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Original Article

# INCREASE OF REPORTS OF SUSPECTED ADVERSE DRUG REACTIONS IN ONCOLOGY

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**ABSTRACT**

**Objective**: The information of safety of antineoplastic agents derives solely from clinical studies that have a number of limitations, such as the number of patients enrolled, selected case studies, follow-up of short duration; therefore, it is not possible to identify the complete profile of safety and possible side effects of the drugs under study. ADRs monitoring and reporting programmes aim to identifying and quantifying the risks associated with the use of drugs provided in a hospital setting. The main objectives of this study were to evaluate the ADRs that occurred during hospitalization for chemotherapy in 7 cancer centers, and to facilitate the development of a monitoring system of pharmacovigilance.

**Methods:** An observational study was conducted in 7 cancer centers in the Emilia Romagna region over a period of 2 years, from January 2012 to January 2014. This study was based on an analysis of ADRs reported. Several parameters were utilised in the data evaluation, including drug and reaction characteristics.

**Results:** From January 2012 to January 2014 No. 884 ADRs were included in National Network of pharmacovigilance. The highest ADR rate (57.4%) was found in the adult females with a mean age of 62. The oncology drug most frequently reported were taxanes and platinum derivates.

**Conclusion:** The results obtained will contribute to the development of strategies for the pharmacovigilance service in 7 cancer centers, which will improve the quality of ADR reporting and ensure safer oncology drug use.

**Keywords**: Chemotherapy, Adverse drug reactions, Pharmacovigilance.

## INTRODUCTION

An adverse drug reaction (ADR) is defined by the World Health Organization (WHO) as any noxious, unintended, or undesired effect of a drug that occurs at doses used in humans for prophylaxis, diagnosis, or therapy [1].

The critical issues that lead to having a low signal compared to drugs commonly used are related to the underestimation of the phenomenon typical of the therapeutic approach in oncology, the complexity of the therapeutic care paths and the process of management of oral therapies.

In 2012, about No. 70,150 reports of ADRs have been received and processed every month and subsequently made them available for signal detection and analysis of data by the European Medicines Agency (EMA). Out of these reports, 15% were associated with antineoplastic drugs since this reflects the low reporting of the total number of drugs used in clinical practice [2]. In Italy, from 2004 to 2010 the incidence of reports of suspected ADRs to antineoplastic drugs included in RNF has progressively increased from 4.6% to 22.5%. Among these, a significant proportion was classified as severe (34.7 %) and a not insignificant share has also generated 209 deaths (4.5 %).

The reporting of ADRs has become an important component of monitoring and evaluation activities performed in hospitals [3]. These informations may be useful for identifying and minimising preventable ADRs and generally for enhancing the ability of prescribers to manage the ADRs more effectively. The reporting of ADRs is also essential to monitor the progress made in error prevention [4]. The present study was developed to determine the frequency of ADRs that occur in oncology patients and to describe the types of drugs involved.

## MATERIALS AND METHODS

### Study design

An observational study was conducted over a period of 2 years from January 2012 to January 2014 in 7 cancer centers. The study was based on the ADRs reported by multiple center in the Emilia Romagna region (the Cancer Center IRST IRCCS, the Hospital S. Orsola Malpighi of Bologna, the Hospital of Ravenna, the University Hospital of Parma, the Hospital of Rimini, the University Hospital of *Ferrara, the Hospital of* Reggio Emilia); the reports were coordinated by clinical pharmacists. Male and female adult patients were included in the study.

### Functioning of the ADR reporting system

Meetings were held with education and training of clinicians on the purpose and content of the New Pharmacovigilance Legislation; pharmacists are operating alongside of clinicians in the process of reporting of suspected ADRs and have explored the most relevant clinical cases. Attendees were encouraged to report all suspected ADRs using various reporting modalities, such as using a printed ADR notification form or directly reporting ADRs to an attending clinical pharmacist. In suspected cases, patients' past medical history and medication history were collected. To provide complementary information concerning adverse reactions, especially unexpected reactions, ADRs were spontaneously reported as part of standard care. Grade toxicity III, IV and V and all allergic reactions of any grade have been considered and reported, according to the Common Terminology Criteria for Adverse Events (CTCAE 4.02).

After initial notification of a suspected ADR, additional details were collected concerning previous allergies, concomitant medications, comorbidities, ADR management and outcome, and other details necessary for evaluation. The physician responsible for the case was consulted when additional details and clarification were necessary.

### Patient characteristics

Male and female adult patients receiving chemotherapy were included in the study and the age and sex of patients were investigated.

### Reaction characteristics

Severe reactions were evaluated compared to the total reactions; anatomical devices have been analysed.

**Drug characteristics**

All intravenous and oral oncology drugs used for chemotherapy were included in the study.

**RESULTS**

Since the start of the project (January 2012) a total of No.884 ADRs (27.4% in 2012 and 72.6% for the whole year 2013) was included in the National Network of Pharmacovigilance. This data reflects an increase, compared to the previous period to the start of the project, of 458% (from No. 140 ADRs in the two years 2010-2011 to No. 642 ADRs in the two years 2012-2013). All 7 cancer centers have had a significant increase in reporting. With regard to the severity of the reactions in the course of the project, it is noted that the total number of reactions classified as "serious" corresponds to 30% (266/884) of the total according to the WHO gold standard, which defines that at least 30% of the ADRs must be serious to have a good system of pharmacovigilance. ADRs were more frequent in females (57.4%; 507/884) than in males (42.6%; 377/884).

The mean age of females was 62 and of male 66. The highest percentage of reports (25%), according to the MedDRA system organ class (SOC), relates to suspected adverse reactions arising in the skin, followed by hematologic reactions (22%; 194/884), gastrointestinal reactions (11%; 97/884), respiratory reactions (11%; 97/884), cardiology reactions (11%; 97/884), skeletal muscle reactions (8%; 71/884), neurological reactions (7%; 62/884) and other non reported (5%; 44/884). The incidence of ADRs in the monotherapy was 79% (698/884); in patients receiving combination therapy 21 % (186/884) of reported ADRs.

A total of 938 actives for a total of 884 ADR forms have been reported and included in National Network of Pharmacovigilance. The five actives most frequently reported were paclitaxel (19.9%; 187/938), oxaliplatin (16.1%; 151/938), carboplatin (14%; 131/938), fluorouracil (11.2%; 105/938) and gemcitabine (10%; 94/938).

**DISCUSSION**

The aim of pharmacovigilance is to assess the post-marketing safety of drugs. In oncology, adverse drug reactions are still under reported. The fundamental role of various professionals, such as oncologists and hematologists, specialists, hospital pharmacists and nursing staff, as well as the patients, can highlight adverse events associated to chemotherapy, both in the phase immediately after the administration of drugs, especially innovative, and in the late toxicity and ADRs from interactions between drugs used for comorbidities.
There is no agreement among studies regarding the incidence of ADRs in oncology. Certain authors [5, 6] have reported that women are more susceptible to ADRs, possibly due to their high medication use, and metabolic alterations due to hormone levels. Other researchers [7, 9] have found the incidence of ADRs to be unrelated to gender, which supports our finding that ADRs did not differ significantly between men and women.

In our study, the ADRs were more frequently experienced in women (57.4%), most of which are subjected to chemotherapy treatment for breast cancer.

The drugs most reported are traditional and non-innovative, although that the use of innovative drugs, such as targeted therapies, is increasingly common in oncology.

**CONCLUSION**

The project, which involved 7 regional centers, has achieved important results regarding the increase in the overall reporting (from No. 140 reports in 2011, before the project, to a total of 884 in 2012 and 2013). The presence in the 7 cancer centers of a database of personalized pharmaceuticals prescriptions has allowed us to know ADRs, to share with clinicians and pharmacists dedicated to the operational implementation, the pharmacovigilance project, tracking ADRs not reported. A program of active pharmacovigilance, such as the one we have created in our seven regional institutes, is essential if the objective is to continuously monitor cancer drugs.

**COMPETING INTERESTS**

The authors have no competing interests to declare.

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