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SHORT RESEARCH REPORT

Drug safety surveillance within a strategy for the management of non-chemotherapy drug-induced neutropenia

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Abstract

Background Severe non-chemotherapy drug-induced neutropenia is a rare idiosyncratic drug reaction that is considered potentially fatal. *Objective* To report, in terms of drug safety surveillance, the results of an institutional strategy for NCDIN. *Method* An observational and prospective study including all adult patients who received filgrastim for the treatment of NCDIN from June 2015 to December 2017 was carried out by hematologists and clinical pharmacists. *Results* 13 patients with severe NCDIN were included in the study. The median age was 51 (range 24–80) years old and 46.2% were male. Seven patients had one or more negative prognostic factors (age > 65 years, renal impairment, autoimmune diseases and/or a neutrophil count at diagnosis < 0.1×109 cells/L). A single drug was identified as causative in 3 patients, while in 10 cases, 2–3 drugs were considered as potentially causative. The most frequent drugs were metamizole, piperacillin/tazobactam, dexketoprofen and linezolid, among others. Seven patients developed NCDIN during their hospital stay while 6 were admitted to the emergency department. Patients were using a median of 11 drugs (IQR 8–15) at the time of diagnosis. No deaths were recorded. *Conclusion* Metamizole and piperacillin/tazobactam are the most common drugs linked to non-chemotherapy drug-induced neutropenia in our cohort.

Keywords Agranulocytosis · Dipyrone · Febrile neutropenia · Granulocyte colony-stimulating factor · Pharmacovigilance

Impact on Practice

- Monitoring of drug safety in clinical practice is especially important in the case of rare and serious adverse reactions such as non-chemotherapy drug-induced neutropenia (NCDIN).
- Despite the safety alerts issued by the regulatory agencies, metamizole is still an important cause of drug-induced neutropenia.
- The assessment of causality benefits from a multidisciplinary approach in which self-medication and polypharmacy play an important role.
- Integrating pharmacovigilance programs in the institutional protocols for the management of adverse reactions can help to overcome barriers for low rates of adverse drug reactions reporting.

Introduction

Severe non-chemotherapy drug-induced neutropenia (NCDIN) is an idiosyncratic drug reaction characterized by an absolute neutrophil count (ANC) of under 0.5×10^9 cells/L. The clinical presentation of NCDIN includes patients that remain asymptomatic while others can develop oral mucosal lesions, fever and/or malaise. NCDIN is also associated with a high risk of developing serious infections such as pneumonia, septicemia or intra-abdominal infections. Although the mortality rates have decreased in the last decades, it is still considered a potentially fatal condition [1]. Indeed, several factors have

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been associated with a poorer prognosis: an age over 65 years, the presence of comorbidities such as renal impairment or systemic inflammatory diseases, and ANC at diagnosis below 0.1×10^9 cells/L) [1, 2]. The actual incidence of NCDIN is not accurately known, although it is considered a rare disease [2]. Increasing age and female gender have been pointed out as risk factors for the development of NCDIN [3]. Overall, several studies have shown incidence rates of 1.1 up to 15.4 cases per 1 million population per year [4–6]. The underlying pathological mechanisms of NCDIN are thought to be of immunological origin (drug-dependent antibodies), but the genetic background, concurrent diseases or drugs may also play an important role [7]. These mechanisms are possibly drug-class specific, and the immediate discontinuation of every causative drug to prevent future exposures is an essential part in the management of NCDIN. Several groups of drugs have been consistently associated with the risk of developing NCDIN (Table 1). However, the low overall incidence of NCDIN makes it particularly difficult to obtain quality evidence for other drug classes, such as newer or less common drugs. Pharmacovigilance then plays a central role in stablishing the safety profile of these agents in clinical practice.

Table 1 Common implicated drugs in NCDIN [1, 2]

Antithyroid agents
Carbimazole
Methimazole
Propylthiouracil
Antipsychotics
Clozapine
Olanzapine
Imipramine
Analgesics and antipyretics
Acetaminophen
Diclofenac
Ibuprofen
Metamizole
Naproxen
Antibacterials
Ampicillin
Amoxicillin-clavulanic acid
Ceftriaxone
Cefepime
Trimethoprim-sulfamethoxazole
Vancomycin
Antiepileptics
Phenytoin
Carbamazepine
Others
Sulfasalazine
Deferiprone

Aim of the study

The aims of this paper are to describe a protocol for the management of severe NCDIN in a tertiary hospital and to report its outcomes with focus on drug safety surveillance.

Ethics approval

This study was reviewed and approved by the Therapeutics Committee and the local Ethics Committee (CEIm). The study was conducted according to the principles of the Declaration of Helsinki.

Methods

This observational and prospective study was carried out in a tertiary-level teaching hospital. A panel of one clinical hematologist and three clinical pharmacists was recruited for the development and implementation of the protocol. Adult patients with documented use of filgrastim for the treatment of NCDIN were included in the study. Patients with active viral infections, congenital neutropenia or other underlying hematologic diseases were excluded from the study. Clinical evaluations were performed by hematologists in collaboration with the team responsible for the patient in each case. For pharmacovigilance purposes, patients were followed-up from the diagnosis until achieving an ANC $> 1.5 \times 10^9$ cells/L (hematologic recovery). Data collection, causality assessments and drug-adverse reactions reporting was performed by a team of clinical pharmacists. The Naranjo's scale was used as it was considered a standard in the assessment of causality [8]. In this study, patients' baseline characteristics and results are described by median values and interquartile ranges (IQR) for continuous data, and by frequencies for categorical variables, unless otherwise is indicated. The incidence rate per 10,000 patients was estimated with the number of NCDIN cases and the number of admissions during the study period. For the calculation of its 95% confidence interval (CI), a two-tailed Poisson test was used. Statistical analyses were performed using STATA 13.1 for Mac (StataCorp; US).

Results

The protocol for the management NCDIN, which was fully implemented in mid-2015, includes both inpatients and patients referred to the emergency department. The protocol comprises different measures, such as the withdrawal of any potentially causative drugs, the administration of broad-spectrum antibiotics until achieving an ANC of above 0.5×10^9 cells/L and reverse isolation for patients with severe neutropenia (ANC $< 0.5 \times 10^9$ cells/L). Although the

evidence that supports the use of G-CSF for the management of NCDIN is considered conflicting and comes mainly from retrospective cohort studies, our institutional Pharmacy and Therapeutics Committee reviewed and approved the off-label use of filgrastim in two high-risk situations: non-chemotherapy drug-induced severe neutropenia and patients with one or more poor prognostic factors of the previously mentioned criteria. The approved dose of subcutaneous filgrastim was 5 µg/Kg every 24 h until recovery of ANC $\geq 0.5 \times 10^9$ cells/L for two consecutive days. A daily assessment with neutrophil and lymphocytes counts was set as mandatory, as well as referral to a hematologist for follow-up.

Along with the protocol and as a part of the institutional pharmacovigilance strategy, a pharmacovigilance surveillance program on severe NCDIN in adult patients was initiated. In order to identify the patients, a reporting system linked to the prescription of filgrastim was included in the computerized physician order entry software (CPOE). As a patient is prescribed filgrastim, physicians have to select one of the available indications (cancer patients receiving myelosuppressive chemotherapy mobilization of hematopoietic progenitor cells and suspicion of NCDIN, among others) and, thereby an alert is generated.

From June 2015 to December 2017, 13 patients with suspected non-chemotherapy drug-induced neutropenia have been included in the study, of which all were severe at the time of diagnosis. Patients' clinical characteristics are described in Table 2. Seven patients had one or more negative prognostic factors, and two patients had a history of autoimmune diseases (inflammatory bowel disease and lupus). A single drug was considered as causative only in 3 patients, while in the remaining 10 cases, two to three drugs had to be considered as potentially causative after the assessment. The 13 cases of NCDIN (all graded as "probable" by Naranjo's algorithm) were reported through the Spanish Pharmacovigilance System. The most common suspected drugs in this cohort of patients were metamizole (8) and piperacillin/tazobactam (5). Other identified drugs were dexketoprofen (3), linezolid (3), amoxicillin/clavulanic (1), meropenem (1), valganciclovir (1), metoclopramide (1), vancomycin (1), allopurinol (1), sulfamethoxazole and trimethoprim (1), tigecycline (1) mycophenolate mofetil (1). Seven patients developed NCDIN during their hospital stay. This was mainly related to the long use (more than 5 days) of beta-lactam antibiotics [piperacillin/tazobactam (4), meropenem, (1)], analgesics or antipyretics [metamizole (6), dexketoprofen (3)] and linezolid (3). In terms of concomitant medications, patients were using a median of 11 drugs (IQR 8–15) at the time of the adverse event took place. No deaths were attributed to NCDIN in our cohort of patients. The number of hospital admissions during the study period was 125,199 and the incidence rate of NCDIN per 10,000 patients was 1.04 (95% CI 0.24–5.57).

Discussion

Clinicians' burden of work, difficulties in recognizing an adverse reaction or lack of knowledge about the pharmacovigilance reporting system have been identified as barriers to the reporting of adverse drug reactions [9]. While pharmacovigilance is an essential part of safe use of drugs, a systematic review showed a median of under-reporting as high as 94% for all adverse reactions and 85% for severe adverse reactions [10]. With this in mind, the goals of our pharmacovigilance program were to increase the number of adverse drug reaction reports and to improve their quality. The main challenge we found in the evaluation of these 13 cases of suspected NCDIN was to establish the causal relationship between the use of a certain drug and the development of the adverse event. In fact, polypharmacy was a constant in this population, as our patients were taking a median of 11 drugs at the time they were admitted. Therefore, this is a complex process that requires a detailed anamnesis and

Table 2 Characteristics of the patients

Variable	
Sex, *n* (%)	
Male	6 (46.2)
Female	7 (53.8)
Median age, years (range)	51 (24–80)
Autoimmune diseases, *n* (%)	
Yes	2 (15.4)
No	11 (84.6)
ANC nadir, cells/L (IQR)	0.1×10^9 (0–0.1×10^9)
Median of doses of filgrastim received per patient, *n* (IQR)	2 (2–5)
Median length of hospital stay, days (IQR)	26 (9–50)
Median of duration of severe neutropenia, days (IQR)	2 (2–5)

ANC absolute neutrophil count, *IQR* interquartile range

self-medication and over-the-counter drugs have to be carefully considered [2]. In our opinion, the utility of causality algorithms (such as Naranjo's scale) is scarce in this serious adverse reaction, as the re-exposure of patients to the potentially causal drug is an unethical practice.

After more than 2 years, we consider this program a valuable experience that helped us to improve knowledge of the safety profile of drugs in our clinical practice. Based on this study, we have been able to estimate an incidence rate of 1.04 cases of NCDIN per 10,000 patients, which is similar to other reported incidence rates [11]. Although limited by the size of our cohort, this pharmacovigilance program has also allowed us to identify specific risks for the development of NCDIN in the community considering our drug-use patterns. This was the case for metamizole, a pyrazolone derivative with anti-inflammatory properties that is widely used in European countries for the treatment of postoperative and colic pain. Although a clear association of metamizole use with the development of NCDIN was established more than 10 years ago [12, 13], our study shows that this is still an important issue. In fact, the Spanish Medicines and Medical Devices Agency (AEMPS) issued in the year 2018 a safety communication to healthcare professionals intending to raise awareness about the use of metamizole and the risk of NCDIN, particularly in certain groups of patients (elderly patients or patients with a history of previous hematologic adverse reactions, among others) [14]. It is also remarkable that, despite the rate of new drug approvals, the main causative drugs belonged to the already known classes of drugs (betalactam antibiotics, analgesics), which seems to be a constant [15].

In our opinion, the availability of a protocol facilitates an early management of severe NCDIN, which includes both pharmacological and non-pharmacological measures. It is possible that such measures may have a positive impact on health outcomes as our mortality rate contrasts with others previously reported rates of 5–10% [1]. Although we consider that the CPOE built-in paperless reporting system has been a useful tool to record patients with suspected severe NCDIN, it is also the main limitation of this study since the inclusion of patients relies on physician's identification of the adverse reaction. Therefore, we are currently developing a bundle of clinical rules that will be added to our clinical surveillance system HIGEA® (Yerbabuena Software, ES). This software integrates clinical data from different sources (CPOE, electronic health records and laboratory data) and generates an alert according to certain clinical rules (e.g. patient receiving a betalactamic antibiotic for more than 5 days and an ANC $< 0.5 \times 10^9$ cells/L). With the use of these information systems, we expect that we will help healthcare professionals to overcome the barriers for the reporting of adverse drug reactions. In our opinion, future studies should focus on the impact of information technologies to ensure a safer use of drugs, based on information directly obtained from our communities.

Conclusion

This drug safety surveillance program helped us to identify that metamizole and piperacillin/tazobactam are associated with the risk of development of NCDIN in our clinical practice, both in the inpatient and emergency department settings. The implementation of a protocol that integrates treatment and pharmacovigilance in NCDIN patients has improved involvement in the reporting of this rare but serious drug adverse reaction.

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