ADVERSE DRUG REACTIONS IN ONCOLOGY: INTENSIVE MONITORING PROGRAM ON DRUG TOXICITY OF BIOTECHNOLOGICAL MEDICATIONS AND TARGET THERAPIES IN ONCOLOGIC PATIENTS - THE ALEXANDROS OBSERVATIONAL STUDY

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Oncologic patients are particularly susceptible to adverse drug reactions (ADRs) (Wahlang, Laishram et al. 2017). In this population, the sensitivity to ADRs results from several factors, including the narrow therapeutic index of some chemotherapeutic drugs, multidrug regimens, and comorbidities. Malnutrition and organ dysfunctions often occur too, and these factors may modify drug pharmacokinetics, thus making drug efficacy and safety less predictable. (Chan, Soh et al. 2014). In this scenario, the identification of ADRs during registrative clinical trials can be particularly challenging. Therefore, monitoring patients' safety during these treatments in clinical practice should be a priority (Tuccori, Montagnani et al. 2015). The aims of the ALEXANDROS study were to evaluate the occurrence of ADRs associated to antineoplastic target therapies (both biotechnological drugs and small molecules) and to assess their potential interactions. This retrospective, observational, no-profit study was carried out at the Unit of Oncology of the University Hospital of Florence. Patients >18 years-old accessing the Unit of Oncology from July 2014th to July 2016th with solid tumour diagnoses, treated with target therapies (Anatomical Therapeutic Classifications, ATCs: L01XC - monoclonal antibodies; L01XE - protein kinase inhibitors) were included in the analysis. Patients' data were retrieved from medical records using the Patient Data Form available on Pharmacowikilance (a platform developed by the Tuscan Regional Centre of Pharmacovigilance for the management of prospective and retrospective safety observational studies), including demographic information, medical history, pharmacological treatments, and ADRs. Potential drug-drug interactions were assessed also by checking the drug-drug combinations expected to result in an interaction on Micromedex®. Overall, 130 cancer patients were included in the study with a mean age of 64.28 years (standard deviation, SD ± 12.12). All the included patients were Caucasian and 89 were females. Based on primary cancer diagnosis, the patients had the following distribution: 39 colorectal cancer, 27 lung cancer, 26 breast cancer, 25 ovarian cancer, 8 kidney cancer, 3 gastric cancer and 2 hepatic cancer. Metastases were reported in 71 patients. Over the study period, 234 adverse events (AEs) and 223 ADRs associated with target therapies were reported (105 patients had at least one ADR, range 1-8 ADRs per patient). Among the 223 ADRs, 27 were serious (21 patients had at least one serious ADR, range 1-3 serious ADRs per patient) and 10.31% were unexpected. The most frequently reported ADRs (at least 5 cases for a single ADR) were: cutaneous toxicity (n=31), diarrhoea (n=27), neutropenia (n=23), mucositis (n=18), nausea (n=15), hypertension (n=15), palmar-plantar erythrodysesthesia (n=11), asthenia (n=10), hypertransaminasemia (n=5). ADR outcomes had the following distribution: resolved (41.29% of cases), resolving (39.35%), not resolved (8.39%), not specified (7.09%) and resolved with sequalae (3.87%). The most frequently combinations of suspected drug-ADR were: bevacizumab-neutropenia (n=15); bevacizumab-nausea (n=10);

bevacizumab-diarrhoea (n=6); bevacizumab-hypertension (n=5); cetuximab-cutaneous toxicity (n=9); erlotinib-cutaneous toxicity (n=17); erlotinib-diarrhoea (n=5); and erlotinib-mucositis (n=5). The mean number of drugs per patient was 7.27 (SD ± 4.5), including at least 1 target therapy drug per patient. Thirty-six drug-drug combinations including a target therapy for which a drug-drug interaction was expected were identified: erlotinib-esomeprazole (n=1); erlotinib-lansoprazole (n=13); erlotinib-magaldrate (n=6); erlotinib-omeprazole (n=6); erlotinib-pantoprazole (n=7); gefitinib-lansoprazole (n.=1); sunitinib-sotalol (n=2). None of these combinations actually resulted in the expected adverse event. In conclusion, this study confirms that drug safety monitoring in cancer patients is a priority issue. Healthcare professionals working in oncology units should be adequately stimulated in the activity of ADR detection and reporting.

References

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