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SHORT RESEARCH REPORT

Prevalence of potential drug–drug interactions in outpatients on treatment with parenteral antineoplastic drugs

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Abstract

Background As live expectancy and cancer incidence growing, polypharmacy in oncology patients is also increasing, raising the risk of developing potential drug–drug interactions.*Objective* To assess the prevalence of clinically relevant potential drug–drug interactions among cancer patients who receive parenteral treatment at our outpatient clinic. *Method* Retrospective observational study which included randomly selected patients who had received parenteral treatment from November 1st 2016 to January 31st 2017. Interactions were checked in 3 databases, and classified as clinically relevant or not and in three categories of severity: contraindicated, consider modification or monitor. *Results* A total of 273 patients were included; of which seventy three (26.7%) had at least one clinically relevant potential drug–drug interaction. Amongst them, 54 (74%) had at least one classified as monitor treatment, 50 (68.5%) as contraindicated and 26 (35.6%) as consider modification. The number of chronic prescriptions was associated with a higher risk of drug interactions. *Conclusion* Around one in four patients on treatment with parenteral antineoplastic drugs presented a clinically relevant potential drug–drug interaction. A systematic assessment of drug–drug interactions should be implemented to reduce the risk of clinically relevant drug–drug interactions.

Keywords Antineoplastic agents · Drug–drug interactions · Neoplasms · Outpatients · Polypharmacy

Impacts on practice

- Potential drug–drug interactions (PDDI), defined as the occurrence of a potentially harmful combination of prescribed drugs in a given patient, are found in approximately one in four patients undergoing parenteral antineoplastic treatment.
- The greater the number of chronic prescriptions the higher risk of having a potential drug-drug interaction.
- A systematic assessment of potentia drug interactions in patients undergoing parenteral cancer treatment should be implemented to reduce the risk of clinically relevant drug-drug interactions.

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Introduction

As life expectancy and cancer incidence grow, the number of medications taken by oncology patients is also increasing [1, 2], raising the risk of developing potential drug–drug interactions (PDDI), defined as the occurrence of a potentially harmful combination of prescribed drugs in a given patient [3].

In 2007, Riechelmann et al. analysed the results of a questionnaire on regular medication in 405 patients receiving systemic cancer treatment, and found that 27% had at least one PDDI [3]. Girre et al. reviewed the medications of 105 cancer patients, finding that 32 (33%) had some PDDI [4]. A cross-sectional study in outpatients receiving intravenous cancer treatment showed that 33.9% had at least one major PDDI [5], and in 2015, a prospective study found 120 clinically relevant PDDI in 81 patients [6]. In the study by Popa et al. an association was found between PDDI and haematological toxicity [7].

In Spain, one study found 41% of clinically significant interactions among oncology patients, and another, 81% of

treatment sheets with a PDDI among oncology inpatients [8, 9].

Our health area serves a population of 324,000 people and over 2000 ambulatory patients annually receive treatment for cancer. Currently, there is no systematic assessment of PDDI among patients who receive parenteral antineoplastic drugs and we have no data on the prevalence of PDDI at our outpatient clinic.

Aim of the study

Our aim was to assess the prevalence of clinically relevant PDDI among cancer patients who receive parenteral treatment at our outpatient clinic. Secondary objectives were to describe the epidemiology of the PDDI in terms of severity and analyse the number of PDDI according to age, type of diagnosis (haematology vs. non-haematology) and the number of chronic prescriptions.

Ethics approval

This study was approved by the Ethics Committee of the Balearic Islands with No. IB 3391/17 EPA and authorized by the Spanish Agency for Medicines and Health Care Products (AEMPS).

Methods

This was a retrospective observational study in patients diagnosed with cancer who had received at least one dose of parenteral antineoplastic treatment at the Hospital Universitari Son Espases outpatient clinic (Palma de Mallorca, Spain).

Patients who had received parenteral treatment from November 1st 2016 to January 31st 2017 were randomly selected using the Excel RAND function until the necessary sample size was reached. The review of their treatments was made between February and September 2017, and each patient treatment was analysed once regardless of the treatment cycle or day.

We recorded demographic characteristics, diagnosis, antineoplastic treatments, support medications and chronic prescriptions for comorbidities. Data sources were the software used for prescription of antineoplastic treatments in the hospital, the application where the chronic medication was prescribed and the electronic medical records of the hospital and Primary Care.

As none of the databases is complete, we considered it acceptable to check the patient treatments in three databases in order to analyse the presence of drug–drug interactions: Lexicomp® Drug interactions, Micromedex Solutions® Drugs Interactions and BOT Plus 2.0. The first two are international reference databases with the best scores amongst the 5 most common drug–drug interaction software programs [10], and the last is the national reference database for the summary of product characteristics in Spain. Furthermore, all are available in our daily work. PDDI were classified into three categories of severity:

- Contraindicated: Interactions classified as grade X in Lexicomp®, contraindicated in Micromedex® and to avoid in BOT Plus 2.0.
- Consider modification: Interactions classified as grade D in Lexicomp®, major in Micromedex® and caution in BOT Plus 2.0.
- Monitor: Interactions classified as grade C in Lexicomp®, moderate in Micromedex® or risk of duplication or increase dosing interval in BOT Plus 2.0.

In case of discrepancy, we selected the most restrictive classification. Of the recorded PDDI, the clinically relevant PDDI were selected by consensus, and defined as those which may justify a treatment modification independently of the category of severity.

Inclusion criteria Ambulatory patients older than 15 years of age who had received at least one dose of parenteral antineoplastics at the outpatient clinic of our Hospital from November 1st 2016 to January 31st 2017.

Exclusion criteria no information on chronic medication, inpatients, patients younger than 16 years of age, patients on a clinical trial and patients from another health area.

Sample size

The calculated sample size was 273 patients. We supposed a 20% prevalence of clinically relevant PDDI, a precision of 5%, an error probability lower than 5% and a potential missing of 10%.

Statistical analyses

Patients were codified and all the data recorded on an Access database. Results were analysed using SPSS software version 23. The main outcome was the proportion of patients with at least one clinically relevant PDDI ± 95% confidence interval (95% CI). Descriptive statistics were used to illustrate patient characteristics and the Shapiro–Wilk test was applied to test for normal distribution. The Mann–Whitney test was used to analyse the number of PDDI according to the characteristics of the patients: age (< 65 vs. ≥ 65 years), type of diagnosis (haematology vs. non-haematology),

Table 1 Patient and treatments characteristics

	Total (n = 273)	%
Sex		
Male	159	58.2
Female	114	41.8
Age (years)		
Median (interquartile range)	61 (18)	
< 65	161	59
≥ 65	112	41
Type of diagnosis		
Haematological disease	50	18.3
Non-haematological disease	223	81.7
Metastatic disease	131	58.7
Adjuvant	62	27.8
Neo-adjuvant	30	13.4
Diagnosis		
Breast cancer	65	23.8
Colorectal cancer	45	16.5
Non-hodgkin lymphoma	35	12.8
Ovarian cancer	13	4.8
Head and neck cancer	13	4.8
Other	63	23
Antineoplastic treatment		
Median (interquartile range)	2 (1)	
Monoclonal antibodies	118	43.2
Platinum compounds	96	35.2
Pyrimidine analogues	77	28.2
Taxanes	51	18.7
Other antineoplastic agents	28	10.3
Vinca alkaloids and analogues	24	8.8
Nitrogen mustard analogues	20	7.3
Anthracyclines and related substances	20	7.3
Aromatase inhibitors	15	5.5
Others	52	19.0
Monoclonal antibody monotherapy	55	20.1
Rituximab	20	7.3
Trastuzumab	11	4.0
Nivolumab	9	3.3
Bevacizumab	6	2.2
T-DM1	3	1.1
Obinutuzumab	2	0.7
Ofatumumab	2	0.7
Cetuximab	1	0.4
Panitumumab	1	0.4
Support medications		
Median (interquartile range)	3 (1)	
Glucocorticoids	191	70.0
Serotonin (5HT3) antagonists	149	54.6
Substituted alkylamines	87	31.9
H2-receptor antagonists	44	16.1
Electrolyte solutions	41	15.0
Anilides	36	13.2
Other antiemetics	31	11.4
Colony stimulating factors	28	10.3
Detoxifying agents for antineoplastic treatment	26	9.5
Other antianemic preparations	15	5.5
Others	34	12.5
Number of comorbidities		
0	89	32.6
1	76	27.8
2	43	15.8
≥ 3	65	23.8
Number of chronic medications		
≤ 3	70	25.6
4 to 6	98	35.9
7 to 10	70	25.6
≥ 11	35	12.8

and the number of chronic prescriptions (< 4 vs. ≥ 4 active principles).

Results

A total of 534 patients received at least one dose of antineoplastic treatment at our outpatient clinic, of which 273 were randomly selected for review. Table 1 shows the main patient and treatments characteristics.

Seventy three patients (26.7%) [95% confidence interval (CI) 21.5% to 32%] had at least one clinically relevant PDDI. Of those 73 patients, at least one clinically relevant PDDI classified as contraindicated was found in 50 (68.5%) patients, at least one clinically relevant PDDI classified as consider modification in 26 (35.6%) patients and at least one PDDI classified as monitor treatment in 54 (74%) patients. Table 2 shows information about doublets of antineoplastic medications and other drugs causing clinically relevant PDDI.

According to the 3 databases used, nearly two hundred patients (n = 196; 71.8%) presented at least one PDDI. Most of the patients presented at least one PDDI classified as monitor treatment (n = 171; 87.2%), 129 (65.8%) patients had at least one PDDI classified as consider modification, and 54 (27.6%) patients had at least one PDDI classified as contraindicated.

Using the Mann–Whitney test we only found a relationship when comparing the number of PDDI between patients with less than 4 chronic prescriptions to patients with 4 or more chronic prescriptions (median (interquartile range): 0 (1) vs. 4 (5), $p < 0.001$, respectively).There were no

Table 2 Drugs and clinically relevant PDDI

Doublets of drugs	Number of clinically relevant PDDI	% of patients (n = 73) (%)
Frequency of doublets of antineoplastic medications and other drugs causing clinically relevant PDDI		
Oxaliplatin and dipyrone	10	13.7
Fluorouracil and dipyrone	7	9.6
Bevacizumab and dipyrone	6	8.2
Paclitaxel and dipyrone	6	8.2
Carboplatin and dipyrone	4	5.5
Paclitaxel and simvastatin	4	5.5
Fluorouracil and hydrochlorothiazide	3	4.1
Zoledronic acid and dipyrone	3	4.1
Bortezomib and dipyrone	2	2.7
Cyclophosphamide and fluconazole	2	2.7
Cisplatin and dipyrone	2	2.7
Oxaliplatin and citalopram	2	2.7
Docetaxel and dipyrone	2	2.7
Doxorubicin and fluconazole	2	2.7
Vincristine and fluconazole	2	2.7
Gemcitabine and dipyrone	2	2.7
Pemetrexed and ibuprofen	2	2.7
Zoledronic acid and omeprazole	2	2.7
Rituximab and dipyrone	2	2.7
Vinorelbine and dipyrone	2	2.7
Others	49	67.1

Doublets of drugs	Toxic effect	Patient management
Examples of the most frequent doublets of antineoplastic medications and other drugs, the toxic effect and the patient management recommendations		
Myelosuppressive agents with dipyrone	To enhance the myelosuppresive effect of antineoplastic agents	Avoid concurrent use of dipyrone with any myelosuppressive agent. If concurrent therapy is required, monitor closely for myelosuppression
Fluorouracil, oxaliplatin and other QTc-prolonging agents with citalopram or quetiapine	To enhance the QTc-prolonging effect of QTc-prolonging agents	Avoid concomitant use of highest risk QTc-prolonging agents (citalopram, quetiapine…) with any other QTc-prolonging agent when possible or use such combinations accompanied by close monitoring for evidence of QT prolongation or other alterations of cardiac rhythm
Paclitaxel with clopidogrel or gemfibrozil	To decrease the metabolism of paclitaxel	Monitor closely for evidence of severe neuropathy or neutropenia
		Consider modification of gemfibrozil in order to avoid the increased risk of paclitaxel toxicities
Paclitaxel and simvastatin	To alter paclitaxel plasma concentrations	If concomitant use is required, monitoring and dose adjustment of paclitaxel may be warranted

PDDI potential drug–drug interactions

differences on PDDI according to age ($p = 0.091$) and type of diagnosis ($p = 0.627$). In order to check our results, we also used the Spearman correlation test between age and PDDI ($r_s = 0.089$, $p = 0.142$) and between the number of chronic prescriptions and PDDI ($r_s = 0.596$, $p < 0.001$). A r_s closer to 1 indicates a higher and statistically significant correlation between the number of chronic prescriptions and PDDI.

Discussion

We found a prevalence of 26.7% patients with a clinically relevant PDDI and 71.8% with any type of PDDI.

Although the classification of clinically relevant PDDI used and the population included might be slightly different, our results are very similar to those obtained by previous authors [3–6, 8]. On the other hand, Popa et al. only detected 10.7% of clinically relevant PDDI, which is perhaps due to the more specific population (haematology patients older than 70 years of age) [7]. Fernández de Palencia et al. found 81% of treatment sheets with PDDI, but we have no data either on the number of patients with at least one PDDI or the number of clinically relevant PDDI [9].

We reached the necessary sample size to estimate the prevalence of PDDI and our study is the only one we have found that uses three databases to check the PDDI. Nevertheless, this work has several limitations. First of all, we only took into account drugs recorded on the applications reviewed, and we did not interview the patients to ask about self-medication or alternative treatments. Secondly, the authors made the classification of whether a PDDI was clinically relevant or not, and in some cases, this led to discrepancies. Another limitation is that it is a retrospective study from one centre, with no patient characteristics such as gender or renal/hepatic dysfunction being taken into account. Randomization can reduce some of this bias, and we believe that three months is an adequate period to select a representative population. Lastly, we did not investigate the clinical outcomes associated with PDDI, and although this aspect is undoubtedly the most important, it was not part of our objective in the present study. However, we will consider it for future research. Future studies should perhaps include a multicentre and prospective design, patient interview, and a multidisciplinary team to assess the PDDI and the clinical consequences.

Conclusion

In conclusion, around one in four patients on treatment with parenteral antineoplastic drugs presented a clinically relevant PDDI. As previously described, the risk of having a PDDI seems to increase with the higher number of chronic prescriptions. According to our results, a systematic assessment of PDDI in these patients should be implemented to reduce the risk of clinically relevant PDDI.

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