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ORIGINAL ARTICLE

Prognostic impact of polypharmacy and drug interactions in patients with advanced cancer

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Abstract

The risk of potential drug–drug interactions (PDI) is poorly studied in oncology. We included 105 patients with advanced non-small-cell lung cancer (NSCLC), 100 patients with advanced breast cancer (BC) and 100 patients of the palliative care unit (PCU) receiving systemic palliative treatment between 2010 and 2015. All patients suffered from advanced incurable cancer and received basic palliative care. PDI were assessed using the hospINDEX of all drugs approved in Switzerland in combination with a specific drug interaction software. Primary study objective was to assess the prognostic impact of PDI per patient cohort using Kaplan–Meier statistics. The median number of comedications was 5 (range 0–15). Major-risk PDI were detected in 74 patients (24.3%). The number of comedications was significantly associated with PDI ($p < 0.0001$). Major-risk PDI increased from 14% in patients with < 4 comedications to 24% in patients with 4–7 comedications, 40% with 8–11 comedications and 67% in patients with > 11 comedications. Median overall survival (OS) was 8.6 months in NSCLC, 33 months in BC and 1.2 months in PCU patients. PDI were significantly associated with inferior OS in BC (HR = 1.32, 95% CI 1.01–1.74, $p = 0.049$), but not in NSCLC (HR = 1.11, 95% CI 0.84–1.47, $p = 0.45$) or PCU (HR = 1.12, 95% CI 0.86–1.45, $p = 0.41$). PDI remained significantly associated with OS in BC (HR = 1.32, $p = 0.049$) in the adjusted model. In conclusion, PDI are frequent in patients with advanced cancer and increased caution with polypharmacy is warranted when treating such patients.

Keywords Drug safety · Drug interactions · Breast cancer · Lung cancer · Anticancer drugs

Introduction

A drug–drug interaction is defined as the pharmacological or clinical event owed to co-exposure of a drug with another drug that modifies the patient's response to therapy [1, 2]. Drug interactions can result from a variety of processes at the pharmaceutical, pharmacokinetic and/or pharmacodynamic level, and can have different outcomes by increasing or decreasing the therapeutic efficacy or toxicity of a specific treatment [3]. Importantly, many drug interactions as detected by chart reviews or computer algorithms may not necessarily be associated with a clinically relevant

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modification of the patients's response to treatment and may, therefore, rather be called potential drug–drug interactions (PDI) [4].

Tumor patients are subject to frequent polypharmacy, and this is particularly true for elderly patients with advanced cancer. At the same time, the risk of clinically relevant PDI increases with the number of concurrently administered drugs (comedication). Guthrie et al. have described a 5-times elevated risk of clinically relevant PDI with at least 5 concurrently administered drugs, and a 12-times elevated risk with at least 10 concurrently administered drugs [5]. The possible clinical consequences of PDI not only depend on the administered drugs, but also on different other factors including the patient's general health status, age, comorbidities, potential organ dysfunction, the (narrow) therapeutic window of the administered drugs, germline genetic make-up of the individual patient and/or additional unidentified factors [6–8]. Additional complicating factors include the intake of over-the-counter (OTC) or alternative medicines [9] as well as herbal medicines including mistletoe, St. John's wort (Hypericum perforatum) or supplementals such as high-dose vitamins and potential food-drug interactions with oral anticancer drugs [10–12]. Drug interactions are of particular interest in oncology due to the narrow therapeutic window of anticancer drugs, and frequent comorbidities in cancer patients including liver and kidney dysfunction [13]. While both oral and intravenous anticancer drugs are at risk of PDI, oral anticancer drugs are at particular risk, as they are usually metabolized via the cytochrome P450 (CYP) enzyme system mainly localized in the liver but also in other tissues such as the lungs, gut and skin, and are thus prone to drug interactions caused by CYP inducers or inhibitors, including food ingredients, drugs or herbal medicines (e.g., St. John's wort) or are the source of PDI as they are CYP inducers or inhibitors themselves [14, 15]. Up to one-third of cancer patients are prone to clinically relevant drug interactions, and roughly 2% of hospital admissions in cancer patients have been attributed to drug interactions [13, 16–18]. Additionally, the prevention of errors in the pharmacological management of cancer patients may be hampered by a less-than-optimal communication between specialists and patients [19] and potentially by patients' impaired cognitive function. Patients may choose not to report their use of complementary or alternative medicines as they believe that their treating oncologist may not support such alternative drug use [20] or simply because they think that 'natural additives' or 'food supplements' are not regarded as drug therapy .

There is virtually no data on the prognostic impact of PDI in cancer patients despite the substantial proportion of cancer patients being at risk for PDI. There is one clinical study that described a threefold increased risk of chemotherapy-related toxicities in cancer patients experiencing 'level-1' PDI [21]. In the present study, we assessed the prognostic impact of PDI in 3 cohorts of patients with advanced cancer using the hospINDEX of all drugs approved in Switzerland in combination with a specialized drug interaction software.

Materials and methods

Dataset

This retrospective, non-randomized, observational study was carried out at the Cantonal Hospital St. Gallen (Switzerland). It was approved by the Ethics Committee of Eastern Switzerland (2016-00283). All procedures performed in this trial were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its amendments. The 3 cohorts intended to include 100 patients each with advanced non-small-cell lung cancer (NSCLC), advanced breast cancer (BC) and 100 inpatients of the palliative care unit (PCU). Main eligibility criteria included patients with cytologically or histologically confirmed advanced NSCLC stage IV without detectable EGFR mutations or ALK translocations (NSCLC cohort), patients with cytologically or histologically confirmed advanced or metastatic breast cancer (BC cohort) or patients with advanced or metastatic solid tumors being treated at the palliative care unit (PCU cohort). All patients of the NSCLC and BC cohorts initiated palliative first-line systemic treatment between January 2011 and December 2013, and all patients of the PCU cohort were receiving inpatient care between January 2013 and December 2013. PCU patients did not necessarily receive specific systemic anticancer treatment. All patients had to have a complete dataset with regards to patient age, gender, WHO performance status, body weight, comedication including anticancer and non-anticancer drugs, clinical or pathological tumor stage, histology, systemic anticancer treatment received, Charlson comorbidity index and overall survival (OS) status from the time of starting palliative first-line systemic treatment (NSCLC, BC) and from the time of entering the PCU (PCU patients), respectively (Table 1). Clinical data and comedication was assessed when palliative first-line treatment was initiated (NSCLC and BC cohorts) or at the time of referral to the palliative care unit (PCU cohort). OS was similarly calculated from the time at which palliative first-line treatment was initiated (NSCLC and BC cohorts) or from the time of referral to the palliative ward (PCU cohort). The Charlson comorbidity index was calculated as described previously [22].

Table 1 Patient Demographics and Clincal Characteristics

Demographic or clinical characteristic	NSCLC cohort ($n=105$)		BC cohort ($N=100$)		PCU cohort ($N=100$)	
	No. of patients	%	No. of patients	%	No. of patients	%
Age, years						
Median	64		61.5		69	
Range	32–85		30–92		41–98	
≥ 65	52	50	45	45	66	66
Gender						
Male	77	73			52	52
Female	28	27	100	100	48	48
ECOG performance status						
0	22	21	40	40	4	4
1	69	66	48	48	43	43
2	14	13	9	9	27	27
3			3	3	20	20
4					6	6
Charlson Comorbidity Score						
< 6	11	11	5	5	14	14
6	44	42	70	70	48	48
7	32	31	19	19	23	23
> 7	18	17	6	6	15	15
Smoking status						
Never-smoker	7	7	NA		NA	
Current smoker	49	47	NA		NA	
Former smoker	49	47	NA		NA	
Total number of concurrent drugs						
Median	7		5		6	
Range	2–15		1–11		0–15	
Number of non-anticancer drugs						
Median	5		4		5	
Range	0–14		0–9		0–15	
Number of anticancer drugs						
Median	2		2		0	
Range	1–3		1–3		0–3	
Potential drug interactions (PDI)						
No PDI	26	25	53	53	57	57
Low-risk PDI	49	47	21	21	21	21
Major-risk PDI	30	29	26	26	22	22

NSCLC non-small-cell lung cancer, *BC* breast cancer, *PCU* palliative care unit, *PDI* potential drug interaction

Assessment of the risk of potential drug interactions in individual patients

All anticancer and non-anticancer drugs including herbal remedies were assessed in all individual patients. Drugs were subsequently coded by the individual Swissmedic (Swiss Drug Authority) approval number and categorized into 30 non-anticancer drug classes and 12 anticancer drug classes (Table 2). Experimental, non-approved anticancer drugs were similarly categorized into the respective pharmacological group. We used the CDS Web Services drug interaction software tool (HCI Solutions AG, Bern, Switzerland) to assess the presence of PDI in individual patients. The CDS Web Services is based on the hospINDEX database of all drugs approved in Switzerland; the hospINDEX is regularly updated and its comprehensiveness on assessing PDI has been confirmed [23]. The CDS Web Services tool groups PDI into 3 main categories according to the severity of potential clinical consequences; these 3 categories include 'no PDI', 'low-risk PDI' and 'high-risk PDI' (with the latter including the 2 subcategories 'major-risk PDI' and 'absolute contraindication'). Individual PDI for the category

Table 2 Comedication

Demographic or Clinical characteristic	NSCLC cohort ($n=105$)		BC cohort ($N=100$)		PCU cohort ($N=100$)		p value
	No. of patients	%	No. of patients	%	No. of patients	%	
Non-anticancer drugs							
Antiarrhythmics	5	4.8	1	1	2	2	0.22
Calcium antagonists	15	14.3	6	6	13	13	0.14
Sartans	7	6.7	1	1	3	3	0.51
Non-steroidal antirheumatic drugs	44	41.9	39	39	52	52	0.21
Low-dose aspirin	34	32.4	5	5	11	11	<0.001
Beta-blockers	29	27.6	14	14	21	21	0.57
Antibiotics	8	7.6	2	2	18	18	<0.001
Immunosuppressants	4	3.8	1	1	0	0	0.08
Minerals and nutrients	15	14.3	30	30	37	37	<0.001
Selective serotonin reuptake inhibitors	14	13.3	14	14	22	22	0.18
Oral anticoagulants	15	14.3	12	12	27	27	0.01
Opioids	19	18.1	8	8	8	8	0.03
Opiates	27	25.7	15	15	45	45	<0.001
ACE inhibitors	22	20.9	17	17	9	9	0.06
Herbs	3	2.9	9	9	9	9	0.13
Proton pump inhibitors	41	39.1	36	36	55	55	0.01
Steroids	17	16.2	18	18	21	21	0.68
Neuroleptics	9	8.6	3	3	21	21	<0.001
Antidiabetics	10	9.5	7	7	6	6	0.62
Prokinetics	14	13.3	15	15	24	24	0.10
Antiepileptics	3	2.9	4	4	3	3	0.88
Bronchodilators	23	21.9	2	2	7	7	<0.001
Benzodiazepines	14	13.3	17	17	19	19	0.54
Diuretics	14	13.3	15	15	23	23	0.15
Statins	28	26.7	6	6	4	4	<0.001
Laxatives	5	4.8	2	2	4	4	<0.001
Vitamins	31	29.5	8	8	17	17	<0.001
Hormone supplementation	11	10.5	8	8	6	6	0.51
Other non-anticancer drugs	31	29.5	21	21	48	48	0.10
Anticancer drugs							
Monoclonal antibodies	6	5.7	52	52	3	3	<0.001
Endocrine agents	0	0	12	12	7	7	<0.01
Anthracyclines	0	0	11	11	0	0	<0.001
Fluoropyrimidines	0	0	15	15	3	3	<0.001
Tyrosine kinase inhibitors	2	1.9	5	5	3	3	0.46
Platinum salts	95	90.5	6	6	2	2	<0.001
Alkylators	0	0	7	7	0	0	<0.001
Topoisomerase inhibitors	3	2.8	0	0	1	1	0.19
Gemcitabine	6	5.7	4	4	0	0	0.06
Antitubulins	59	56.2	29	29	2	2	<0.001
Antifolates	36	34.3	1	1	0	0	<0.001
Bisphosphonates	2	1.9	4	4	1	1	0.35
mTor inhibitors	0	0	0	0	1	1	0.36

'major-risk PDI' were extracted from the source data and assessed for their type of PDI, i.e., pharmacokinetic or pharmacodynamic interaction, and for the type of involved drugs.

Statistical analysis

The primary study objective was to assess the potential correlation between PDI and OS according to the Kaplan–Meier and Cox proportional hazards models. This analysis was separately done in each of the three patient cohorts. We intended to include a total of 300 study patients, 100 each for advanced NSCLC receiving first-line palliative treatment, 100 for advanced BC receiving first-line palliative treatment and 100 for patients of the palliative care unit (PCU). The study had 84% power to detect a 25% decrease of OS in patients with major-risk PDI according to the specific drug interaction software used (HCI Solutions, Bern, Switzerland). At this point, major-risk PDI include drug combinations that are defined as 'contraindication' by the CDS Web Services drug interaction software. We estimated to have a proportion of patients with major-risk PDI between 25 and 30% based on previous data published by van Leeuwen et al. [24]. Overall survival was calculated from the time of initiating palliative systemic treatment (NSCLC, BC cohorts) and from the time of inpatient admission (PCU cohort). Survival analysis was additionally done using the total number of drugs used per patient. Survival analysis was finally done correcting for patient age, gender (NSCLC, PCU), Charlson comorbidity index and ECOG performance score using Cox proportional hazards models. Correlation analysis was performed between the individual number of drugs used and PDI using analysis of variance (ANOVA). Similarly, distribution of the different drug classes over patient cohorts (i.e., NSCLC, BC, PCU) was performed using ANOVA. Assessment of PDI was done as outlined in the Section on *'Assessment of the risk for drug–drug interaction in individual patients'*, which corresponds to the official PDI assessment tool at the Cantonal Hospital St.Gallen.

Results

Study patients

Based on the inclusion criteria, we included 124 patients with EGFR wildtype and ALK-negative, advanced NSCLC, from which 19 patients were excluded due to incomplete clinical data (NSCLC cohort). We included 113 patients with advanced BC, from which 13 were excluded due to incomplete clinical data (BC cohort). Finally, we included 100 patients from the palliative ward with complete clinical data (PCU cohort). Statistical analysis was performed in a total of 305 fully evaluable patients with advanced cancer. Patient characteristics are outlined in Table 1. Patients in the PCU cohort suffered from a variety of advanced malignancies, most frequently colorectal ($n=12$), prostate ($n=10$), breast or gynecological (each $n=9$), cholangio-pancreatic or gastric or NSCLC (each $n=8$). In the NSCLC cohort, 68 patients had adenocarcinoma histology, 30 patients squamous-cell histology and 4 patients large-cell histology; 49 patients each were current or former smokers while 7 patients were never-smokers. In the BC cohort, systemic treatment included combined chemotherapy and HER2-targeted treatment in 30%, chemotherapy only in 28% of patients, anti-HER2 monoclonal antibodies in 23% of patients, endocrine treatment in 8%, combined endocrine and HER2-targeted treatment in 6% and combined chemotherapy and bevacizumab in another 6%.

Comedication and risk of potential drug interactions

The total number of non-anticancer and anticancer drugs is outlined in Table 1. The specific drug categories within the 3 patient cohorts are outlined in Table 2. While NSCLC patients received significantly more low-dose aspirin, bronchodilators, statins and vitamins as compared to the other cohorts ($p<0.001$, Table 2), PCU patients received significantly more antibiotics, minerals and nutrients, opiates/opioids and neuroleptics as compared to the other cohorts ($p<0.001$, Table 2). This reflects frequent comorbidities such as coronary artery disease or COPD in NSCLC patients or frequent symptoms such as pain and infections in PCU patients. Similarly, the use of anticancer drugs was different between NSCLC and BC, reflecting the different indications (Table 2). The majority of PCU patients did not receive specific anticancer drugs ($n=83$), 12 PCU patients received one anticancer drug, 4 PCU patients 2 anticancer drugs and a single PCU patient received 3 concurrent anticancer drugs. In the overall population, low-risk PDI were found in 91 (29.8%) patients. Major-risk PDI were found in 78 (25.6%) patients overall, including 30 (28.5%) NSCLC patients, 26 (26%) BC patients and 22 (22%) PCU patients (Table 1). The total number of administered drugs was significantly associated with PDI in all 3 cohorts ($p<0.0001$). In the overall population, major-risk PDI increased from 17.1% in patients with < 4 coadministered drugs to 26.2% in patients with 4–7 drugs, 40% with 8–11 drugs and 83.3% in patients with > 11 coadministered drugs. The total number of coadministered drugs is outlined per PDI risk category (no PDIs, low-risk PDI, major-risk PDI) in the overall population (Fig. 1a), the NSCLC cohort (Fig. 1b), BC cohort (Fig. 1c) and PCU cohort (Fig. 1d). All drug combinations associated with major-risk PDI are listed in Table 3. Most common major-risk PDI include the combination of low-dose acetylsalicylic acid (ASA) plus metamizole or non-steroidal anti-inflammatory drugs (NSAID) in 21 cases, the combination of ASA or NSAID, ACE inhibitors and diuretics in 16 cases and taxanes plus trastuzumab in 11 cases. As in the case of taxanes and trastuzumab, a commonly used drug combination may still be identified as potentially resulting in a major-risk PDI

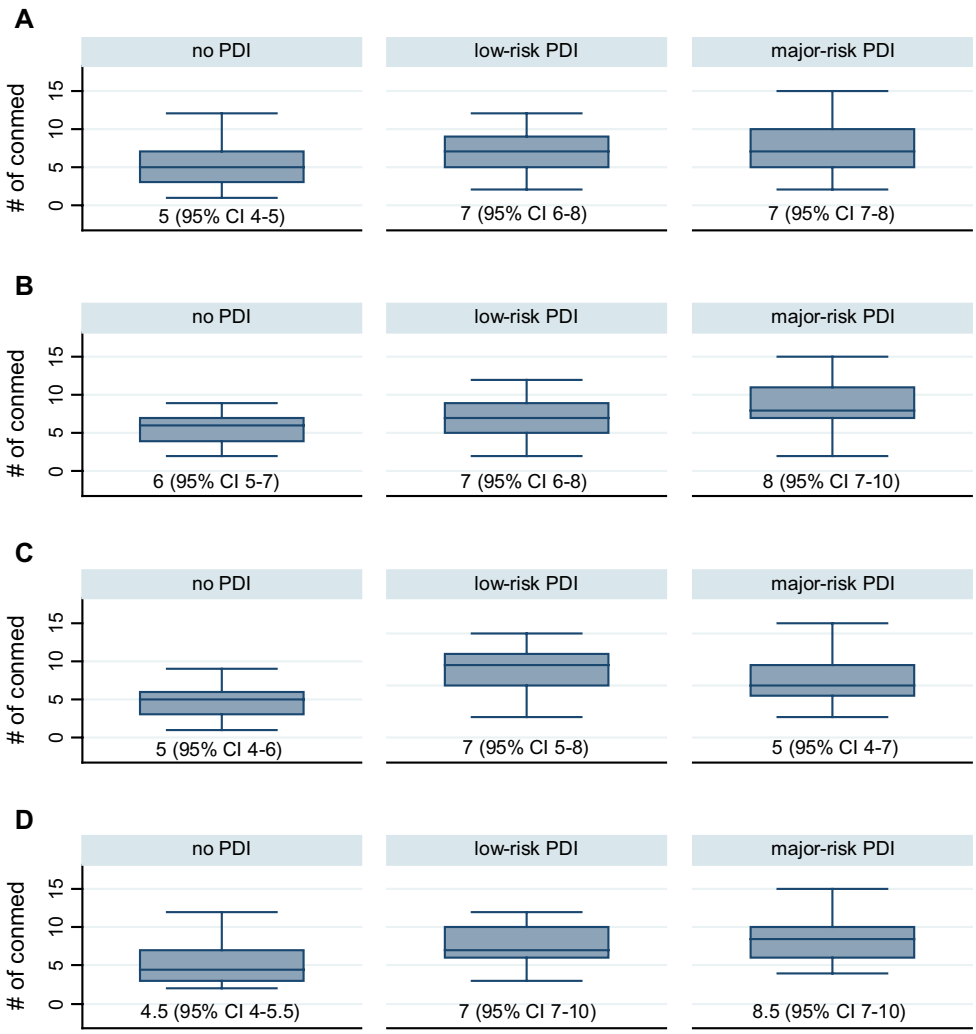

Fig. 1 Box plots showing the correlation between the number of comedications (conmed) on the *Y* axis and potential drug interaction (PDI) categories (no PDI, low-risk PDI, major-risk PDI). This association is separately shown for the overall patient population (**a**), for patients with advanced non-small-cell lung cancer (**b**), patients with advanced breast cancer (**c**) and patients of the palliative care unit (**d**)

due to an increased risk of (additive) cardiac dysfunction (Table 3). As the case of taxanes and trastuzumab is a widely accepted and commonly used anticancer drug combination in patients with early or advanced BC and a substantial proportion of BC women received this combination, we added a sensitivity analysis for the primary study endpoint with/without BC women receiving the taxanes/trastuzumab drug combination.

Comedication, risk of potential drug interactions and clinical outcome

With a maximum follow-up of 6.6 years for both NSCLC and BC, and 4.6 years for PCU, there were 97 deaths in the NSCLC cohort, 72 deaths in the BC cohort and 96 deaths in the PCU cohort, respectively. Median OS was 8.6 months in NSCLC, 33 months in BC and 1.2 months in PCU patients. Major-risk PDI were significantly associated with inferior OS in patients with advanced BC (HR = 1.32, 95% CI 1.01–1.74, $p = 0.049$) (Fig. 2), but not in patients with advanced NSCLC (HR = 1.11, 95% CI 0.84–1.47, $p = 0.45$) and also not in PCU patients (HR = 1.12, 95% CI 0.86–1.45, $p = 0.41$). Major-risk PDI were not significantly associated with inferior OS in the overall study population (HR = 1.12, 95% CI 0.96–1.30, $p = 0.15$). Major-risk PDI remained significantly associated with inferior OS in patients with advanced BC in the adjusted model after correcting for patient age, Charlson comorbidity index and ECOG performance score (HR = 1.32, $p = 0.049$). Major-risk PDI were not significantly associated with inferior OS in patients with NSCLC (HR = 1.15, 95% CI 0.86–1.54, $p = 0.34$) or in PCU patients (HR = 1.07, 95% CI 0.82–1.42, $p = 0.61$) in the adjusted model after correcting for patient age, gender, Charlson comorbidity index and ECOG performance score. In the BC cohort, median OS was 34.8 months (95% CI 20.2–77.5) in patients with no PDI, 26.2 (95% CI 13.4–54) in patients with low-risk PDI and 27 months (95% CI 13.9–37.8) in patients with major-risk PDI ($p = 0.049$). The respective OS numbers for NSCLC patients were 9/10.3/6.5 months ($p = 0.449$) and for PCU patients it was

Table 3 Characteristics of major potential drug interactions in the overall study population

Interaction	No of cases	PK/PD	Description	Severity
ASA × NSAID	21	PD	Decreased tc inhibition and cardiovascular protection	Major risk
NSAID × ACE-inhibitor × diuretics	16	PK	Increased risk of renal dysfunction	Major risk
Taxanes × trastuzumab	14	PD	Increased risk of cardiac dysfunction	Major risk
Opioids[a] × SSRI/TCA	11	PD	Increased risk of ss	Major risk
Steroids × NSAID/ASA	8	PD	Increased risk of gastrointestinal bleeding	Major risk
Cisplatin × paclitaxel	5	PD	Increased risk of neurotoxicity	Major risk
ASA × SSRI	5	PD	Increased risk of bleeding	Major risk
Anthracycline × cyclophosphamide	4	PD	Increased risk of cardiac dysfunction	Major risk
Bisoprolol × amidodarone	3	PD	Increased risk of bradycardia, hypotension, torsade-de-pointes	Major risk
Allopurinol × ACE-inhibitor	2	PD	Increased risk of leucocytopenia	Major risk
Metoclopramide × crizotinib	2	PD	Increased risk of bradycardia and syncope	Major risk
VKA × CYP2C9 inhibitors[b]	2	PK	Increased risk of bleeding	Contraindication
Paclitaxel × clopidogrel	2	PK	Decreased elimination of paclitaxel by clopidogrel	Major risk
Metoclopramide × sertraline	2	PD	Increased risk of SS and extrapyramidale symptoms	Major risk
VKA × levothyroxine	2	PD	Increased risk of bleeding	Major risk
Ondansetron × amiodarone	1	PD	Increased risk of torsade-de-pointes	Contraindication
Amiodarone × moxifloxacin	1	PD	Increased risk of torsade-de-pointes	Contraindication
Hydroxyzin × escitalopram	1	PD	Increased risk of torsade-de-pointes	Contraindication
MgHydrox × MMF	1	PK	Reduced absorption and activity of MMF	Major risk
CSA × MMF	1	PK	Lower plasma concentrations of MMF	Major risk
CSA × pravastatin	1	PK	Increased risk of myopathy and rhabdomyolysis	Major risk
NSAID × VKA	1	PD	Increased risk of gastrointestinal bleeding	Major risk
MgHydrox × ciprofloxacine	1	PK	Decreased absorption of ciprofloxacin	Major risk
Quetiapine × escitalopram	1	PD	Increased risk of torsade-de-pointes	Major risk
Esomeprazole × erlotinib	1	PK	Decreased absorption of erlotinib	Major risk
Phenobarbital × colecalciferol	1	PK	Increased excretion and inactivity of colecalciferol	Major risk
Fentanyl × amiodarone	1	PD	Increased risk of bradycardia and hypotension	Major risk
Amiloride × valsartan	1	PD	Increased risk of hyperkalemia	Major risk

No number, *PK* pharmacokinetic, *PD* pharmacodynamic, *ASA* acetylsalicylic acid, *SSRI* selective serotonin reuptake inhibitors, *NSAID* non-steroidal anti-inflammatory drugs, *MMF* mycophenolate mofetil, *MgHydrox* magnesium hydroxide, *Tc* thrombocytes, *SS* serotonin syndrome (shivering, hyperreflexia, increased temperature, vital sign instability, encephalopathy, restlessness, sweating), *VKA* oral vitamin K antagonists (in particular phenprocoumon), *TCA* tricyclic antidepressant (in particular amitriptylin), *CSA* cyclosporine A

[a]Fentanyl, tramadol

[b]Tamoxifen, capecitabine

1.4/1/1 months ($p = 0.411$). In a sensitivity analysis excluding major-risk PDI resulting from the trastuzumab/taxane drug combination in advanced BC patients, major-risk PDI were non-significantly associated with inferior OS in the adjusted model (HR = 1.24, 95% CI 0.97–1.58, $p = 0.08$). In the overall population, median OS was 11 months in patients with < 4 coadministered drugs, 12.7 months in patients with 4–7 drugs, and decreased to 7.5 months in patients with 8–11 drugs and 3.6 months in patients with > 11 coadministered drugs ($p = 0.002$). The median OS in the BC cohort was 44.8 months, 34.8 months, 31.3 months, and 22.5 months, respectively ($p = 0.48$). While the number of comedications (< 4, 4–7, 8–11, > 11 drugs) was significantly associated with inferior OS in the overall study population (HR = 1.23, 95% CI 1.06–1.44, $p = 0.008$), this was not found in the NSCLC (HR = 1.09, 95% CI 0.90–1.31, $p = 0.38$), BC (HR = 1.10, 95% CI 0.85–1.42, $p = 0.48$) or PCU cohort (HR = 0.96, 95% CI 0.82–1.13, $p = 0.62$).

Discussion

Drug interactions are responsible for approximately 30% of adverse drug reactions [1, 2]. Cancer patients are at particular risk for drug interactions due to the narrow therapeutic window of anticancer drugs and potential complicating factors such as polypharmacy, organ dysfunction and frequent comorbidity. Anticancer therapy and in particular chemotherapy often comes along with the use of multiple supportive drugs including antiemetics, steroids, laxatives or

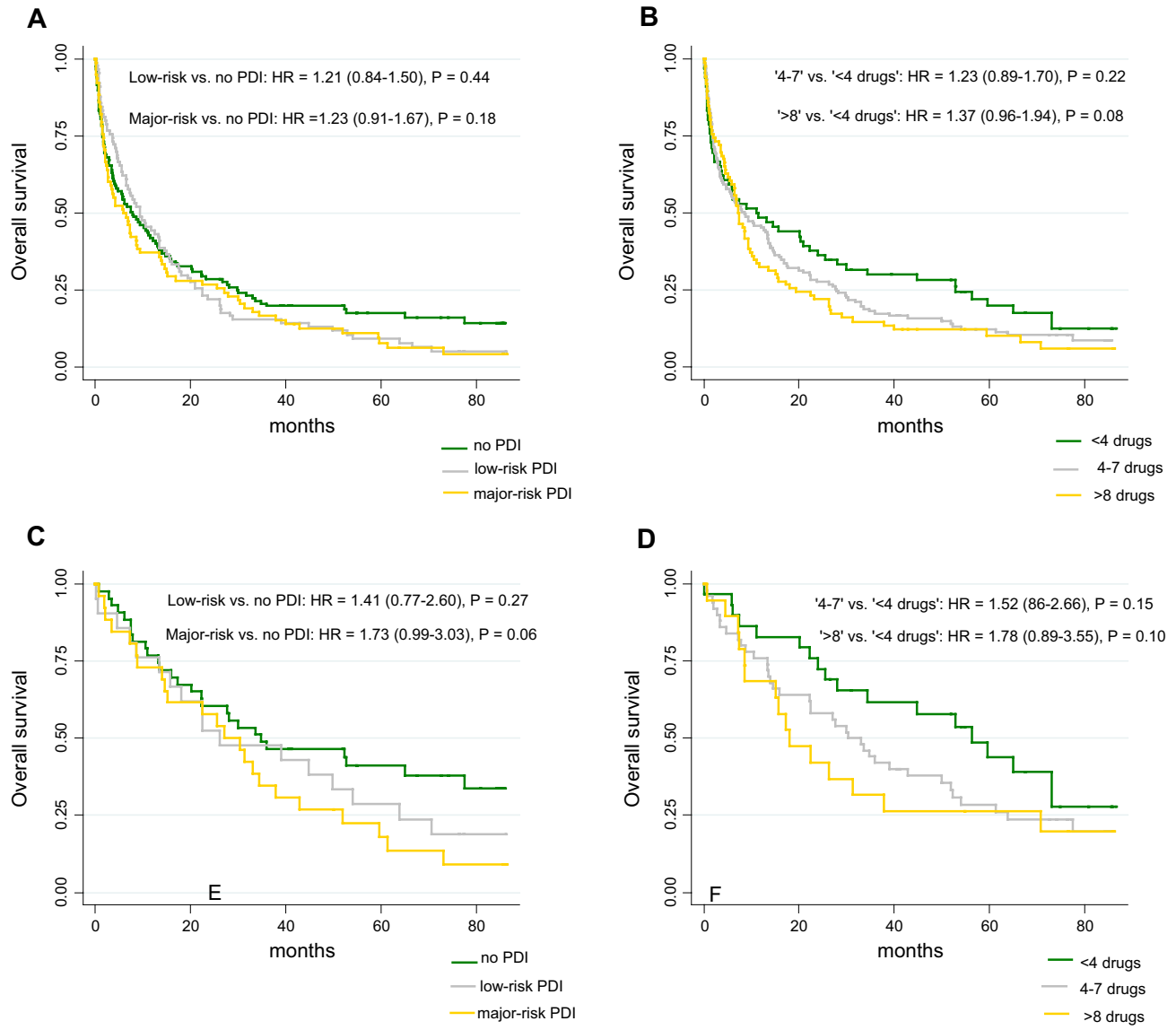

Fig. 2 Overall survival according to potential drug interaction (PDI) categories (**a, c, e, g**) and the number of comedications (**b, d, f, h**) in the overall study population (**a, b**), in patients with advanced breast cancer (**c, d**), advanced NSCLC (**e, f**) and patients of the palliative care unit (PCU) (**g, h**)

antihistamines. These drugs add to the medications used to treat comorbid conditions such as cardiovascular, urogenital or gastrointestinal diseases.

In this retrospective cohort study, a CDS Web Services drug interaction software-based analysis identified the presence of PDI as a factor with a statistically significant association with OS in patients with advanced BC receiving first-line systemic treatment. To our knowledge, this is the first clinical study to detect such an association of PDI with overall survival in cancer patients. Data on the clinical impact of drug interactions in oncology are very limited. While there are good data supporting the presence of PDI in patients being exposed to substantial polypharmacy [25–33], there are no published data on the prognostic impact of PDI on survival in cancer patients as to our knowledge. In the present study, OS was significantly associated with PDI in patients with BC (34.9 months in patients with no PDI, 26.2 in patients with low-risk PDI and 27 months in patients with major-risk PDI). A similar numerical trend was found for PDI and OS in NSCLC patients (9 months in patients with no PDI, 10.3 months in patients with low-risk PDI and 6.5 months in patients with major-risk PDI), but this association was not statistically significant. There may be different reasons for the fact that significant associations of PDI with OS was limited to patients with advanced BC and not found in the other study patients. Most importantly, patients

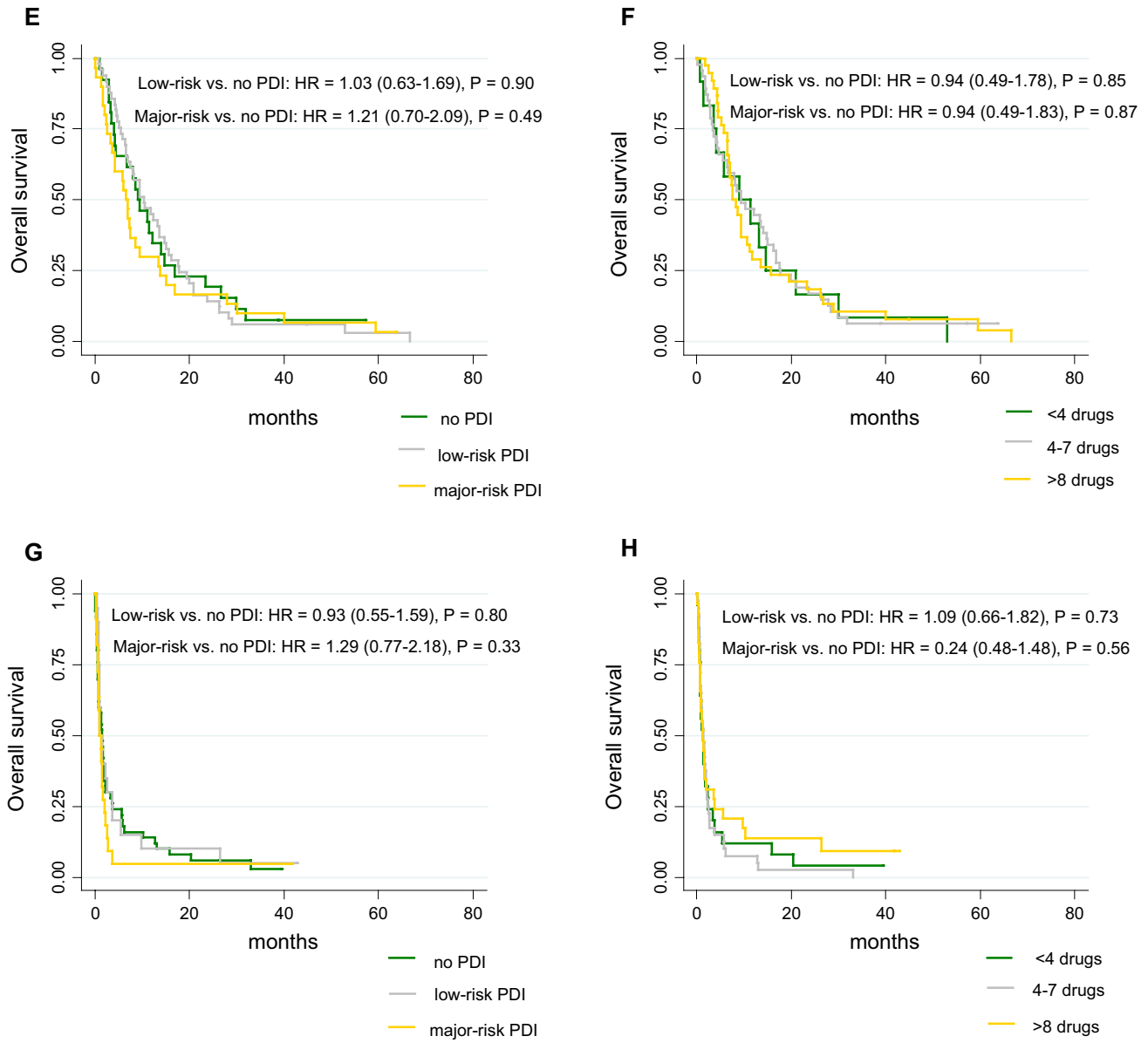

Fig. 2 (continued)

with BC had the longest survival of all 3 patient cohorts (33 months as compared to 8.6 months in patients with advanced NSCLC and only 1.2 months in PCU patients), and therefore, the biggest chance for PDI to impact overall survival. The very short survival in the PCU cohort may explain why any association between the presence of PDI and survival is blunted as survival becomes primarily dependent on acute factors such as the multimorbid health status, organ dysfunction or complicating infections. Additionally, the moderate or strong prognostic impact of ECOG performance status in NSCLC or PCU patients (Fig. 3) may also have overridden a potential impact of PDI in those 2 patient groups, although univariate analysis should not usually be sensitive to collinearity between various covariates. In PCU patients, the highly palliative situation may also have resulted in withholding chemotherapy or potentially life-saving therapies such as, e.g., antibiotics.

At the same time, the current study shows the extent of polypharmacy in cancer patients in general. While 33% of all patients received more than 7 concurrently administered drugs, this proportion was highest in NSCLC patients (44%), followed by PCU patients (33%) and lowest in BC patients (19%). While the median number of concurrent drugs in our cancer patient population was 6, this was higher than has been described for a general (non-cancer) population at a comparable median age (4 concurrent drugs) [5]. The

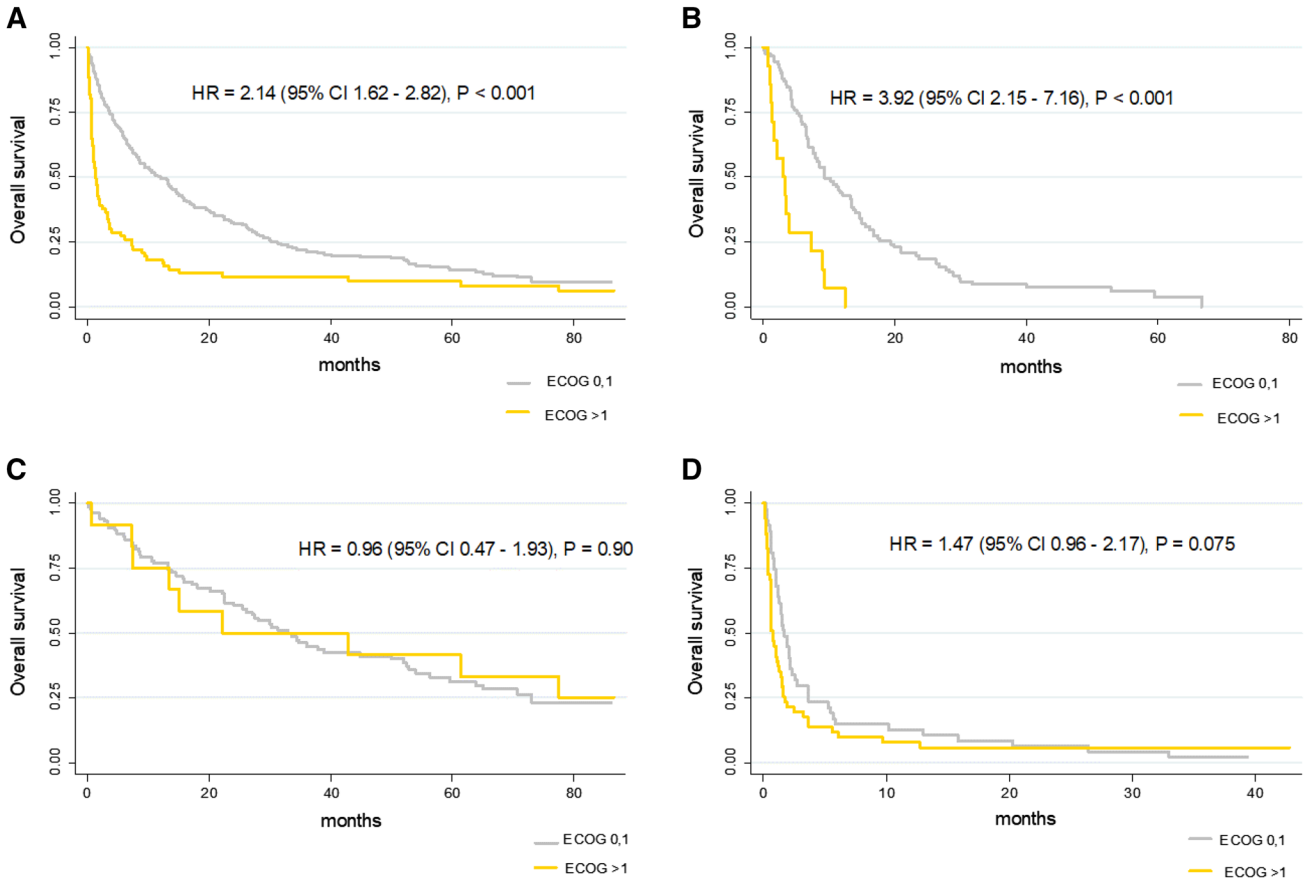

Fig. 3 Overall survival according to ECOG performance status in the overall study population (**a**), patients with advanced non-small-cell lung cancer (**b**), patients with advanced breast cancer (**c**) and patients of the palliative care unit (**d**)

study of Guthrie and colleagues, however, assessed the year 2010, and the same study has indeed shown that the amount of comedication increases over time [5]. While no PDI were detected in 44.6% of the patients, 29.8% of the patients had at least one low-risk PDI, and 25.6% of the patients had at least one major-risk PDI in the overall population. The proportion of patients with at least one PDI in our study (55.4%) is very comparable to what has been described by van Leeuwen and colleagues among 278 cancer patients (58%) [24]. In the study by van Leeuwen and colleagues, 34% of all PDI were classified as major-risk PDI while 60% were classified as moderate-risk PDI [24]. While drugs such as oral vitamin K antagonists (VKA), quinolones, antiepileptics and hydrochlorothiazides were most commonly involved in PDI in the study of van Leeuwen and colleagues [24], we identified combinations between ASA and NSAID, between ASA or NSAID and ACE inhibitors or diuretics, or combinations of opiates/opioids with selective serotonin inhibitors (SSRI) as most frequently involved in major-risk PDI. Besides the case were a widely used drug combination such as the anti-HER2 monoclonal antibody trastuzumab and a taxane is listed as a major-risk PDI (i.e., increased of cardial dysfunction), some PDI may primarily be based on low-evidence clinical data. The latter is true for the combination of low-dose ASA and NSAIDs resulting in decreased thrombocyte inhibition that has been described in a rather small prospective, placebo-controlled crossover study [34] and case reports [35]. In the clinical trial by Meek et al., ibuprofen and naproxen inhibited the antithrombocyte activity of ASA below the non-response threshold, but a clinically relevant effect was not found with the selective COX2-inhibitor meloxicam and there remains some controversy as to whether there is a general pharmacodynamic drug interaction between NSAIDs and ASA on the level of ASA's antiaggregatory effects.

The present study is limited by the relatively moderate patient number per disease cohort, the fact that it was retrospective and we were not able to correct for multiple potential prognostic factors. Nevertheless, the 2 cohorts of BC and NSCLC were rather homogeneous, all patients had metastatic disease and were receiving first-line palliative systemic treatment. As a general note of caution, we were not able to confirm whether PDIs as identified by the drug interaction software used did in fact translate into specific adverse events at the individual level. Quite likely, patients

with more severe comorbidities may also receive a higher number of comedications which subsequently raises the risk of PDI. We intended to correct for the patient's comorbidity by adjusting for the individual ECOG performance score as well as the Charlson comorbidity index. With regards to the latter, having a metastatic tumor already gives these patients 6 risk points on the Charlson index, resulting in decreased sensitivity of the latter in this group of patients.

The lack of optimal communication among specialists and patients may have a role in identifying the risk of drug interactions and acting upon such potential risks by avoiding respective drug combinations. This may be done by withdrawing critical drugs or by replacing critical with non-critical or less-critical drugs, e.g., by switching from enzyme-inducing antiepileptic drugs to non-enzyme-inducing antiepileptic drugs. Despite the identified limitations, this study highlights the urgent need of implementing specific clinical management of cancer patients with new strategies to prevent or minimize harmful PDI. In conclusion, PDI are frequent in patients with advanced cancer and may have an impact on survival in specific groups of cancer patients. Polypharmacy is a known strong risk factor for PDI and increased caution with polypharmacy is warranted when treating patients with advanced cancer.

Compliance with ethical standards

Conflict of interest The authors declare no competing interests concerning this work.

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