considered carefully. Although many TKIs show a clinically relevant DDI with a PPI based on altered pH dependant solubility, it is unknown whether this DDI can be extrapolated to all TKIs with known pH dependant solubility. Therefore, a solid in-depth evaluation of known literature and a clear understanding of pharmacology is needed for the risk assessment of this DDI [19].

The past decade there has seen a shifting paradigm towards therapeutic drug monitoring (TDM) in managing DDIs. Especially for most TKIs, there is a clear relationship between exposure, toxicity and treatment efficacy and recommendations have been developed for the integration of TDM for this class of anticancer drugs [20–23]. For certain anticancer agents TDM offers a practical way to manage DDIs, where dose adjustments can be made if drug plasma levels are outside the therapeutic window. To explore further application of TDM, more research is needed to confirm the relevance of TDM as an instrument to be leveraged in the management of DDIs in oncology.

Current studies clearly show that DDIs frequently occur in cancer patients and are often clinically relevant [24–27]. The assessment and advice given by the Multidisciplinary Expert Group contributes to an efficient and evidence-based electronic DDI medication surveillance, where these guidelines provide an important tool in the prescribing of anticancer drugs, thereby optimizing treatment efficacy and improving patient safety.

Conclusion

As the complexity of anticancer therapy increases, more specific screening tools for the detection of DDIs are necessary to increase the efficacy and limit the toxicity of anticancer therapy. This article gives a clear overview of clinically relevant DDIs with anticancer therapy. Furthermore, a straightforward approach for assessment and integration of DDI guidelines into the national electronic prescribing system is provided and may offer a structured, evidence-based, and consensus-based tool for DDI medication surveillance during anticancer therapy. The overview and specific universal tools given in this study may help (hemato-)oncologists and pharmacists to be more aware of DDIs during anticancer therapy and may lead to a closer collaboration in the assessment, management,

and integration of these DDIs into national electronic prescribing systems.

Study highlights

Drug-drug interactions (DDIs) with anticancer drugs are common and can significantly affect efficacy and toxicity of treatment. Since 2006, a Dutch Multidisciplinary Expert Group has assessed the clinical significance of DDIs in oncology and provides recommendations for the management of these DDIs.

A transparent methodology and outcomes of an evidence- and consensus-based assessment of DDIs concerning anticancer drugs is presented. Integration of DDI guidelines into the national electronic prescribing system is essential to achieve optimal efficacy and minimal toxicity in patients receiving anticancer therapy. A clear overview of clinically relevant DDIs with anticancer therapy provides clinicians with a structured, evidence-based, and consensus-built tool for anticancer therapy surveillance and management.

Author contributions

RvL: Formal analysis; Investigation; Methodology; Validation; Visualization; Writing – original draft. **MIC:** Data curation; Formal analysis; Methodology; Project administration; Software; Validation; Writing – review &editing **AR:** Formal analysis; Methodology; Validation; Writing – review & editing. **AT:** Formal analysis; Methodology; Validation; Writing – review & editing. **BV:** Formal analysis; Methodology; Validation; Writing – review & editing. **WK:** Formal analysis; Methodology; Validation; Writing – review & editing. **BW:** Data curation; Formal analysis; Methodology; Project administration; Software; Validation; Visualization; Writing – review & editing. **NS:** Formal analysis; Methodology; Validation; Writing – review & editing. **OV:** Formal analysis; Methodology; Validation; Writing – review & editing. **TvG:** Formal analysis; Methodology; Validation; Writing – review & editing. **FI:** Conceptualization; Formal analysis; Funding acquisition; Investigation; Methodology; Supervision; Validation; Writing – original draft; Writing – review & editing.

Conflict of interest

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Supplementary materials

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