Experience with Lexicomp® Online Drug Database for Medication Review and Drug-Drug Interaction Analysis within a Comprehensive Geriatric Assessment in Elderly Cancer Patients

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Abstract: *Background*: We studied the use of Lexicomp®, an online drug information database, for adequate identification of drug-drug interactions (DDIs) within Comprehensive Geriatric Assessment (CGA) in cancer patients.

Materials and Methods: Data of 149 onco-geriatric patients were reviewed. Sixty-three percent participated in an observational study recruiting head and neck cancer patients (*H&N-group*), 37% in a registry recruiting general oncology patients (*GO-group*). Baseline drug information was collected by a health professional, through the medical interview within CGA. Drug class usage was quantified and potential DDIs were assessed and categorized (risk rating "C": monitor therapy, "D": consider therapy modification, "X": avoid combination) with Lexicomp®.

Results: On average, *H&N* and *GO-patients* took 5 and 8 prescription drugs at presentation, respectively. An average of 4 drugs were added in both groups as part of their proposed therapy. Potential DDIs (n=211 H&N; n=247 GO) were detected by Lexicomp® in 64.9% (85.3% "C", 14.7% "D", 0% "X") and 83.6% (83.4% "C", 15.8% "D", 0.8% "X") of *H&N* and *GO* patients, respectively, at therapy start. Administration of cancer-therapy-related drugs lead to additional DDIs (n=75 *H&N*; n=68 *GO*) in 73.7% and 58.3% of *H&N* and *GO* cases, respectively. DDIs occurred mainly with supportive drugs (100% *H&N* and 83.8% *GO*). Sixteen percent of potential DDIs were identified with anti-neoplastic drugs in the *GO-group*. In 28.7% and 60.0% of *H&N* and *GO* patients, respectively, at least one drug was not recognized by Lexicomp®.

Conclusions: Use of Lexicomp® drug database within CGA is feasible. It could reduce the administration of inappropriate drugs, and in that way improve the quality of patient-individualized therapy.

Keywords: Elderly cancer patients, polypharmacy, Comprehensive Geriatric Assessment, Lexicomp® online drug database, drug-drug interactions, safe prescription behavior, cancer treatment.

INTRODUCTION

The ongoing demographic revolution has led to an increased cancer incidence, since 60% of cancers are diagnosed in patients of 65 years and older [1]. Elderly cancer patients pose a challenge to oncology practice, since the coexisting co-morbidity conditions and associated polypharmacy could interfere with safe cancer therapy and therefore require close monitoring [2]. Polypharmacy is defined as the concurrent use of several different medications, including more than one medication from the same drug classification [3]. Wright and Warpula summarized that most community-dwelling patients older than 65 years take at least 3 medications daily, more than 40% of persons aged ≥65 use five or more different drugs per week, and for 12%

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medication use comprises 10 or more different drugs [4, 5]. An increased risk of adverse drug reactions and reduced adherence to the medication regimen are problems that are often encountered in this population [6]. Moreover, physicians might confuse physiological changes due to drug-drug interactions (DDIs) with the symptoms and signs of cancer or other co-morbidities, as well as cancer-therapy related toxicity [7]. Therefore, medication review is an essential part of a Comprehensive Geriatric Assessment (CGA). A CGA is a multidimensional evaluation detecting geriatric problems in different health domains, such as nutrition, cognition, function, psycho-social status, and co-morbidity, and is considered the key treatment approach in elderly cancer patients [8]. Currently, several online drug information databases are available to assist physicians in enhancing safe prescription behavior [9]. The use of electronic databases has shown positive influence on physicians' awareness for potentially inappropriate drug administration, and consequently patient morbidity and mortality, cost management and formulary compliance [10].

We aimed to describe medication use in an elderly cancer population and to evaluate the use of Lexicomp® interaction analyser, an online drug information database, within CGA for adequate identification of potentially harmful DDIs.

MATERIALS AND METHODS

Patient Selection

We retrospectively reviewed data of 149 elderly cancer patients. Sixty-three percent (n=94) of patients participated in an observational study (approved by the respective institutional review boards) recruiting head and neck cancer patients ("*H&N-group*") at General Hospital Groeninge (Kortrijk, Belgium) and Ghent University Hospital (Ghent, Belgium) between January 2010 and February 2012. Consenting patients were eligible if they were ≥65 years old, and had been diagnosed with a histologically confirmed squamous cell carcinoma of the head and neck. Patients were all scheduled for curative primary or adjuvant radiotherapy with or without systemic treatment. All patients received a CGA prior to therapy start [11]. The remaining thirty-seven percent (n=55) of patients were obtained from a local registry of the General Hospital Groeninge, collecting data from General Oncology patients ("*GO-group*") between November 2010 and February 2012, as part of an observational study that was approved by the institutional review board. Consenting patients were registered in the database if they were ≥70 years old and were diagnosed with a solid tumour or haematologic malignancy, scheduled for cancer therapy with curative, palliative or symptomatic intent. Patients underwent a CGA after positive screening on the "G8" or "Vulnerable Elders Survey-13 (VES-13)", two recently validated screening instruments for identification of 'vulnerable' elderly cancer patients in need of a full CGA, or at request by the physician [12, 13].

Medication Review

Drug information of all patients was collected, once before therapy decision or at therapy start, by a health professional, through the medical records and patient interview within CGA. A distinction was made between the chronic prescription drugs, e.g. medications the patient was taking at time of presentation at the oncology department, and the anti-neoplastic and supportive care medicines that were administered in light of the cancer treatment. Supportive care medications, as described in this manuscript, comprise both the supportive drugs as part of the chemotherapy regimen, as well as all other prescription drugs that were specifically administered for the purpose of improving cancer(therapy) tolerance at the time of CGA. Individual drug class usage was quantified and classified according to the *Belgian Center for Pharmacotherapeutic Information* (*BCFI/CBIP*) [14, 15]. Relevant potential DDIs were assessed and categorized (risk rating categories "C": monitor therapy, "D": consider therapy modification, "X": avoid combination) by use of Lexicomp® interaction analyser (Table **1**). Lexicomp® (Lexicomp, Inc., Ohio, USA) is an online drug information database, accessible through a subscription to UpToDate (UpToDate Inc., MA, USA), a clinical decision support system, and enables identification of potential DDIs and patient management guidelines [16]. Each interaction outline provides a risk rating category, which reflects both the level of urgency and the nature of actions necessary to respond to an interaction. The risk rating categories are described in Table **1**. We only retained "C", "D" and "X"-risk ratings, as these are the most relevant for use in a clinical setting. Descriptive statistics were used to summarize patient and tumour characteristics, and medication use, with IBM SPSS v. 19 (SPSS Inc., Chicago, USA).

RESULTS

The *H&N-group* consisted of elderly head and neck cancer patients (86.2% male; mean age 72, range 65 – 86 years), with tumours of the larynx (45.7%), pharynx (33.0%), oral cavity (13.8%), or involved neck nodes of an occult primary (7.4%). The *GO-group* consisted of elderly incident cancer patients (45.5% male; mean age 78, range 65 – 90 years), with primary tumours of

Table 1: Risk Rating Categories as Presented by Lexicomp® for Each Drug-Drug Interaction

Risk rating	Action	Description
A	No known interaction	Data have not demonstrated either pharmacodynamic or pharmacokinetic interactions between the specified agents
B	No action needed	Data demonstrate that the specified agents may interact with each other, but there is little to no evidence of clinical concern resulting from their concomitant use
C	Monitor therapy	Data demonstrate that the specified agents may interact with each other in a clinically significant manner. The benefits of concomitant use of these two medications usually outweigh the risks. An appropriate monitoring plan should be implemented to identify potential negative effects. Dosage adjustments of one or both agents may be needed in a minority of patients.
D	Consider therapy modification	Data demonstrate that the two medications may interact with each other in a clinically significant manner. A patient-specific assessment must be conducted to determine whether the benefits of concomitant therapy outweight the risks. Specific actions must be taken in order to realize the benefits and/or minimize the toxicity resulting from concomitant use of the agents. These actions may include aggressive monitoring, empiric dosage changes or choosing alternative agents.
X	Avoid combination	Data demonstrate that the specified agents may interact with each other in a clinically significant matter. The risks associated with concomitant use of these agents usually outweigh the benefits. These agents are generally considered contraindicated.

The clarification of the risk rating categories was obtained from http://www.uptodate.com.

Table 2: Demographic, Tumour and Treatment Characteristics

	Head and neck (H&N) Group (n=94)	General Oncology (GO) group (n=55)
Age [Years]		
Mean	72	78
Range	65-86	65-90
Gender [% (n)]		
Male	86.2 (81)	45.5 (25)
Female	13.8 (13)	54.5 (30)
Cancer diagnosis [% (n)]		
H&N cancer	100 (94)	7.3 (4)
Larynx	45.7 (43)	
Pharynx	33.0 (31)	
Oral cavity	13.8 (13)	
Occult primary	7.4 (7)	
Urological		27.3 (15)
Gynaecological		23.6 (13)
Gastro-intestinal		16.4 (9)
Breast		12.7 (7)
Skin		5.5 (3)
Hematological		3.6 (2)
Occult primary		3.6 (2)
Treatment intent [% (n)]		
Curative	100.0 (94)	18.2 (10)
Palliative		32.7 (18)
Symptomatic		14.5 (8)
Treatment undetermined		34.5 (19)

the following regions: urological (27.3%), gynaecological (23.6%), gastro-intestinal (16.4%), breast (12.7%), head and neck (7.3%), skin (5.5%), hematological (3.6%) and occult primary (3.6%) (Table **2**).

On average, patients in the *H&N* and *GO-group* took respectively 5 (range 0-15) and 8 (range 1-19) chronic prescription drugs at presentation (Table **3**). For the *H&N group*, these drugs belonged mainly to the following categories: anti-hypertensives (18.6%), lipid-lowering drugs (10.0%), hypnotic agents (8.8%), analgesics (8.8%), gastro-duodenal disorder-related drugs consisting mainly of H_2-receptor antagonists (H2RA) and proton-pump inhibitors (PPIs) (6.3%), anti-diabetics (6.3%), anti-thrombotics (5.3%) and anti-depressants (5.1%). Prescription drugs for the *GO-group* comprised mainly drugs of the following categories: anti-hypertensives (15.0%), analgesics (10.5%), gastro-duodenal disorder-related drugs (mainly H2RAs and PPIs) (10.0%), hypnotics (10.0%), lipid-lowering drugs (6.0%), anti-thrombotics (5.7%), diuretics (3.8%), and anti-diabetics (3.6%).

In addition, fourty percent (n=38) of *H&N patients* received curative radiation therapy in combination with concomitant systemic treatment, consisting of weekly or 3-weekly cisplatinum (73.7%) or weekly cetuximab (26.3%) (Table **4**). About half of *GO-patients* (50.9%) were scheduled for anti-neoplastic therapy at the time of CGA. Eight of the *GO-patients* (14.5%) patients were only scheduled for symptomatic treatment, consisting mainly of gastro-duodenal disorder-related agents (11.1%), anti-emetics (11.1%), analgesics (11.1%), hypnotic agents (11.1%) and bisphosphonates (8.3%). For nineteen (34.5%) of the *GO-patients*, the therapy plan was still undetermined at the time of medication review (Table **2**).

In the *H&N* group, 4 additional cancer-therapy related drugs that were generally administered, were included in the analyses, i.e. the anti-neoplastic drug and the supportive drugs that are included within the chemo(or bio-)therapy regimen. Indeed, both cisplatin and cetuximab can be administered in combination with anti-emetics and glucocorticoids, i.e. methylprednisolon, aprepitant and ondansetron, and methylprednisolon and ranitidin, respectively. In addition, levocetirizine, an H_1-antihistaminic, was included prior to cetuximab administration. An average of 4 drugs were added for the *GO-group* (range 1-12) as part of their cancer therapy (Table **5**). Alkylating agents were the most administered anti-neoplastic drugs in both the *H&N* and *GO* group (Table **4**). Most of the supportive drugs that were administered to the 28 patients receiving anti-neoplastic therapy in the *GO-group*, were anti-emetics (35.2%), glucocorticoid agents (29.6%), anti-histaminics and gastric-duodenal disorder-related agents (both 6.8%), and analgesics (5.1%).

Potentially relevant DDIs (n=211 *H&N*, n=247 *GO*) were detected by Lexicomp® interaction analyser in 64.9% (85.3% "C", 14.7% "D", 0% "X") and 83.6% (83.4% "C", 15.8% "D", 0.8% "X") of all patients within the *H&N*- and *GO-group*, respectively, before therapy start (Table **3**). In 86.9% of cases in the *H&N group*, at least one of the suggestions (average 1.47; range 0-3)

Table 3: Medication Use and Potential Drug-Drug Interactions (DDIs) of all Patients, at Presentation at the Oncology Department

Chronic prescription drug characteristics of all patients under study	H&N Group (n=94)	GO-group (n=55)
Chronic prescription drugs		
Average [n]	5	8
Range	0-15	1-19
Drug-drug interactions		
Average [n]	2	5
Range	0-17	0-20
Total number of DDIs [% (n)]	100.0 (211)	100.0 (247)
Risk rating "C"	85.3 (180)	83.4 (206)
Risk rating "D"	14.7 (31)	15.8 (39)
Risk rating "X"	0 (0)	0.8 (2)
Number of patients exposed to potential DDIs [% (n)]	64.9 (61)	83.6 (46)

DDI: drug-drug interaction; risk rating "C": monitor therapy; risk rating "D": consider therapy modification; risk rating "X": avoid combination.

Table 4: Anti-Neoplastic Drugs Used in Elderly Cancer Patients Undergoing CGA

Drug classification	Drug name	Number of patients [% (n)]
H&N group (n=38)		
Chemotherapeutics		
Alkylating agent(s)	cisplatin (Platinol®)	73.7 (28)
Other		
Monoclonal antibodie(s)	cetuximab (Erbitux®)	26.3 (10)
GO group (n=28)		
Chemotherapeutics		
Alkylating agents	cisplatin (Platinol®), temozolamide (Temodal®), carboplatin (Carboplatinum®), dacarbazine (DTIC®), cyclophosphamide (Endoxan®)	57.1 (16)
Antimetabolites	gemcitabine (Gemzar®), 5-Fluoro-Uracil (Fluoro-Uracil®)	17.9 (5)
Antitumoural antibiotics	pegylated liposomal doxorubicin (Caelyx®), doxorubicin (Adriamycin®)	7.1 (2)
Topo-isomerase inhibitors	topotecan (Hycamtin®)	3.6 (1)
Microtubular inhibitors	vincristinesulfate (Oncovin®), docetaxel (Taxotere®)	14.3 (4)
Other		
Monoclonal antibodies	cetuximab (Erbitux®), rituximab (Mabthera®)	7.1 (2)
Tyrosine-Kinase inhibitors	sorafenib (Nexavar®), sunitinib (Sutent®), pazopanib (Votrient®),	7.1 (2)
Anti-hormonal treatment	letrozole (Femara®), goserilin (Zoladex®), exemestane (Aromasin®)	10.7 (3)
Immunomodulators and immunosuppressants	temsirolimus (Torisel®), everolimus (Afinitor®)	7.1 (2)

to monitor or adapt the chronic prescription drugs -in order to avoid DDIs - was retained in the final physicians' conclusion of the CGA report (data not shown). In accordance with the high prevalence of anti-hypertensive agents, the proposed suggestions consisted mainly of a close monitoring of the blood pressure, heart rate and biochemistry (urea and electrolytes). In contrast to the *H&N group*, we could not obtain similar data for the *GO-group*, since medical supervision of CGA conclusion in the *GO* was performed by the referring physician, and not by a clinical pharmacologist, as was the case in the *H&N* group.

Table **5** describes data of a subset-analysis, considering only those *H&N* (n=38) and *GO* (n=36) patients that were planned for (systemic) cancer therapy. An average total medication use of 8 and 11 drugs during cancer treatment was reported in the *H&N* and *GO-group*, respectively, potentially exposing 78.9% of *H&N* and 88.9% of *GO patients* to an average of 3 (86.0% "C", 14.0% "D", 0% "X"; n=129) or 6 (78.7% "C", 20.3% "D", 1.0% "X"; n=207) DDIs, respectively. Patients took an average of 4 and 7 chronic prescription drugs in the *H&N* and *GO*-group, respectively, potentially exposing 55.3% of *H&N* and 80.6% of *GO patients* to an average of 1 (79.6% "C", 20.4% "D", 0% "X"; n=54) or 4 (82.0% "C", 17.3% "D", 0.7% "X"; n=139) DDIs, respectively. Inclusion of the proposed anti-neoplastic and supportive care drugs (on top of the chronic prescription drugs) led to additional notifications of potential DDIs in 73.7% of cases (90.7% "C", 9.3% "D", 0% "X"; n=75) for the *H&N group*, and 58.3% of patients (72.1% "C", 26.5% "D", 1.5% "X"; n=68) within the *GO-group*. Potential DDIs identified in the *H&N group* occurred only with supportive drugs, no interactions with the anti-cancer drugs (cisplatin or cetuximab) were identified. In contrast, in the *GO-group* 83.8% and 16.2% of DDIs were identified with respectively supportive care and anti-neoplastic medicines (Table **5**). Last, we noted that in 28.7% of *H&N patients*, and 60.0% of the *GO patients*, a full medication review was not completed, since some (components of) medications (10.5% of all medications) were not recognized by Lexicomp® Interaction analyser. An overview of the drugs (available in Belgium) that were not recognized is listed in Table **6**.

DISCUSSION

The aging of the population poses new challenges to medical practice, including pharmacotherapy. Oncology physicians are confronted with a growing

Table 5: Medication Use and Potential Drug-Drug Interactions (DDIs) of Subsets of Patients Scheduled for (Systemic) Cancer Therapy (with Curative, Palliative, or Symptomatic Intent)

	H&N Group (n=38)[a]	GO-group (n=36)[a]
Characteristics of all drugs the patient was taking during cancer treatment, including chronic prescription drugs, anti-neoplastic and supportive care drugs		
Drug characteristics		
Average [n]	8	11
Range	4-17	4-18
Drug-drug interactions		
Average [n]	3	6
Range	0-13	0-19
Total number of DDIs [% (n)]	100.0 (129)	100.0 (207)
Risk rating "C"	86.0 (111)	78.7 (163)
Risk rating "D"	14.0 (18)	20.3 (42)
Risk rating "X"	0 (0)	1.0 (2)
Number of patients exposed to potential DDIs [% (n)]	78.9 (30)	88.9 (32)
Chronic prescription drug characteristics		
Chronic prescription drugs		
Average [n]	4	7
Range	0-13	1-17
Drug-drug interactions		
Average [n]	1	4
Range	0-9	0-17
Total number of DDIs [% (n)]	100.0 (54)	100.0 (139)
Risk rating "C"	79.6 (43)	82.0 (114)
Risk rating "D"	20.4 (11)	17.3 (24)
Risk rating "X"	0 (0)	0.7 (1)
Number of patients exposed to potential DDIs [% (n)]	55.3 (21)	80.6 (29)
Cancer drug characteristics		
Anti-neoplastic and cancer supportive drugs		
Average [n]	4	4
Range	-**	1-12
Additional DDIs [n]		
Average	2	2
Range	0-6	0-11
Total number of DDIs [% (n)]	100.0 (75)	100.0 (68)
Risk rating "C"	90.7 (68)	72.1 (49)
Risk rating "D"	9.3 (7)	26.5 (18)
Risk rating "X"	0 (0)	1.5 (1)
With supportive drugs		
Total number of interactions [% (n)]	100.0 (75)	83.8 (57)
With anti-neoplastic drugs		
Total number of interactions [% (n)]	0 (0)	16.2 (11)
Number of patients exposed to potential DDIs [% (n)]	73.7 (28)	58.3 (21)

[a]number of patients that received anti-neoplastic therapy or treatment with symptomatic intent; **Four drugs (one anti-neoplastic drug and three additional supportive drugs) were per chemo(bio)therapy regimen included in the interaction analysis of H&N cancer patients; DDI: drug-drug interaction; risk rating "C": monitor therapy; risk rating "D": consider therapy modification; risk rating "X": avoid combination.

number of older cancer patients, and are consequently forced to take into account the coexisting co-morbidities and the associated polypharmacy [8, 17].

We aimed to describe therapeutic drug use in this elderly cancer population and to describe our experience with Lexicomp® interaction analyser, an online drug database, within CGA for adequate

Table 6: Drugs Not Recognized by Lexicomp®, and therefore not Included in the Analysis

Generic drug name	Commercial drug name	Drug class
estriol	Aacifemine®	Sex hormones
altizide and spironolacton	Aldactazine®	Diuretics
iron, sucrose, vitamin C, folium acid	B-fer®*	Vitamins and minerals
aceclofenac	Biofenac®	NSAID
canrenoaat	Canrenol®	Diuretics
celiprolol	Celiprolol®	Antihypertensives
clotiazepam	Clozan®	Hypnotics, sedatives and anxiolytics
molsidomine	Coruno®, Corvaton®	Anti-anginal drugs
diosmine and flavonoids	Daflon®	Vein- and capillarotropics
flupentixol and melitracen	Deanxit®	Antipsychotics
nandrolon (decanoaat)	Deca-durabolin®	Sex hormones
dandelion, artichoke, carduus marianus	Detoxicaps®*	Support in the detoxification process
ebastine	Estivan®	H_1 antihistaminics
gliquidon	Glurenorm®	Antidiabetics
picosulphate	Laxoberon®	Laxatives
mianserin	Lerivon®	Antidepressants
alizapride	Litican®	Anti-emetics
lormetazepam	Loramet®	Hypnotics, sedatives and anxioloytics
fenprocoumon	Marcoumar®	Antitrombotic
moxonidin	Moxonidine®	Antihypertensives
folic acid, ferrous, l-arginin, aspartaat	Neo-genyl action®*	Minerals
lormetazepam	Noctamid®	Hypnotics, sedatives and anxiolytics
naftidrofuryl	Praxilene®	Drugs for vascular disorders
serenoa repens-extract	Prosta-urgenin®	Drugs for the genitourinary tract
dosulepine	Prothiaden®	Antidepressants
otilonium	Spasmomen®	Spasmolytics
thiamazol	Strumazol®	Drugs for thyroid gland disorders
anetholtrithion	Sulfarlem®	Drugs for buccopharyngeal disorders
sulpiride	Sulpiride®	Antipsychotics
multivitamins	Supradyn®*	Vitamins and minerals
ornidazol	Tiberal®	Antiparasitic drugs
proglumetacine	Tolindol®	NSAID
nifurtoinol	Urfadyn®	Antibacterial agent
barnidipine	Vasexten®	Antihypertensives
o-(beta-hydroxyethyl)-rutosiden	Venoruton®	Vein and capillarotropics
lercanidipine	Zanidip®	Antihypertensives

*medications not incorporated in the BCFI 2009 [15].

identification of potentially harmful DDIs. Our data confirm that a medication review should be an indispensable domain within CGA. Moreover, the use of Lexicomp® online drug database is - although time-consuming - feasible for this purpose.

Incident *H&N* and *GO-patients* took an average of 5 and 8 concurrent drugs, respectively, upon presentation at the oncology departments. *H&N* cancer patients are known to present with multiple co-morbid illnesses, at least in part, related to a history of alcohol

and tobacco use [18]. The higher number of chronic prescription drugs in the *GO-group* could be related to the older age of the population (different inclusion criteria) and the fact that most *GO* patients are treated with palliative intent in contrast to the *H&N* cancer patients who started an anti-cancer treatment with curative intent. Our data are in line with literature reporting the use of ≥5 different medications weekly in 40% of patients aged ≥65 years, and even ≥10 drugs in 12% of the elderly population [4, 5]. A recent study evaluating elderly patients diagnosed with a gynaecological cancer described that 41% of the patients under study took 4 or more medications [19]. Blower *et al*. wrote that 39% regularly took ≥5 drugs daily, and Wildiers *et al*. stated a drug use of 7 or more medications in 29% of oncology patients [7, 20].

An average of four drugs were added as part of the cancer therapy plan. Supportive care medications are typically administered in combination with anti-neoplastic drugs to treat cancer(therapy)-related complications. In the *GO-group* medication use within the scope of cancer therapy ranged from 1 to 12. Davis *et al*. reported that patients on palliative medicine services often receive ≥5 drugs for symptom relief alone [21].

In our study, Lexicomp® detected potential DDIs in 78.9% and 88.9% of *H&N* and *GO* patients scheduled for (systemic) cancer therapy, respectively, highlighting the importance of a medication review within CGA. Potential DDIs with chronic prescription drugs were detected in 64.9% and 83.6% of all *H&N* and *GO* patients, respectively. This percentage is probably an underestimation since not all the prescription drugs could be included in the interaction analysis as some were not (completely) recognized (Table **6**). However, it is much higher than the 25% of older patients actually experiencing an adverse drug effect, as reported by Chutka *et al*. and Giron *et al*. [22, 23]. Lazarou *et al*. stated that an elderly patient taking ≥5 drugs has a 35% chance of experiencing an adverse drug reaction (ADR) [24]. A possible explanation for the higher percentage of potential DDIs compared to actual ADRs, could be the fact that ADRs are influenced by (higher) drug doses, route of administration as well as patient physiological factors, characteristics that are not (always) taken into account by Lexicomp®. Although Lexicomp® provides valuable drug information, and is considered a top ranked online information database according to a recent publication by Clauson *et al*.[9], it is known that drug databases often display interactions that are irrelevant or clinically unimportant, leading to "alert fatigue". In 86.9% of cases in the *H&N group*, an average of 1 suggestion was retained in the conclusion of the CGA report, to increase awareness of a potential DDI, in comparison to the 2 DDIs that were on average notified by Lexicomp®. Most of these suggestions implied a monitoring of the DDI and could be considered less clinically relevant than risk rating "D" or "X" interactions. In a recent study of Rivkin *et al*. only 14 to 25% of all level "D" and "X" DDIs were considered clinically important by the pharmacist [25].

Addition of cancer-therapy related drugs lead to additional DDIs in 73.7% and 58.3% of *H&N* and *GO* patients. The higher number of DDIs detected in the *H&N group* (n=75 *H&N*; n=68 *GO*) could be related to the high prevalence of cardiovascular co-morbidities. Almost one fifth of *H&N patients* took anti-hypertensive agents. Drugs administered within this scope are known to require tight monitoring (90.7% "C": monitor therapy) [7]. However, the DDIs in the *GO-group* are more severe, with almost one third of interactions requiring drug modification or preclusion of concomitant drug use. Cancer patients are at particularly high risk of DDIs because, additional to medications required for their morbidities, cancer treatment commonly involves multiple medications (some with narrow therapeutic indices), including cytotoxic chemotherapy, hormonal agents, and supportive care drugs [7]. In total, *GO-patients* showed a higher daily medication intake during cancer therapy, and more potential DDIs were detected in this group. This corresponds with previous publications reporting that the risk of DDIs increases markedly with the number of concomitant drugs [26].

In the future, attempts should be undertaken to improve online drug databases by continuous updating of marketed drugs and elimination of clinically unimportant DDIs. Moreover, software should be developed enabling integration of the electronic medical records with inclusion of cancer therapy orders (inclusion of anti-neoplastic and supportive drugs), chronic prescription drugs, age and physiological factors important for drug processing such as kidney and liver function.

The results of this retrospective study should be interpreted with some caution due to limitations in the study design. First, since the medication review was assessed within CGA, the treatment plan was often yet undetermined, in part because the CGA is used to determine the (anti-neoplastic) treatment of choice. Secondly, supportive drugs such as narcotic analgesics or mucositis cocktail-type mouth washes that are often

subsequently administered during the course of therapy, were not consistently incorporated in the analysis. The medication review represents only drug use at one point in time and therefore implies a possible underestimation of the actual drug administration during cancer therapy. Thirdly, a small underestimation of DDIs is likely since not every (component of) drug was recognized by Lexicomp® (Table **6**). However, some of these drugs were also not incorporated in the BCFI, or are only available on the Belgian market and are not marketed in other countries such as the USA. Moreover, our analysis is limited to the presentation of potential DDIs. Although this is an important part of medication review, as mentioned earlier, drug-disease interactions, side effects, accurate dosing and route of drug administration, and patient physiological factors should also be taken into account. Additionally, the Beers criteria or Assessing Care of Vulnerable Elders (ACOVE) guidelines could also provide useful tools for enhancing appropriate drug prescription in elderly patients [27, 28]. Finally, the DDIs reported are only a theoretical description. No records were available of actual adverse drug events that were experienced during treatment. Exploratory analysis of the difference in total DDIs between H&N patients (in 90/94 evaluable patients) that required hospitalization during radio(chemo)therapy versus those who did not, could not reveal a statistically significant difference (Mann Whitney U, P=0.869; unpublished observations). However, the utility of Lexicomp® should be further examined in a future randomized controlled prospective trial recording both theoretical DDIs, as assessed with Lexicomp®, and actual ADRs.

In conclusion, medication review should be an essential part of CGA, as it enables the detection of many potentially inappropriate drug combinations. Use of Lexicomp® online drug database is feasible and could possibly reduce the administration of inappropriate drugs and/or enhance patient monitoring by increasing physician awareness for potentially severe drug interactions. However, optimisation of existing drug databases is needed, in particular to enable use in countries other than the USA. Moreover, software is warranted that integrates electronic medical records and prescription modules and could lead to more time-efficient use of interaction analyzers such as Lexicomp®. Last, an experienced health care provider such as a geriatrician, a clinical pharmacist or pharmacologist remains indispensible to evaluate outcome data for adequate retention of relevant interactions.

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