Evaluation of the systemic and therapeutic repercussions caused by drug interactions in oncology patients

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SUMMARY

INTRODUCTION: Drug interaction is an important cause of global morbidity. It is of particular importance in cancer patients since they are often in use of polypharmacy, related to interactions between the drugs and the chemotherapeutics used.

OBJECTIVE: To evaluate the drug interaction between chemotherapy and other drugs in cancer patients.

METHODS: A cross-sectional study carried out in the outpatient oncology department of a public tertiary hospital. Two hundred thirty-five patients were included, and the drugs they were using were identified. Using the MedScape and Epocrates database, we evaluated the interactions between medications and chemotherapy by defining their frequency and dividing their severity from interaction into mild, close monitoring necessity and severe.

RESULTS: 161 patients had some drug interaction. We identified 9 types of mild interactions, 23 types of interactions with close monitoring necessity, and 2 types of serious interactions. The most frequent interactions were between fluorouracil and leucovorin (32 cases) and cyclophosphamide and doxorubicin (19 cases). Serious interactions were between aspirin and pemetrexed; and leucovorin and Bactrim.

CONCLUSION: In the present study, drug interactions were frequent, including serious interactions with a potential increase in morbidity and mortality. Thus, it is necessary for oncologists to draw up a therapeutic plan considering potential interactions between prescribed chemotherapy and current medications in use by patients.

KEYWORDS: Drug interactions. Antineoplastic agents/adverse effects. Medical oncology.

INTRODUCTION

According to the World Health Organization (WHO), drug interaction is the main cause of morbidity and mortality in the world.¹ Data indicate that, in the United States, annually, over 2 million of patients...
who are hospitalized suffer from adverse reactions to drugs, and approximately 100,000 die from it. Drug interaction, defined as an increase or reduction of the clinical effect of a given drug due to the interference of another, is responsible for about 3% to 5% of these cases.\(^2\) This is because drug interactions can interfere in both pharmacokinetics and pharmacodynamics by inducing or inhibiting cytochrome P450, which can lead to a synergistic, additive or antagonistic effect of some drugs, thus compromising their effectiveness.\(^3\)

In general, the patients who are mostly exposed to this scenario are those who make use of polypharmacy, such as oncology patients, who need to make use of drugs not only to treat the cancer itself, but also due to the toxicity induced by the treatment and syndromes related to neoplasia, in addition to the drugs used for possible comorbidities.\(^4\)

In addition, several studies have investigated drugs with the potential to interfere with chemotherapy, showing remarkable rates of drug interaction.\(^5\)\(^-\)\(^9\) As an example, it is known that drugs used to treat psychiatric disorders such as carbamazepine, phenytoin, phenobarbital, primidone, and valproic acid interact with chemotherapy treatments in general.\(^5\)

Other drugs such as fentanyl, midazolam, captopril, and potassium chloride have also shown a high prevalence of drug interaction.\(^10\)

However, the main problem lies in the use of drugs whose effects on treatment are unknown and which are often bought without restrictions by the patients, who self-medicate, usually without informing the oncologist.\(^11\)\(^,\)\(^12\)

Similarly, van Leeuwen et al.\(^7\) predicted that over half of the patients in the use of chemotherapeutic agents present some kind of drug interaction, and a third of them suffer serious consequences.\(^13\)

Due to this scenario, it is necessary to know the drugs that have the potential to interfere with the efficacy of chemotherapeutic agents, so that oncologists can draw a plan of action more accurate and individualized in order to improve the treatment offered to the patients.

**OBJECTIVES**

**General objective**

Assess drug interaction between chemotherapy and other drugs that are taken by cancer patients, with or without medical guidance.

**Specific objectives**

Assess the adverse effects resulting from drug interactions that might interfere with the prognosis and quality of life of patients under antineoplastic treatment.

List the drugs whose interaction is identified by this study.

Assess the effects of the drug interactions found.

**METHODS**

**Study design**

This is a cross-sectional study that analyzed patients treated by the Oncology Service linked to the FMABC (State Hospital Mário Covas, in Santo André and School Hospital Padre Anchieta, in São Bernardo do Campo). The patients were invited to participate in the study, with a previous explanation that their participation was voluntary and that their personal information would remain confidential.

We considered eligible for the study patients with age greater than or equal to 18 years, able to read and understand Portuguese and who were or were to be submitted to chemotherapy. We excluded from the study all patients younger than 18 years old, illiterate and who had not undergone chemotherapy or had no indication of a chemotherapy regimen.

After approval by the ethics committee, 235 patients were included in this study, which was based on data collection by means of an interview in which the patient answered open questions and in the evaluation of possible interactions between the drugs reported with the aid of Epocrates And MedScape applications. These free electronic applications for smartphones use, exclusively, the names of medications taken by each patient, indicating, when present, the possibility of interaction between them. The use of the applications was done by the researchers of this study, who reported the information to the participants. The information relating to the current chemotherapeutic treatment were obtained from the records of each individual patient.

After signing the Informed Consent Form - ICF, patients filled out an identification form with their clinical and demographic data, as well as a questionnaire in which they should indicate the drugs used by them: those who used without medical guidance as well as those prescribed, besides their chemotherapeutic agents.

The questionnaire contains general data of the
patient, as staging of neoplasia, previous surgery, 
beginning of chemotherapy; clinical data, in which 
the drugs taken were disclosed, as well as the dos- 
es administered and an assessment of signs and 
symptoms based on the information referring to the 
treatment during chemotherapy; and complemen-
tary data, obtained by means of a simpler questions, 
aiming to evaluate all drugs used, their dosage and 
symptoms.

The researcher, at the time of inclusion, was re-
sponsible for clarifying the purpose of the study and 
assisting the subjects in answering the question-
naires.

In relation to the risks and benefits, the present 
study had a minimal risk in relation to the emotional 
context of the patient, since it caused them to reflect 
on questions that involve the disease, but there were 
no risks related to the physical health of patients. In 
addition, there is an indirect benefit from the imple-
mentation of future projects which, based on the col-
lected data, can contribute to the improvement of the 
quality of life of these patients.

RESULTS

The present study included 235 patients. Of these, 
161 had some drug interaction in accordance with 
the criterion of Epocrates. Their sociodemographic 
characteristics are presented in Table 1.

We then excluded interactions that did not in-
volve chemotherapy drugs, dividing them remain-
ing between “chemotherapy and chemotherapy” or 
“chemotherapy and non-chemotherapy. The interac-
tions found and their frequency are shown in Table 2.

The interactions were divided into “mild”, “close 
monitoring” and “serious”, as shown in the “drug in-
teraction Checker” of MedScape. In the chemother-
apy vs. non-chemotherapy group, we found eight 
types of mild interactions, 14 that required close 
monitoring and two considered serious. Whereas 
in the chemotherapy vs. chemotherapy group, we 
found a mild interaction, nine interactions with the 
need for close monitoring and no serious interaction. 
The results can be found in Table 3.

DISCUSSION

In oncological treatment, the concern with possible 
drug interactions should always be raised by the 
oncologist. It is worth noting that certain interac-
tions are expected and may even be desired, especia-
lly in regard to interactions between chemotherapy 
drugs, between which there is a synergism of action, 
for example. In this context, we can cite as examples 
of known interactions 5-fluorouracil and leucovo-
lin\textsuperscript{14}, or doxorubicin/cyclophospha-
mine followed by paclitaxel\textsuperscript{15}. 

Also in the context of the expected associations, 
the most prevalent drug interaction was between 
fluorouracil and leucovorin (32 cases), and it occurs 
during the antineoplastic treatment, with increased 
toxicity of the medication due to the effect of phar-
macodynamic synergism. The same goes for the sec-
ond most frequent drug interaction, cyclophospha-
mide, and doxorubicin.\textsuperscript{16}

| TABLE 1. SOCIODEMOGRAPHIC DATA | N = 161 |
|-------------------------------|--------|
| Gender                        |        |
|                               | Female | 62   | 38.5% |
|                               | Male   | 99   | 61.5% |
| Age                           |        |
|                               | Mean   | 61 years |
|                               | Interval | 27 to 85 years |
| Marital status                |        |
|                               | Single | 45   | 27.9% |
|                               | Married| 100  | 62.1% |
|                               | Widow(er) | 16 | 9.9% |
| Formal education              |        |
|                               | Illiterate | 6 | 3.7% |
|                               | Incomplete elementary school | 66 | 40.9% |
|                               | Complete elementary school | 18 | 11.1% |
|                               | Incomplete secondary school | 10 | 6.2% |
|                               | Complete secondary school | 40 | 24.8% |
|                               | Incomplete undergraduate program | 11 | 6.8% |
|                               | Complete undergraduate program | 10 | 6.2% |
| Ethnicity                     |        |
|                               | White | 92   | 57.1% |
|                               | Brown | 37   | 22.9% |
|                               | Black | 18   | 11.1% |
|                               | Indigenous | 8 | 4.9% |
|                               | Others | 6 | 3.7% |
| Occupation                    |        |
|                               | Works | 58   | 36.0% |
|                               | Does not work | 103 | 63.9% |
| Origin                        |        |
|                               | The ABC region | 144 | 89.4% |
|                               | Others | 17 | 10.5% |
| Site of the primary neoplasia |        |
|                               | Head and neck | 7 | 4.3% |
|                               | Lung | 13 | 8.0% |
|                               | Gastrointestinal tract | 58 | 36.0% |
|                               | Urinary tract | 8 | 4.9% |
|                               | Gynecologic | 50 | 31.0% |
|                               | Others | 25 | 15.5% |
### TABLE 2. ANALYSIS OF DEGREES OF INTERACTIONS

| Chemotherapy vs. Non-chemotherapy | Frequency | Chemotherapy vs. Chemotherapy | Frequency |
|-----------------------------------|-----------|-------------------------------|-----------|
| Vincristine Prednisone            | 4         | Cisplatin + Paclitaxel         | 3         |
| Docetaxel Prednisone              | 2         |                               |           |
| Dexamethasone                     | 2         |                               |           |
| Primidone                         | 1         |                               |           |
| Paclitaxel Budesonide             | 1         |                               |           |
| Captopril                         | 1         |                               |           |
| Glimepiride Prednisone            | 1         |                               |           |
| Aspirin                           | 1         |                               |           |
| Paclitaxel Losartan               | 6         | Fluouracil + Leucovorin       | 32        |
| Dexamethasone                     | 4         | Cyclophosphamide + Doxorubicin| 19        |
| Simvastatin                       | 3         | Paclitaxel + Doxorubicin      | 7         |
| Phenytoin                         | 1         | Paclitaxel + Trastuzumab      | 3         |
| Rosuvastatin                      | 1         | Irinotecan + Bevacizumab      | 2         |
| Cyclosporine                      | 1         | Paclitaxel + Lapatinib        | 1         |
| Cyclophosphamide                  | 1         | Cisplatin + Cyclophosphamide  | 1         |
| Allopurinol                       | 1         | Cisplatin Decarbazine         | 1         |
| Doxorubicin                       | 2         | Fluouracil + Bevacizumab      | 1         |
| Docetaxel Simvastatin             | 2         |                               |           |
| Irinotecan                        | 2         |                               |           |
| Bortezomib Omeprazole             | 1         |                               |           |
| Etoposide Dexamethasone           | 1         |                               |           |
| Eloxatin Zidovudine               | 1         |                               |           |
| Pemetrexed Acetylsalicyc Acid     | 1         |                               |           |
| Leucovorin Bactrim                | 1         |                               |           |

### TABLE 3. SEVERITY OF INTERACTIONS

| Severity of interaction | Chemotherapy vs. Non-chemotherapy (Unexpected interactions) | Chemotherapy vs. Chemotherapy (Expected interaction) |
|-------------------------|-------------------------------------------------------------|-----------------------------------------------------|
| Mild                    | Vincristine Prednisone                                      | Cisplatin + Paclitaxel                               |
|                         | Docetaxel Prednisone; Dexamethasone Primidone               |                                                     |
|                         | Paclitaxel Budesonide; Captopril                            |                                                     |
| Close monitoring        | Glimepiride Prednisone; Aspirin                              | Fluouracil + Leucovorin                             |
|                         | Paclitaxel Losartan; Dexamethasone Simvastatin; Phenytoin Rosuvastatin; Cyclophosphamide | Cyclophosphamide + Doxorubicin                       |
|                         | Cyclophosphamide Enexaparin; Allopurinol                     | Paclitaxel + Trastuzumab                             |
|                         | Doxorubicin Dexamethasone                                    | Irinotecan + Bevacizumab                             |
|                         | Docetaxel Simvastatin                                        | Paclitaxel + Lapatinib                               |
|                         | Irinotecan Dexamethasone                                     |                                                     |
|                         | Bortezomib Omeprazole                                        |                                                     |
|                         | Etoposide Dexamethasone                                      |                                                     |
|                         | Eloxatin Zidovudine                                           |                                                     |
| Severe                  | Pemetrexed Acetylsalicyc acid                                |                                                     |
|                         | Leucovorin Bactrim                                           |                                                     |
The third most frequent interaction, paclitaxel and doxorubicin, even though it was already expected to have increased toxicity related to their combined use bringing an improved oncologic prognosis, it should be mentioned that the interaction between them includes increased levels of doxorubicin, considering the decrease of renal clearance of creatinine generated by paclitaxel. Thus, it is observed that associations of chemotherapeutic agents may present, concomitantly, intentional drug interactions associated to harmful interactions.

Among the serious interactions, the one between aspirin (acetylsalicylic acid; ASA) and pemetrexed is noteworthy. Pemetrexed is a chemotherapeutic agent indicated for the treatment of non-small cell lung cancer, while acetylsalicylic acid is used as secondary prophylaxis of new cardiovascular events. Considering the frequency of concomitance of these comorbidities, both in part secondary to smoking, there is the possibility of a same patient receiving the association of pemetrexed and ASA. Despite this, these medications should not be associated, since aspirin increases the levels of pemetrexed due to decreased renal excretion of the chemotherapeutic agent. It is worth mentioning that this association should be undertaken with caution in patients with normal renal function (creatinine clearance > 80 ml/min) and avoided in patients with preserved renal function, because, due to this factor, aspirin can raise the levels of pemetrexed and cause adverse events.

To avoid such interaction, one possibility would be to replace acetylsalicylic acid by another antiplatelet agent that also causes reduction of cardiovascular risk during the period of oncological treatment, such as clopidogrel, which presents no drug interactions with the pemetrexed.

Another serious interaction was found between leucovorin and Bactrim (trimethoprim and sulfamethoxazole). Leucovorin corresponds to a drug used, among other reasons, in association with fluorouracil, for adjuvant chemotherapeutic treatment of colorectal cancer and for recovery in patients treated with high doses of methotrexate. Bactrim, in turn, corresponds to an antibiotic often used for infectious prophylaxis in oncologic patients who are immunosuppressed during the chemotherapeutic treatment. Thus, there is the possibility of the same patient using both drugs simultaneously, and leucovorin decreases the effect of trimethoprim due to a mechanism of pharmacodynamic antagonism.

To avoid the interaction between leucovorin and Bactrim, the antibiotic can be replaced for another that is effective and does not interact with the leucovorin.

As discussed, it is observed that drugs used for oncologic therapy are not an exception in the context of drug interactions. In addition, these drugs have important cytotoxic effects and feature many pharmacokinetic and pharmacodynamic variations among patients. As noted, the use of combinations and the number of drugs involved in the treatment increases the likelihood of such interactions.

Thus, the presence of drug interactions among cancer patients is noteworthy. In this scenario, in addition to the associations made intentionally by oncologists with the purpose of increasing the effectiveness of the treatment, there are also those that occur without the supervision of these professionals, arising mainly from drugs taken without informing the medical team.

Furthermore, oncology patients are particularly prone to polypharmacy, making use of several drugs simultaneously. Thus, in addition to the greater risk of drug interactions, more than one interaction can be present in the same patient, increasing the possibility of unwanted effects and worsen prognosis.

An important example of multiple interactions in oncologic patients corresponds to that of chemotherapeutic agents, such as paclitaxel associated with simvastatin and losartan, drugs widely prescribed in older patients. Although beneficial in isolation, paclitaxel presents drug interaction with both other drugs, with the need for close monitoring. Simvastatin and losartan lead to unwanted increases in the levels of paclitaxel, increasing its toxicity; paclitaxel brings an increased risk of myopathy related to simvastatin. Multiple interactions such as this should be carefully assessed by the oncologist, especially in patients in use of multiple drugs simultaneously.

The serious interactions found were between aspirin and pemetrexed, and leucovorin and Bactrim. Although the present study has found only individual cases of the concomitant use of drugs with serious drug interaction, this can probably be explained by the limitation of the small number of patients included, since the high prevalence of the use of these medications indicates that the frequency of unwanted interactions is possibly even higher. Thus, it reinforces the idea that physicians should be alert...
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CONCLUSION

Drug interactions were frequent in oncologic patients. Although the majority of interactions was related to the synergistic effect already expected between chemotherapy drugs, there were unexpected serious interactions and interactions with the need of close monitoring. The main interactions found were the severe increase of chemotherapy toxicity due to the worsening of renal function, which may increase the mortality related to the treatment; and the reduction of the effect of antibiotic medication, related to an increased risk of bacterial infection and, consequently, an increase in mortality.

Thus, it is necessary that oncologists create a therapy plan considering possible drug interactions between the chemotherapy prescribed and other drugs used by the patients in order to ensure a better oncologic prognosis.

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