Analysis of drug-drug interactions (DDIs) in an inpatient oncology ward within the TRACTION prospective observational cohort study

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INTRODUCTION

Drug-drug interactions (DDIs) occur when two or more drugs interact on a pharmacokinetic and/or pharmacodynamic level. The clinical outcome of DDIs includes an increased risk of adverse drug reactions (ADR) and decreased patients survival [1]. The impact of DDIs becomes clinically significant with medications that have a narrow therapeutic window [2]. A prospective observational study conducted on 1008 oncology patients reported ADRs in 591 of them, with a prevalence rate of 58.6% [3]. A study reported that 6 to 14% of patients may experience hospitalization due to ADRs [4]. Other Authors reported that approximately 4% of the cancer patients may even die because of ADR caused by DDIs [5]. Cancer patients often are elderly patients with complex polypharmacy. Therefore they are at risk of developing Drug-Drug Interactions which are significantly underreported in oncology practice.

The TRACTION study was designed to analyse the impact of DDI and find strategies to manage them in a real world setting.

OBJECTIVES

The aim of this study is to evaluate the prevalence of DDIs in patients admitted to an Oncology ward of a Comprehensive Cancer Center and their clinical relevance and to analyse the reliability of available scientific evidence. Secondary objectives are to assess the Adverse Events incidence, analyse their potential correlation with DDIs and describe population characteristics.

METHODS

TRACTION is an observational non-interventional study designed to assess the incidence of DDIs in a prospective cohort of cancer patients admitted to the ward of IOV Oncology 1 (Italy). It was approved by the local Ethics Committee on 12 December 2022 (prot. N. 24458/22).

Inclusion Criteria

- Age ≥ 18 years;
- Histological diagnosis of cancer, any site;
- Admission to the IOV Oncology 1 ward;
- Current treatment with systemic chemotherapy, target agent, or immunotherapy, with latest dose received within one month prior to admission.

Exclusion Criteria

-Concomitant treatment with complemetary medicines (Chinese traditional medicine, Ayurvedic medicine, etc.);

-Patient unable to give written informed consent to the protocol due to psychological or social reasons;

-Patients enrolled in other pharmacological clinical trials.

DDIs

The DDIs were identified through a dedicated software (Lexicorp), scientific databases and published articles, and then categorized as Pharmacokinetic or Pharmacodynamic, clinical relevance in terms of level of risk of adverse events and level of scientific evidence.

Toxicities

Adverse Events were collected from clinical charts within one month from admission and were graded according to CTCAE v4.0. The potential correlation with DDIs was then analyzed by a Multidisciplinary team comprising a Clinical Pharmacologist and Oncologists.

Data collection

Patients data were anonymized and collected in an electronic Case Report Form.

RESULTS

Patients (Tab. 1)

99 patients were enrolled from February to June 2023 and eligible for analysis, median age 61 years (IQR: 44.7-66.7).

Patients were treated for the neoadjuvant (21.2%), adjuvant (15.2%), metastatic setting (44.4%) or hematological disease (19.9%). Most frequent cancer types were sarcoma (32.33%), gastrointestinal (22.22%) and hematological disease (21.21%). 73.77% of the patietiens were admitted for scheduled procedures while 23.23% due to unexpected clinical reasons.

Table 1	Variables	N.
Gender	Males	50 (50.5)
	Females	49 (49.5)
Age	Median	61 years (IQR: 44.7-66.7)
Tumor location	Sarcoma	32 (32.3)
	Gastrointestinal	22 (22.2)
	Hematological	21 (21.2)
	Genitourinary	6 (6.1)
	Lung	6 (6.1)
	Other	12 (12.1)
Treatment setting	Neoadjuvant	21 (21.2)
	Adjuvant	15 (15.2)
	Metastatic,	44 (44.4)
	Hematological	19 (19.2)
Comorbidities	Yes	73 (73.7)
	No	26 (26.3)
	Median number of comorbidities	2 (IQR: 1-2)
Reason for hospitalization	Treatment administration	73 (73.7)
	Clinical worsening/disease progression/adverse events	23 (23.3)
	Other reasons	3 (3.0)

Polypharmacy

During hospital stay, the median number of drugs per patient was 11 (range: 0-19, IQR: 9-13). The median number of concomitant drugs taken at home was 6 (range: 0 – 10, IQR: 4-8), while the median number of supportive medications for anticancer therapy was 4 (range: 0-7, IQR:1-5), the median number of concomitant anticancer drugs was 2 (range: 0-4, IQR: 1-3).

Toxicities

55 patients registerd at least one adverse events (AE) before hospital admission (23 patients of them, registered a G3-G4 AE), 39 patients had at least one AE during the hospital stay (11 G3-G4) and 54 patients had at least one AE in the 30 days post discharge (23 G3-G4). 16 death occured, 1 during the hospital stay and 15 in the following 30 days but any of them seems to be DDI related.

DDIs

DDIs were reported in 86 patients, for a total of 434 of different drug combinations. Following analysis of risk of ADRs and reliability of scientific evidence, only 109 were considered as potentially clinically relevant (crDDIs). The median number of crDDIs per patients was 1 (range: 0-6, IQR: 0-2), 97 pharmacokinetic in type (89.0%) and 12 pharmacodynamic (11%). The most important crDDIs are summarized in Table 2.

Clinical relevant potential DDI had a prevalence of 58.58%.

Table 2	Severity	Mechanism	Consequences of DDI	Patients at risk	Potential Toxicity
Methotrexate / pantoprazole or lansoprazole	Moderate	Inhibitors of the Proton Pump (PPI) may delay the elimination of methotrexate	↑ methotrexate	15	Renal toxicity, neurotoxicity, mucositis
Fluconazole / Vincristine	Moderate	Inhibition of CYP3A4 (hepatic metabolism)	↑ vincristine	5	Neurological toxicity
Methotrexate / Bactrim	Major	Trimethoprim can inhibit renal excretion fo methotrexate and compete with albumin binding	↑ methotrexate	5	Renal toxicity, neurotoxicity, mucositis
Aprepitant / Ifosfamide	Moderate	Inhibition of CYP3A4 (hepatic metabolism)	↑ ifosfamide	18	Hematological toxicity, renal toxicity, neurological toxicity
Aprepitant / Doxorubicin	Moderate	Inhibition of CYP3A4 (hepatic metabolism)	↑ doxorubicin	9	Hematological toxicity, mucositis, cardiotoxicity
Alprazolam / Amlodipine	Moderate	Consider the use of other antiemetics	↑ alprazolam	3	drowsiness, confusion, lack of coordination, memory impairment, increased anxiety

Risk factors

Age, sex and comorbidities are not statistically related to DDIs (p=0.1030, p=0.7563 and p=0.9316 respectively). The only statistically relevant association was the number of comedications (p=0.0189). There is 30% of probability increase for each additional drug.

DISCUSSION

Considering the vulnerability of cancer patients and their predisposition to polypharmacy, the current analysis confirms a high number of potential DDIs. However, not all the relevant ones will affect patients' health. The digital screening cannot differentiate between undesirable DDI and wanted ones. As a matter of fact, oncology therapies often look for additive effects between drugs in order to achieve better results with less toxicity. Moreover, the software does not consider each patient's characteristics (ex. sex, liver function, renal function, etc.). Only the multidisciplinary team evaluation could really distinguish which DDI may really put the patient at risk.

CONCLUSIONS

The risk of DDIs is not negligible in patients admitted to an Oncology ward. A clinical Pharmacologist should evaluate each incoming patient's polypharmacy when a hospitalization occurs. This assessment would support oncologists and avoid potential DDI-related ADRs.

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