Journal of Oncological Sciences 4 (2018) 80–84

Contents lists available at ScienceDirect

Journal of Oncological Sciences

journal homepage: https://www.elsevier.com/locate/jons

A retrospective study on potential drug interactions: A single center experience

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ARTICLE INFO

Article history:
Received 16 February 2018
Received in revised form
29 May 2018
Accepted 19 June 2018
Available online 9 July 2018

Keywords:
Cancer patients
Oncology
Polypharmacy
Drug interaction
Chemotherapy

ABSTRACT

Background: In this study, it is aimed to explain the type and frequency of potential drug-drug interactions (pDDI) in patients a Medical oncology service.
Methods: This study retrospective descriptive design. pDDIs were identified using the checker programme (Medscape®). Interactions were classified according to their clinical relevance as minor, moderate and major as appropriate.
Results: The prevalence of pDDIs was 71.3% and median age was 61 years-old (interquartile range 54–68) and female to male ratio was 116/211. The median number of drugs per patient was 8 (interquartile range 5–10). A total of 1102 pDDIs of 327 hospitalized cancer patients were identified. Of those, 16.7% were major and 61.8% moderate, respectively. Concomitant use of opioids was the most common interaction in our study.
Conclusions: Drug interactions were common in hospitalized cancer patients. In order to prevent potential hazardous effect of pDDI, awareness of the physicians should be increased about this issue.

1. Introduction

Drug-drug interaction (DDI) is defined as a situation in which a drug modify the action or effects of another drug, lead to alter the patient's response to therapy.[1–3] It is a common problem[4,5] and the rate of adverse drug reaction is 20–30% in routine clinical practice.[6,7] In addition, the mortality rate related to DDI is approximately 4%.[7,8] DDIs have various levels of severity ranging from mild to severe fatal events.[4] Drug interactions can categorized into 2 groups; potential drug drug interaction and real drug interaction. PDDI is defined as the occurrence of a potentially harmful combination. Real drug interaction can be demonstrated in clinical practice.[5,9] Pharmacologically, drug interactions are separated into three classes: a. Pharmaceutical interactions occurs when mixing chemically incompatible drugs outside the body; b. Pharmacodynamic interactions synergistic, additive, antagonistic and sequence-dependent effects may occurs when two drug are used concomitantly; c. Pharmacokinetic interactions occurs when a drug interferes with the absorption, distribution, metabolism and/or excretion of another drug.[1,9,10] DDIs have three possible consequences as altered the effectiveness or increased adverse events of the drugs or unexpected response.[1,5] The severity of fatal events related to DDIs may correlate with the polypharmacy[11,12] in hospitalized patients.[10] Not only polypharmacy, but also disease burden, length of stay and demographic and clinical characteristics of the patient also effect this potential hazardous event.

Patients with cancer are at high risk of DDIs as chemotherapeutic drugs are used in multi-drug combination regimens. These patients also use medications for cancer-related syndromes such as pain, emesis and infection. However, an additional problem is that cancer incidence increases with aging. Also elderly patients usually have multiple comorbidities and receive multiple drugs to treat these comorbidities.[1,12,13] Unfortunately, the patients receiving medical treatment for cancer is at high risk for potential drug

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Peer review under responsibility of Turkish Society of Medical Oncology.

https://doi.org/10.1016/j.jons.2018.06.001

interactions. This polypharmacy increases the risk DDIs in oncology practice. In our study, we aimed to assess the frequency and severity of pDDI in hospitalized cancer patients.

2. Methods

Data collection were started after Trakya University Ethics Committee approved the study.

2.1. Patients

This retrospective study was conducted between January and April 2017 in our medical oncology service. A total of 327 patients who were hospitalized more than 24 h were analyzed. Patients who received drugs in a clinical trial programme were excluded.

2.2. Study design

Drugs were categorized into two groups as chemotherapy and other drugs (drugs used for supportive treatment and drugs used in treatment of comorbidities). When a drug formulation included two or more active pharmaceutical ingredients like piperacillin/tazobactam each drug was counted separately in the analysis. However, when a patient who receiving the same medication in more than one formulation (e.g. intravenous and oral tramadol) was counted only once. Drug interactions were identified by using the checker programme (reference.medscape.com/drug-interactionchecker). PDDI was classified into three categories according to a level of severity as minor, moderate and major. “Minor” DDIs were defined as drug combinations likely to have no significant clinical relevance; “moderate” as drug combinations where a drug may modify the effect of the another drug and need to be monitored closely; “major” as drug combinations that should be usually avoided or may potentially lead to serious clinical consequences.

2.3. Statistical analysis

Descriptive statistics (mean, median) were applied to characterize all study sample with regard to demographics, cancer type, treatment objective, type of anticancer agents, comorbidities, number of drugs per patient and interaction characteristics. The difference between the groups was compared using Chi-square or Fisher's Exact tests. All data were analyzed using the Statistical Package for the Social (SPSS) version 16.0 (SPSS Inc. Chicago, IL) computer programme and a value of $p < 0.05$ was considered statistically significant.

3. Results

3.1. General characteristics

Table 1 showed the demographic and clinical characteristics of the patients. The median age was 61 years (interquartile range 54–68) and female to male ratio was 211/116. The most common underlying diseases were gastrointestinal cancer (30.9%), followed by lung (25.0%) and genitourinary (13.5%) cancer. Two hundred-three (80.4%) patients had metastasis and 39.1% of these (n = 128) had at least one comorbid disease. The majority of patients had hypertension (73.4%), diabetes mellitus (25.7%). In addition, the median length of hospital stay of patients was 5 days (interquartile range 2–10) and fifty patients (15.3%) died during hospitalization. Ninety-eight patients received chemotherapy during admission. Approximately three quarters (76.2%) of the patients were hospitalized for palliative care. Thirty-four patients (10.4%) did not take any medication for the treatment of their primary disease.

Table 1
Characteristics of patients, N = 327.

Characteristic	n	%
Age (years)		
Median (Interquartile range)	61 (54–68)	–
Gender		
Male/Female	211/116	64.5/35.5
Chemotherapy ratio	98	30.0
Underlying disease		
Gastrointestinal cancer	101	30.9
Lung cancer	82	25.0
Genitourinary cancer	44	13.5
Head and neck cancer	31	9.5
Hepatobiliary cancer	26	7.9
Breast cancer	19	5.8
Others	24	7.4
Patients with comorbidity	128	39.1
Hypertension	94	73.4
Diabetes Mellitus	33	25.7
Hypothyroidism	5	3.9
Coronary arterial disease	4	3.1
Length of stay (days)		
Median (Interquartile range)	5 (2–10)	–
Death		
Yes/No	50/277	15.3/84.7
Metastatic stage	263	80.4
Reason for admission		
Chemotherapy	78	23.8
Palliative care	249	76.2
Cancer treatment		
Chemotherapy	214	65.4
None	34	10.4
Chemotherapy + Antibody	31	9.5
Supportive Care	23	7.0
TKI/mTORs	14	4.3
Antihormonal therapy	8	2.5
Chemotherapy + antihormonal therapy	2	0.6
Antibody	1	0.3

3.2. Drug-drug interactions

PDDI was detected in 233 patients (71.3%) who had at least one interaction, while 94 patients did not show any interaction. The median number of drugs per patient was 8 (interquartile range 5–10). The maximum number of drug used during the admission was 22. Table 2 showed that a total of 1102 potential drug-drug interactions were detected among the patients who received 2 or more medications. Only 21 (1.9%) of these were with chemotherapy drugs. Most of the interactions (n = 1081, 98.1%) were together with supportive care medications. Major and moderate pDDIs were detected as 16.7% and 61.9%, respectively.

Table 3 demonstrated the common pDDIs in patients who received the multiple medications. The most frequent agents included at pDDIs were opioids, SSRIs, corticosteroids, nonsteroidal

Table 2
Drug-drug interactions.

pDDI	n	%
pDDI		
Yes/No	233/94	71.3/28.7
Number of drugs per patient		
Median (Interquartile range)	8 (5–10)	–
Minimum-Maximum	1–22	
Total	1102	100
Chemotherapy-related	21	1.9
Other drugs related	1081	98.1
Level of severity		
Major	184	16.7
Moderate	682	61.9
Minor	236	21.4

Table 3
The most common pDDIs involving drugs used for palliative treatment and comorbidity.

Drug Combination	n	Description	Severity
Opioids x Opioids[a]	77	Either increases effects of the other with pharmacodynamic synergism, increase serotonin levels	Major
Enoxaparin x Piperacillin-tazobactam	29	Piperacillin increases effects of enoxaparin by anticoagulation	Major
SSRI[b] x Opioids	14	Either increases toxicity of the other by serotonin levels	Major
Metocloropamide x SSRI	7	Both increase serotonin levels	Major
Enoxaparin x Corticosteroids[c]	48	Increasing bleeding risk	Moderate
Dexametasone x Tramadol	42	Dexametasone increases the level/effect of tramadol with pharmacodynamic synergism	Moderate
Dexametasone x Fentanyl	20	Dexamethasone decreases the level or effect of fentanyl	Moderate
Fentanyl x Furosemide	15	Fentanyl decreases effects of furosemide	Moderate
Enoxaparin x NSAID/aspirin	15	Both increase anticoagulation	Moderate
Dexametasone x PPI	62	Dexamethasone decreases the level/effect of PPI by affecting hepatic/intestinal enzyme CYP3A4 metabolism	Minor
Amlodipin x Corticosteroids	21	Corticosteroids decrease the level/effect of amlodipin by affecting hepatic/intestinal enzyme CYP3A4 metabolism	Minor

[a] Tramadol/morphine/codeine/Fentanyl.
[b] Alprazolam/Escitalopram/Paroxetine/Sertraline.
[c] Dexametasone/methylprednisolone.

anti-inflammatory drugs (NSAID), low molecular weight heparins (LWMH) and proton pump inhibitors. Opioids with opioids, SSRIs with opioids, LMWH with piperacillin, LMWHs with corticosteroids, NSAIDs with LMWHs, corticosteroids with opioids and -proton pump inhibitors were common combinations. Of these, the most common interaction were opioids and opioids (n = 77).

Table 4 showed the pDDIs together with chemotherapy drugs.

It was shown that increased length of stay were significantly associated with pDDIs ($p < 0.05$). The relationship between drug interaction frequency and age was not statistically significant. The result of analysis of risk factor was shown in Table 5.

4. Discussion

Cancer is generally an advanced age disease. The incidence of chronic diseases and polypharmacy rates are also increasing with aging.[11,14] It is known that an increase in the number of medications leads adverse events and drug interactions in cancer patients who were treated with multiple medications including chemotherapy and supportive care medications such as various hormonal treatments, antiemetics, analgesics.[5,13] Additionally, hospitalized patients have a greater risk than outpatients.[15,16] In this retrospective study, at least one drug interaction was found in 71.3% of hospitalized patients. Moreover, 16.7% of these interactions were major-level interactions that may require follow-up in terms of adverse effects. In a study with cancer patients, Leeuwen et al.[17] found drug interactions in 58% of the patients and 33.9% of these interactions were major. Riechelmann et al.[12] in a retrospective study found that 63% of cancer patients have drug interactions which was similar to our study. And 32% of these interactions were major. Although the rate of drug interaction were higher than the data in the literature, major serious interaction rate was lower.

Patients with cancer are at high risk for pDDIs as they use many drugs simultaneously.[10,18] The average of medicine per capita was 8 in our study group. We revealed that the length of stay was more than 5 days which was significantly associated with potential drug interactions. The length of stay of 157 patients in the study group was more than 5 days. Similarly, Riechelmann et al.[12] defined that the length of stay was associated with potential drug interactions that were greater than 6 days. We suggest that less hospital stay leads to decreased potential drug-drug interactions.

Pain is a common symptom in cancer patients. Prevalence and severity are related to many factors such as the stage, location and metastatic site of the disease. Opioids are frequently used in clinical practice in cancer-related pain.[19,20] Opioid analgesics may be interact with many drugs. The effectiveness and adverse events of opioids may increase with pharmacodynamic synergism, via inhibition of serotonin and/or norepinephrine reuptake.[18] The most common potential drug interactions were simultaneous use of different opioids together. There is no simultaneous use of different opioids in the symptomatic treatment of cancer-related pain in World Health Organization (WHO) and European Society for Medical Oncology (ESMO)'s guidelines.[21,22] If we inform healthcare professionals about the correct use of opioids, we can prevent 41.8% of major pDDIs.

Venous thromboembolism occurs commonly in cancer patients and usually treated with low molecular weight heparins (LMWHs) such as enoxaparin.[23,24] In our study, we found that LMWHs were often prescribed with non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids and piperacillin. On the other hand, NSAIDs are one of the most frequently used drug for pain palliation in cancer patients.[17] Simultaneous use of the NSAID and corticosteroid with LMWH have increased the risk of gastrointestinal bleeding and perforation.[25–27] We showed that 92 of the pDDIs was together with LMWHs that could increase the risk of bleeding on account of NSAID, corticosteroid, and piperacillin use. According to

Table 4
PDDIs in chemotherapy drugs.

Drug Combination	n	Description	Severity
Bicalutamide x Fentanyl	2	Bicalutamide increases the level or effect of fentanyl	Major
Escitalopram x Vemurafenib	2	Both increase QTc interval	Major
Irinotecan x Sertraline	1	Sertraline increases the level or effect of irinotecan	Major
Enoxaparin x Fluorouracil	6	Fluorouracil increases effects of enoxaparin	Moderate
Fluorouracil x Tinzaparin	1	Additive risk of bleeding	Moderate
Diltiazem x Doxorubicine/Docetaxel	2	Diltiazem increases the level or effect of these drugs	Moderate
Crizotinib x Fluconazole	1	Fluconazole increases levels of crizotinib paclitaxel with pharmacodinamic mechanism	Moderate
Tramadol x abirateron/crizotinib	2	Abirateron/crizotinib increases levels of tramadol	Moderate
Ciprofloxacin x Goserelin	1	goserelin increases toxicity of ciprofloxacin	Moderate
Diclofenac x Fluorouracil	1	fluorouracil will increase the level or effect of diclofenac	Moderate
Aprepitant x Paclitaxel	2	Aprepitant will increase the level or effect of paclitaxel	Minor

Table 5
Analysis of risk factor.

Variable		Number (%) of patients		
		With Interaction	Without Interaction	Asymp. Sig
Length of stay				
<5 days		112	58	0.026
	% within interaction group	48.1%	61.7%	
≥5 days		121	36	
	% within interaction group	51.9%	38.3%	
Age				
<60 ages		101	47	0.274
	% within interaction group	43.3%	50.0%	
≥60 ages		132	47	
	% within interaction group	56.7%	50.0%	

Chi-Square Tests.

the patients' need in many cases, if necessary, drugs with potential for interaction may be allowed. Oncologist should be alerted in terms of both efficacy and toxicity of the multiple medications.

Another common type of interaction in cancer patients is central nervous system (CNS) interactions. CNS interactions related to SSRIs are mainly reported in patients who receiving opioid analgesics simultaneously. In case of simultaneous use of opioid agonists and SSRIs together, due to the pharmacodynamic synergism, respiratory depression and sedation could be seen.[7,18,28] Therefore, clinical follow-up is important in the way of CNS toxicity of patients receiving this combination commonly used in oncology practice.

There are some limitations. First, retrospective clinical data of from medical records has disadvantages to control for all potential confounding bias that may influence the pDDIs. Second, data about toxicity profile may have missing data due to incomplete identification of adverse events considering the limitation of the retrospective study. Another major limitation was the difficulty in measuring the number of potential interactions that result in clinically adverse effects on the other hand, clinical results of drug interactions in the study were not investigated, but rather on their potential for occurrence. Nevertheless, most interaction control programmes do not consider for the treatment dosage, duration, and individual changes in the patients. Finally, one of our major limitation was to use only one interaction checker programme.

Although the best method to prevent pDDIs is not completely known, it is necessary to be aware of this issue and be particularly careful in groups of patients with increased risk for drug interactions. It is not known whether physicians are well informed about these pDDIs and whether they take precautions to prevent complications. A multidisciplinary approach can be proposed where physicians, pharmacists, nurses are involved in optimizing treatment and preventing interactions. Though, a computer-based scanning method may be a useful tool to interactions.

In conclusion, the incidence of pDDIs are high in especially hospitalized cancer patients and many of them are clinically important. Long-term hospitalized patients are under risk of pDDIs. Screening and identification of drug interactions may prevent the adverse drug events in cancer patients.

Conflict of interest

The authors do not have any conflict of interest to declare.

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