Medication risks in older patients (70+) with cancer and their association with therapy-related toxicity

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Abstract

Objectives

To evaluate medication-related risks in older patients with cancer and their association with severe toxicity during antineoplastic therapy.

Methods

This is a secondary analysis of two prospective, single-center observational studies which included patients ≥ 70 years with cancer. The patients' medication was investigated regarding possible risks: polymedication (defined as the use of ≥ 5 drugs), potentially inadequate medication (PIM; defined by the EU(7)-PIM list), and relevant potential drug-drug interactions (rPDDI; analyzed by the ABDA interaction database). The risks were analyzed at two different time points: before and after start of cancer therapy. Severe toxicity during antineoplastic therapy was captured from medical records according to the Common Terminology Criteria for Adverse Events (CTCAE). The association between Grade ≥ 3 toxicity and medication risks was evaluated by univariate regression.

Results

The study cohort comprised 136 patients (50% female, mean age 77 years). Before the start of cancer therapy, patients took on average 5 drugs as long-term medication and 52% of the patients was exposed to polymedication. More than half of the patients used at least one PIM (mostly drugs for acid-related disorders). Approximately one third of the patients exhibited rPDDI. The prevalence of medication risks increased after start of cancer therapy. rPDDI were significantly associated with the adverse outcome of severe overall and hematologic toxicity.

Conclusion

Medication risks are common in older patients with cancer and associated with treatment-related toxicity. This raises the need for tailored interventions to ensure medication safety in this patient group.

Key words

polymedication, potentially inadequate medication, drug-drug interactions, older patients with cancer, toxicity, onco-geriatrics

Introduction

Older patients with cancer may bear a higher risk of drug-related problems because of altered pharmacokinetics and pharmacodynamics, a higher prevalence of concomitant chronic diseases and a higher number of drugs taken. A retrospective analysis showed that 90% of older patients with cancer exhibited drug-related problems (DRP) and a median of three DRP per patient was reported [1]. Consequently, the National Comprehensive Cancer Network (NCCN) recommends a periodic medication review for older patients with cancer [2]. Also, the evaluation of patients' medication is regarded as an essential aspect of their geriatric assessment [3]. There are in particular three aspects of medication risks which are frequently highlighted for older patients with cancer: polymedication, potentially inadequate medication, and drug-drug interactions. A study with 385 older patients with cancer observed a prevalence of 57% exhibiting polymedication [4]. In this patient group, polymedication was associated with adverse events like falls and chemotherapy toxicity [5]. When judging medication quality in older patients with cancer, it is not only important to consider how many drugs, but also which drugs are used. "Potentially inadequate medication (PIM)" are drugs where risks may outweigh benefits in older patients. The PIM prevalence values reported in literature vary depending on the instrument used. A study with 160 older patients receiving parenteral cancer therapy in an ambulatory clinic indicated that 48.1% used at least one PIM according to the 2015 Beers criteria [6]. PIM drugs were associated with adverse outcomes like postoperative complications, higher mortality, and decreased progression-free survival [5]. Moreover, potential drug-drug interactions are frequent among older patients with cancer: Yeoh et al. detected potential drug-drug interactions as the most frequent drug-related problem (36.4%) in older patients receiving

outpatient chemotherapy [1]. Clinical consequences of those interactions might be serious: A study reported that drug-drug interactions caused unplanned hospitalizations of cancer patients in about 2% of cases [7].

Aim

The aim was (I) to assess the medication risks of older patients with cancer regarding polymedication, potentially inadequate medication as well as drug-drug interactions before and after start of cancer therapy, and (II) to analyze their association with toxicity for evaluating the clinical impact.

Methods

Study design and procedures

This was a secondary analysis of the medication data from two prospective, single-center observational studies, namely a pilot study (n = 20) and the respective evaluation study (n = 120) regarding the prediction performance of the CARG and the CRASH score. Those results have already been described elsewhere [8]. A positive vote of the ethics committee of the Faculty of Medicine of the University of Bonn was granted for both studies and all patients signed an informed consent. The studies took place from March to June 2015 and November 2015 to August 2017. Patients were recruited at the inpatient wards of the Johanniter Hospital Bonn with the following inclusion criteria: ≥ 70 years, diagnosis of a malignancy, German language skills and scheduled to start first-line systemic cancer therapy. Exclusion criteria were moderate to severe cognitive impairment (Mini-Mental State

Examination < 20) or previously started cancer therapy. Because not all patients of the pilot study received a systemic cancer therapy later on, only those patients who were actually treated with a systemic cancer treatment were included. The medication was captured from medical records and analyzed at two time points. First, the medication was investigated at the time of admission to hospital for determining the risks of long-term medication which patients received before start of treatment. Additionally, after start of cancer treatment, the medication risks due to cancer therapy were analyzed regarding antineoplastic agents and supportive care.

Medication

In general, the medication was counted per active ingredient and not per medicinal product itself. All active ingredients with systemic effects were collected and classified according to the Anatomical Therapeutic Chemical Classification (ATC code), level 2 (therapeutic subgroups) [9]. Dietary supplements, medical devices, electrolyte solutions or medical gases were not included. Because the focus on this analysis was on long-term medication, all paused drugs and all drugs just used in case of acute symptoms were excluded. Concerning antineoplastic agents and supportive care medication, all respective drugs reported on the therapy plan of the first cycle were included. For enhancing the clinical relevance of findings, the supportive care medication was only considered as PIM or regarding drug-drug interactions if it was applied more than once per cycle.

Polymedication. In this analysis, polymedication was defined as the concomitant use of ≥ 5 drugs. This cut-off value is commonly used and was associated with adverse outcome in the elderly [10]. Excessive polymedication (“hyperpolymedication”) was defined as the use of $\geq$ 10 drugs as discussed by Sharma et al. [10].

Potentially inadequate medication. The EU(7)-PIM list was used, an explicit PIM list which is widely applicable across Europe and is based on the German PRISCUS list [11]. According to the EU(7)-PIM list, some drugs are only regarded as PIM under certain conditions: for instance proton-pump inhibitors (PPI), are only classified as PIM, if taken longer than eight weeks [11]. If the duration of drug use was unknown, this study classified PPI as PIM except if any evidence was found that the PPI was applied for less than eight weeks.

Relevant potential drug-drug interactions. Drug-drug interactions were classified according to the ABDA (Federal Union of German Associations of Pharmacists) interaction database [12]. The ABDA interaction database is the most commonly used interaction database in German community pharmacies. Because further clinical information was missing, all observed drug-drug interactions were assumed to be potential. For enhancing the clinical relevance of findings, this analysis focused on the severe potential drug-drug interactions, in the following referred to as "relevant potential drug-drug interactions" (rPDDI). Those included the following five ABDA classifications which require an intervention or action by health care providers: "Serious consequences possible – contraindicated"; "serious consequences possible – in certain cases contraindicated"; "serious consequences possible – as precaution contraindicated"; "simultaneous usage not recommended", or "monitoring/modification required". Regarding cancer therapy, all interactions between the antineoplastic agents and supportive care medication were excluded because respective cancer therapy regimens are established in clinical protocols. "Desired" rPDDI (e.g. methotrexate and folic acid) were not counted either. For determining the risk of a drug class being involved as an interaction partner in rPDDI, a prevalence-adjusted ratio was calculated which will be referred to as "interaction propensity", see Equation 1:

$$IP = \frac{F_i}{P_d}$$ *Equation 1*

IP = Interaction propensity

F_i = Frequency of a drug or drug class being involved as interaction partner in rPDDI

P_d = Prevalence of a drug or drug class

Toxicity assessment

The incidence of severe toxicity during the therapy course was captured via a standardized form from medical records according to the Common Terminology Criteria for Adverse Events (CTCAE), version 4.03 [13]. Severe toxicity was defined as CTCAE grade 3 (hospitalization indicated), grade 4 (life-threatening) or grade 5 (treatment-related death). Patients were observed until the end of antineoplastic therapy or for a maximum of six cycles [8].

Statistical analysis

Descriptive analyses were carried out for medication data. Furthermore, a univariate logistic regression was performed for determining whether risks in long-term medication before start of cancer treatment were associated with overall, hematologic, and nonhematologic toxicity. Polymedication, PIM, and rPDDI were treated as continuous as well as categorial variables. Analyses were performed using Microsoft® Excel® 2007 (Microsoft Corporation, Redmond, USA) and IBM® SPSS® Statistics Version 25.0 for Windows (IBM Corporation, Armonk, USA). A p-value of < 0.05 was considered statistically significant and 95% confidence intervals were computed.

Results

Patient characteristics

In total, 136 patients were included from the respective studies. A flow chart of the patient inclusion is given in **Figure 1**. The patient characteristics are displayed in **Table 1**.

Long-term medication before start of cancer treatment

Almost all patients were on long-term medication before the start of cancer therapy, only 8/136 (5.9%) patients did not take any regular long-term medication when being admitted to hospital. On average, patients took 5 drugs (standard deviation (SD), 3.5). Most drugs were only available on prescription (587/683); solely 96/683 drugs comprised over-the-counter (OTC) drugs. The most frequently used drug classes were antithrombotic agents (ATC Code B01; mostly acetylsalicylic acid, ASS), agents acting on the renin-angiotensin system (ATC Code C09; mostly ramipril), and diuretics (ATC Code C03; mostly hydrochlorothiazide). On the drug level, pantoprazole, L-thyroxine, and ASS were the drugs which patients received most often. Drug classes and individual drugs of patients' long-term medication are given in **Supplement 1**.

Polymedication. More than half of patients (52.2%) exhibited polymedication (≥ 5 drugs) and approximately every 10th patient (10.3%) exhibited hyperpolymedication (≥ 10 drugs).

Potentially inadequate medication. Patients took in median one (IQR, 1; range, 0-5) PIM drug. More than half of the patients (52.9%) used at least one PIM drug before start of cancer therapy. By far the most frequent PIM drugs were drugs for acid-related disorders (ATC A02). Consistent with this finding, pantoprazole was the most frequently taken PIM drug (42/136 patients). Other commonly used PIM drug classes comprised drugs used in

diabetes (ATC code A10; mostly sitagliptin), drugs for cardiac therapy (ATC code C01; mostly amiodarone), and calcium channel blockers (ATC code C08; mostly verapamil). An overview of the individual PIM drugs is presented in **Table 2.** The respective drug classes are shown in **Supplement 2.**

Relevant potential drug-drug interactions. Approximately one third of the patients (30.9%) exhibited relevant potential drug-drug interactions (rPDDI) in long-term medication before the start of cancer therapy. The majority of rPDDI was classified as "monitoring/modification required" (67/71) according to the ABDA database. Only 4/71 rPDDI were categorized as "simultaneous usage not recommended". No contraindications were observed. Mostly, rPDDI consisted of pharmacodynamic interactions (40/71); 21/71 rPDDI occurred due to pharmacokinetic reasons. In general, a variety of interaction types was observed; the most frequent rPDDI comprised "anti-diabetic drugs – corticosteroids", "agents acting on the renin-angiotensin system – heparinoids" and "simvastatin – amlodipine". Frequently detected rPDDI are presented in **Table 3**.

The most frequent drug classes being involved in rPDDI were agents acting on the renin-angiotensin system (ATC code C09), beta blocking agents (ATC code C07), and antithrombotic agents (ATC code B01); see **Table 4**. According to the interaction propensity, the drug classes with the highest potential of provoking interactions were cardiac therapy (ATC code C01) and corticosteroids for systemic use (ATC code H02). Surprisingly, although being the drug class most frequently involved in interactions, agents acting on the renin-angiotensin system did not exhibit such a high potential of provoking rPDDI when prevalence was considered.

Antineoplastic agents and supportive care medication

In total, the medication of 128 patients could be assessed after initiation of cancer therapy who received in median 6 (IQR, 2.25; range, 1-12) additional drugs. This comprised in median 2 (IQR, 1; range, 1-5) additional drugs for antineoplastic therapy and in median 4 (IQR, 2.25; range, 0-7) additional drugs for supportive therapy. Regarding antineoplastic agents, most frequently the drug classes “plant alkaloids and other natural products” (ATC code L01C, e.g. paclitaxel) as well as “platinum compounds” (ATC code L01XA, e.g. carboplatin) were prescribed. Concerning supportive care medication, by far the most frequently used drug class was “antiemetics and antinauseants” (ATC code A04, e.g. ondansetron). Details regarding prevalence of antineoplastic agents and supportive care medication are presented in **Supplement 3**.

Potentially inadequate medication. After the start of cancer therapy, 36.7% of patients received further PIM drugs being used more than once per cycle. The most commonly used additional PIM drug was ranitidine (32/128), followed by clemastine (17/128) and proton-pump inhibitors (8/128).

Relevant potential drug-drug interactions. After the start of cancer therapy, 29.7% of patients demonstrated further rPDDI between the long-term medication and the antineoplastic agents/supportive care medication which was used more than once per cycle. The types of interactions were diverse. Most frequently, the rPDDI “NSAIDs – corticosteroids” and “cytotoxic agents – thiazide diuretics”, as well as “anti-diabetic drugs – corticosteroids” were observed; see **Table 3**. The rPDDI were usually categorized as “monitoring/modification required” by the ABDA database classification. Three out of hundred twenty-eight (2.3%) patients exhibited contraindications; no patient exhibited more

than one contraindication. The most severe interaction types involved QT prolonging agents. Most rPDDI consisted of pharmacodynamic interactions (30/50); changes in pharmacokinetics only rarely caused rPDDI (5/50). “Corticosteroids for systemic use” (ATC code H02) was the drug class most frequently causing rPDDI. However, “antibiotics” (ATC code J01) was found to be the drug class with the highest interaction propensity (0.86). This was triggered by the numerous interactions between trimethoprim and ACE inhibitors. Respective details are provided in **Table 5**.

Association of long-term medication before start of cancer treatment with severe toxicity

113 patients were available for outcome analysis with complete follow-up data (further site of treatment unknown, n = 4; follow-up data not completely accessible, n = 3; follow-up not conducted (pilot study), n = 16). Overall toxicity grade $\geq$ 3 was documented in 92 (81.4%) patients; 76 (67.3%) showed hematologic toxicity grade $\geq$ 3 and 67 (59.3%) nonhematologic toxicity grade $\geq$ 3 (for more details regarding toxicity see [8]).

For overall and hematologic toxicity, the occurrence of rPDDI in the long-term medication before start of cancer treatment was significantly associated with grade ≥ 3 toxicity in univariate logistic regression: Patients with rPDDI exhibited an approximately 5-fold risk of developing overall toxicity (OR, 5.067; p = 0.036) and an approximately 4-fold risk of experiencing hematologic toxicity (OR, 3.949; p = 0.010). However, the occurrence of rPDDI was not associated with nonhematologic toxicity. Instead, nonhematologic toxicity was significantly associated with the number of drugs per patient and the number of PIM drugs per patient. Corresponding details are displayed in **Table 6**.

Discussion

To the best of our knowledge, this is the first study analyzing the medication risks regarding polymedication, potentially inadequate medication, and drug-drug interactions for a cohort of older patients with cancer in a German hospital setting and evaluating their impact on therapy-associated toxicity. There is one other German study investigating polymedication and its association with severe therapy-related toxicity in a German hospital setting. However, this study only investigated ovarian cancer patients and did not exclusively focus on older patients [14].

In our study, medication risks were common in older patients with cancer even before the start of cancer therapy: 52.2% of patients were exposed to polymedication, 52.9% to potentially inadequate medication (PIM), and 30.9% to relevant potential drug-drug interactions (rPDDI). Moreover, medication risks showed an impact on adverse outcomes: Relevant potential drug-drug interactions were significantly associated with severe overall and hematologic toxicity.

A strength of this study is evaluating the association of medication risks with adverse outcomes for patients, being essential for assessing the clinical implications of our findings. Moreover, another strength is the investigation of two distinct time points which allowed analyzing the changes in medication before and after the start of cancer therapy. In addition, this is the first study assessing PIM use of older patients with cancer via the EU(7)-PIM list. However, the study is limited by the retrospective character of this analysis. The documentation of drugs in the medical records might have been incomplete, which could have led to an underestimation of drug use. Moreover, information on the duration and

rationale of drug use was partly missing due to the retrospective design, limiting judgment of PIM. However, by selecting an explicit PIM list, only little additional data were required. A further limitation is the moderate sample size of the analysis. Therefore, only a univariate approach could be applied for logistic regression. Further studies with a prospective design and a larger patient cohort are needed to corroborate our results.

Medication risks

Heterogeneous definitions of polymedication, PIM or drug-drug interactions as well as differences in data collection and in counting of drugs have led to varying results in the literature. This limits comparability of our results with previous studies. However, regarding polymedication, similar results can be found: Turner et al. reported a prevalence of 57% for polymedication and 15% for hyperpolymedication [4]. The detected PIM prevalence of our study lies within the range of previously reported results as well: A study by Reis et al. indicated that 48.1% of older patients with cancer used at least one PIM drug (according to 2015 Beers criteria) [6]. Concerning rPDDI, Yeoh et al. found that 55.1% of older patients with cancer are exposed to potential drug-drug interactions [1]. Because our study used the ABDA database classification system which is common in Germany but rather unknown in other countries, our results for drug-drug interactions might differ from other studies. Different interaction information systems have presented deviant listing of interactions and variant severity classifications [15].

Health care providers should be especially vigilant about the drug classes “cardiac therapy” (ATC code C01) and “corticosteroids for systemic use” (ATC code H02) because those show the highest potential of provoking interactions when prevalence was considered. However, it

is important to consider that those specific drug-drug interactions are merely potential. The clinical relevance remains unclear, indicating an interesting field of further research.

After start of cancer therapy, patients received additional PIM and rPDDI in our study, suggesting that the overall number of medication risks increases as well. In contrast, Karuturi et al. found a decrease of PIM prevalence in older patients after the diagnosis of breast or colorectal cancer (PIM prevalence breast cancer: pre-chemotherapy 36.6% vs 0-3 months after start of chemotherapy 27.9% vs 3-6 months after start of chemotherapy 20%) [16].

Since some PIM are required as pre-medication or supportive care medication in cancer therapy, the benefit-risk assessment of some PIM drugs in cancer patients may differ from other older patients. Nevertheless, our analysis included all PIM drugs because, regardless of its use in supportive therapy, they bear risks in older patients which physicians should be aware of. Feng et al. reported only a slight difference in prevalence when neglecting the appropriate PIM drugs for cancer patients compared to including all PIM drugs [17]. Regarding rPDDI between the antineoplastic/supportive care medication and the long-term medication after start of cancer therapy, the results of this analysis advise particular caution when prescribing serotonin 5-HT3 receptor antagonists due to the severity of triggered rPDDI. The two most severe interaction types were both caused by serotonin 5-HT3 receptor antagonists due to their QT prolonging properties which might be of special concern in older patients with frequent cardiovascular diseases. Moreover, special attention is required when administering antibiotics being the drug class with the highest interaction propensity, particularly due to interactions between trimethoprim and ACE inhibitors/sartans. Because both drugs/drug classes may increase potassium levels in serum, a combined use bears the risk of hyperkalemia. Considering that the increasing use of targeted drugs in anticancer

therapy with various CYP-enzyme interactions may further increase the probability for relevant drug-drug-interactions between antineoplastic therapy and long-term medication.

Association with severe toxicity

We analyzed the association of the medication taken before start of treatment with subsequent toxicity during therapy cycles in order to see if pre-existing medication risks (which might be preventable) may influence therapy tolerance. In literature, results were not consistent regarding the association between the number of drugs and severe toxicity in older patients with cancer [5]. In line with our results, a secondary analysis did not find an association of the number of daily drugs before start of chemotherapy and overall chemotherapy-related toxicity [18]. In contrast, Hamaker et al. detected a significant association between baseline polymedication and severe toxicity during cancer treatment of older metastatic breast cancer patients [19]. Concerning PIM, Maggiore et al. did not report any association between PIM use and overall grade ≥ 3 toxicity, consistent with our findings [18]. Occurrence of rPDDI was significantly associated with grade ≥ 3 overall and hematologic toxicity in our study. However, a study by Popa et al. indicated that potential drug-drug interactions were not associated with grade 4 hematologic toxicity [20]. In contrast, grade ≥ 3 nonhematologic toxicity was significantly associated with potential drug-drug interactions of higher severity (“level 1-3”) in that study. These differences might be due to the use of different software for classifying the severity of potential drug-drug interactions.

Conclusion

The results of our analysis indicate that medication risks are common and may trigger toxicity of anticancer therapy in older cancer patients. Apart from toxicity, other patient-

relevant endpoints like hospitalization or survival could be of interest for further analyses. Registry-based trials might be useful for gaining more insight into the consequences of medication risks under real-world conditions. In order to address these risks in daily routine, interprofessional interventions tailored to the particular situation of older patients with cancer have a great potential to enhance patient safety. A pharmacist-led, individualized medication assessment reduced the average number of drug-related problems by 45.5% [21]. Studies showing the efficacy of such interventions are urgently needed.

Implication for practice

Medication risks in older patients with cancer are associated with adverse outcomes and raise the need for tailored interventions to optimize medication use in this vulnerable patient group. Multi-disciplinary care involving oncologists, geriatricians, and clinical pharmacists should be further developed to appropriately tackle the problem of polymedication and PIM in older cancer patients.

Conflict of interest

IO, MK, CS have nothing to disclose. UJ, AHJ, YDK report grants from the Herbert-Worch foundation during the conduct of the studies. MMO reports is currently being employed at Grünenthal GmbH, however this was not the case during her main contribution to this study.

Author Contributions

All authors contributed to the study concept and design, manuscript editing, reviewing and approving the final manuscript. Data acquisition: IO, MMO, MK, CS, AHJ, YDK. Statistical analysis: IO. Data analysis and interpretation: IO, UJ, AHJ, YDK. Manuscript preparation: IO.

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Figure captions

Figure 1 *Flow chart of patient inclusion for medication risk analysis*

Tables

Table 1 *Characteristics of the patients included into the medication risk analysis (n = 136); ECOG, Eastern Cooperative Oncology Group; *considering conditions in addition to primary cancer diagnosis; ** by body location according to the National Cancer Institute (NCI)*

Age [years]		
Mean (SD)	76.9 (4.53)	
Min-max	70-88	
Charlson Comorbidity Index*		
Mean (SD)	1.05 (1.237)	
Min-max	0-7	
Creatinine Clearance (Cockcroft-Gault) [mL/min]		
Mean (SD)	67.2 (22.89)	
Min-max	10-131	
	n	**%**
Sex		
Female	68	50.0
Male	68	50.0
ECOG performance status		
Fully active (0)	45	33.1
Capable of all self-care (1-2)	74	54.4
Limited or no self-care (3-4)	17	12.5
Tumor entity **		
Respiratory	34	25.0
Hematological	57	41.9
Gynecological	5	3.7
Genitourinary	3	2.2
Unknown primary	4	2.9
Musculoskeletal	1	0.7
Digestive/gastrointestinal	16	11.8
Breast	13	9.6
Others	3	2.1

Table 1 (continued)

	n	%
Relapse		
No	118	86.8
Yes	18	13.2
Cancer stage		
I	7	5.1
II	11	8.1
III	31	22.8
IV	68	50.0
Missing	19	14.0
Treatment type		
Chemotherapy	81	59.6
Targeted or immunotherapy	9	6.6
Combined chemotherapy and targeted or immunotherapy	46	33.8

Table 2 *Prevalence of individual PIM drugs in long-term medication before start of cancer therapy (n = 136)*

PIM drug (ATC code)	Number of patients	Proportion of patients with respective drug [%]
Pantoprazole (A02BC02)	42	30.9
Sitagliptin (A10BH01)	8	5.9
Amiodarone (C01BD01)	4	2.9
Verapamil (C08DA01)	4	2.9
Rivaroxaban (B01AF01)	3	2.2
Omeprazole (A02BC01)	3	2.2
Amitriptyline (N06AA09)	3	2.2
Sotalol (C07AA07)	3	2.2
Diclofenac (M01AB05)	2	1.5
Diltiazem (C08DB01)	2	1.5
Methocarbamol (M03BA03)	2	1.5
Metoclopramide (A03FA01)	2	1.5
Pramipexole (N04BC05)	2	1.5
Trospium (G04BD09)	2	1.5

Table 3 *Types of rPDDI, observed in patients before start of cancer therapy (n = 136) and additional rPDDI between antineoplastic agents/supportive care medication and the long-term medication after start of cancer therapy (n = 128), with prevalence, ABDA database classifications, and interaction mechanism/effect; NSAIDs, nonsteroidal anti-inflammatory drugs; * interaction was unintended in this case*

Interactions before start of cancer therapy			
Type of interaction	**Number of interactions**	**ABDA database classification**	**Mechanism/effect of interaction**
Anti-diabetic drugs – corticosteroids	8	Monitoring/modification needed	Hyperglycemic effect of corticosteroids
Agents acting on the renin-angiotensin system – heparinoids	8	Monitoring/modification needed	Increased risk of hyperkalemia
Simvastatin – amlodipine	8	Monitoring/modification needed	Amlodipine inhibits simvastatin metabolism via CYP3A4 leading to higher risk of myopathy
Beta agonists – beta blocker	6	Monitoring/modification needed	Antagonistic effects
ACE inhibitors – allopurinol	5	Monitoring/modification needed	Increased risk of immunologic reactions (mechanism unknown)
Amiodarone – beta blockers	4	Monitoring/modification needed	Additive cardio depressive effects
Thyroid hormones – polyvalent cations	4	Monitoring/modification needed	Decreased effect of thyroid hormones due to reduced resorption
Insulins – cardio selective beta blockers	3	Monitoring/modification needed	increased risk of hypoglycemia, masking of hypoglycemic symptoms
NSAIDs – corticosteroids	3	Monitoring/modification needed	Higher risk of gastrointestinal ulcer
Thiazide-diuretics – vitamin D	3	Monitoring/modification needed	Higher risk of hypercalcemia
Others	19	-	-

Table 3 (continued)

Interactions after start of cancer therapy			
Type of interaction	**Number of interactions**	**ABDA database classification**	**Mechanism/effect of interaction**
NSAIDs – corticosteroids	8	Monitoring/modification needed	Higher risk of gastrointestinal ulcer
Cytotoxic agents – thiazide diuretics	7	Monitoring/modification needed	Increased myelosuppressive effects
Anti-diabetic drugs – corticosteroids	5	Monitoring/modification needed	Hyperglycemic effect of corticosteroids
ACE inhibitors – allopurinol	4	Monitoring/modification needed	Increased risk of immunologic reactions (mechanism unknown)
Hyperkalemic drugs – trimethoprim	4	Monitoring/modification needed	Increased risk of hyperkalemia due to additive effects on potassium levels
QT prolonging drugs – antidepressant	3	Simultaneous usage not recommended	Increased risk of torsades de pointes
QT prolonging drugs – antiarrhythmic agent	3	Serious consequences possible – as precaution contraindicated	Increased risk of torsades de pointes
Loop diuretics – platinum compounds	3	Monitoring/modification needed	Higher risk of nephrotoxicity/ototoxicity
Nitrogen mustard derivatives – allopurinol	3	Monitoring/modification needed	Additive myelotoxic effects
Fluoropyrimidines – folate *	2	Monitoring/modification needed	Higher toxicity of fluoropyrimidines
Others	8	-	-

Table 4 *Frequency of drug classes being involved in rPDDI and the respective interaction propensity (ratio of frequency as interaction partner per total frequency of a drug class); n = 136*

Drug class (ATC code level 2)	Number of detected interactions	Interaction propensity
Agents acting on the renin-angiotensin system (C09)	17	0.26
Beta blocking agents (C07)	13	0.26
Antithrombotic agents (B01)	13	0.19
Corticosteroids for systemic use (H02)	12	0.75
Drugs used in diabetes (A10)	12	0.41
Lipid modifying agents (C10)	11	0.23
Diuretics (C03)	9	0.15
Cardiac therapy (C01)	9	1.0
Calcium channel blockers (C08)	8	0.27
Drugs for obstructive airway diseases (R03)	6	0.25
Others	32	-

Table 5 *Frequency of drug classes being involved in rPDDI between antineoplastic agents/supportive care medication (being used more than once per cycle) and the long-term medication after start of cancer therapy, with the interaction propensity (ratio of frequency as interaction partner per total frequency of a drug); n = 128*

Drug class (ATC code level 2)	Number of detected interactions	Interaction propensity
Corticosteroids for systemic use (H02)	13	0.12
Diuretics (C03)	10	0.16
Antimetabolites (L01B)	9	0.30
Antithrombotic agents (B01)	8	0.11
Agents acting on the renin-angiotensin system (C09)	8	0.12
Antiemetics and antinauseants (A04)	8	0.07
Antigout preparations (M04)	8	0.13
Alkylating agents (L01A)	6	0.13
Drugs used in diabetes (A10)	6	0.21
Antibiotics (J01)	6	0.86
Others	18	-

Table 6 *Univariate logistic regression of overall, nonhematologic, and hematologic grade ≥ 3 toxicity during therapy course related to risks in long-term medication (n = 113); reference: in italic; if no reference is given the variable was treated as continuous; Polymedication: ≥ 5 long-term drugs per patient*

	Odds ratio (95% CI)	**P value**
Overall toxicity		
Number of drugs per patient	1.145 (0.979-1.340)	0.090
Patients *without* vs with polymedication	1.519 (0.584-3.954)	0.391
Number of PIM per patient	1.230 (0.710-2.131)	0.460
Patients *without* vs with at least one PIM	1.310 (0.507-3.385)	0.578
Number of rPDDI per patient	3.843 (0.965-15.312)	0.056
Patients *without* vs with at least one rPDDI	5.067 (1.109-23.140)	0.036
Hematologic toxicity		
Number of drugs per patient	1.037 (0.930-1.157)	0.511
Patients *without* vs with polymedication	1.173 (0.534-2.575)	0.691
Number of PIM per patient	0.908 (0.604-1.364)	0.642
Patients *without* vs with at least one PIM	0.944 (0.430-2.077)	0.887
Number of rPDDI per patient	1.587 (0.899-2.803)	0.111
Patients *without* vs with at least one rPDDI	3.949 (1.382-11.285)	0.010
Nonhematologic toxicity		
Number of drugs per patient	1.138 (1.014-1.277)	0.029
Patients *without* vs with polymedication	1.468 (0.691-3.121)	0.318
Number of PIM per patient	1.675 (1.051-2.669)	0.030
Patients *without* vs with at least one PIM	1.926 (0.900-4.120)	0.091
Number of rPDDI per patient	1.591 (0.952-2.658)	0.076
Patients *without* vs with at least one rPDDI	1.663 (0.715-3.870)	0.238

Supplement 1 *Drugs and drug classes (ATC code level 2) of patients' long-term medication before start of cancer therapy (n = 136); ASS, acetylsalicylic acid; HCT, hydrochlorothiazide*

Drug class (ATC code level 2)	**Number of drug prescriptions**
Antithrombotic agents (B01)	70
Agents acting on the renin-angiotensin system (C09)	65
Diuretics (C03)	59
Beta blocking agents (C07)	50
Lipid modifying agents (C10)	48
Drugs for acid-related disorders (A02)	47
Thyroid therapy (H03)	46
Analgesics (N02)	32
Calcium channel blockers (C08)	30
Drugs used in diabetes (A10)	29
Others	207

Drug	**Number of patients**	**Proportion of patients with respective drug [%]**
Pantoprazole	42	30.9
L-thyroxine	38	27.9
ASS	35	25.7
Simvastatin	31	22.8
HCT	29	21.3
Bisoprolol	22	16.2
Ramipril	22	16.2
Amlodipine	21	15.4
Metoprolol	20	14.7
Candesartan	17	12.5
Metamizole	17	12.5

Supplement 2 *Prevalence of PIM drug classes (ATC code level 2) in long-term medication before start of cancer therapy (n = 136)*

PIM drug class (ATC code level 2)	Number of drug prescriptions
Drugs for acid-related disorders (A02)	47
Drugs used in diabetes (A10)	10
Cardiac therapy (C01)	8
Calcium channel blockers (C08)	7
Psycholeptics (N05)	6
Psychoanaleptics (N06)	5
Antithrombotic agents (B01)	4
Anti-inflammatory and antirheumatic products (M01)	3
Beta blocking agents (C07)	3
Urologicals (G04)	3
Others	11

Supplement 3 *Drug classes (ATC code level 2) and individual drugs which patients received as antineoplastic agents or supportive care medication after start of cancer therapy (n = 128)*

Antineoplastic agents	
Drug class (ATC code level 2)	**Number of drug prescriptions**
Plant alkaloids and other natural products (L01C)	76
Platinum compounds (L01XA)	54
Alkylating agents (L01A)	45
Monoclonal antibodies (L01XC)	40
Antimetabolites (L01B)	30
Corticosteroids for systemic use (H02)	29
Cytotoxic antibiotics and related substances (L01D)	29
Others	8
Drug	**Number of patients**
Paclitaxel	38
Carboplatin	37
Rituximab	33
Cyclophosphamide	30
Doxorubicin	25
Vincristine	23
Prednisolone	13
Predisone	11
Oxaliplatin	10
Fluorouracil	9
Etoposide	9
Bendamustine	8
Gemcitabine	8
Cisplatin	7
Decitabine	6
Bortezomib	5
Dexamethasone	5
Methotrexate	4

Supplement 3 (continued)

Supportive care medication	
Drug class (ATC code level 2)	**Number of drugs prescriptions**
Antiemetics and antinauseants (A04)	116
Antihistamines for systemic use (R06)	71
Corticosteroids for systemic use (H02)	62
Drugs for acid-related disorders (A02)	60
Antigout preparations (M04)	49
Analgesics (N02)	35
Detoxifying agents for antineoplastic treatment (V03AF)	34
Others	38
Drug	**Number of patients**
Ondansetron	109
Dexamethasone	62
Ranitidine	52
Clemastine	50
Allopurinol	49
Paracetamol	35
Mesna	32
Dimetindene	21
Calcium folinate	11

Figures

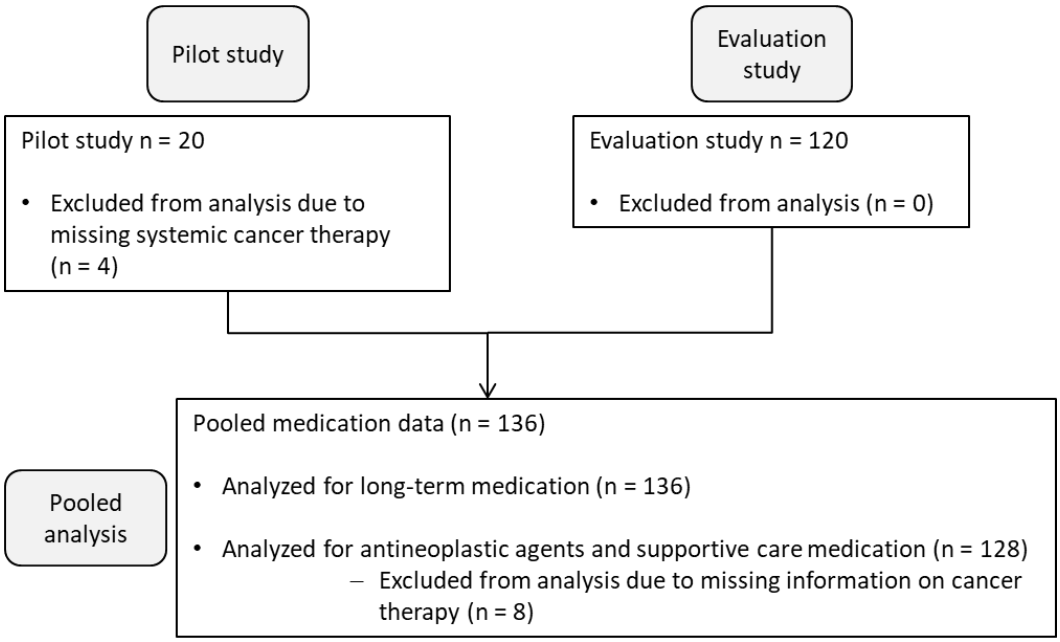

Figure 1