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Idiosyncratic Drug-Induced Severe Neutropenia and Agranulocytosis: State of the Art

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Abstract

In this chapter, we report and discuss the diagnosis and management of idiosyncratic drug-induced, or drug-associated, severe neutropenia, and agranulocytosis (neutrophil count of $<0.5 \times 10^9/L$). In this setting, neutropenia remains a potentially serious adverse event due to the frequency of severe sepsis, with severe deep tissue infections (e.g., pneumonia), life-threatening infections, septicemia, and septic shock in two-thirds of all hospitalized patients. Recently, several poor prognostic factors, impacting the hematological recovery, the duration of hospitalization, and the outcome have been identified that may be helpful when identifying “frailty” patients. These factors include: old age, poor performance status, septicemia or shock, comorbidities such as renal failure, and a neutrophil count below $0.1 \times 10^9/L$. recovery. In this situation, modern management, with broad-spectrum antibiotics in case of any sepsis sign and hematopoietic growth factors (HGF) (particularly G-CSF), is likely to improve the prognosis, with a current mortality rate around 5%.

Keywords: agranulocytosis, neutropenia, drugs, infections, pneumonia, antibiotics, hematopoietic growth factor

1. Introduction

White blood cells, as granulocytes or leukocytes, are an important component of the host defense system, responsible for protection against bacteria, viruses, fungi, and invading parasites [1]. The white blood cells constitute only 1% of the total blood volume. The term neutropenia describes an absolute decrease in neutrophil numbers [1].

Neutropenia is defined by a neutrophil count $<1.5 \times 10^9/L$ ($<1.2 \times 10^9/L$ in black people). The degree of neutropenia predicts the risk of serious bacterial infections. Severe neutropenia is characterized by a profound decrease of circulating neutrophils in case of an absolute lack of circulating neutrophils, classically resulting in a neutrophil count of $<0.5 \times 10^9/L$ [1, 2].

Schultz first introduced the term “agranulocytosis” in 1922, for cases of acute and severe pharyngeal infections, associated with a lack of granulocytes in the blood in relation to drug intake [2]. Such unpredictable event, named “idiosyncratic,” is typically serious, with around 50% of cases exhibiting severe sepsis, and a mortality rate of 10–20% [2, 3].

In this chapter, we report and discuss the diagnosis and management of idiosyncratic drug-induced, or drug-associated, severe neutropenia, and agranulocytosis.

2. Search strategy

A literature search was performed on the *PubMed* database of the *US National Library of Medicine* and *Scholar Google*. We searched for articles published between January 2010 and March 2018, using the following keywords or associations: “drug-induced neutropenia,” “drug-induced agranulocytosis,” “idiosyncratic neutropenia” and “idiosyncratic agranulocytosis”; restrictions included: English- or French-language publications; published from January 1, 2010 to February 31, 2018; human subjects; clinical trials, review articles or guidelines. All of the English and French abstracts were reviewed by at least two senior researchers from our work group (*GRoupes d'Etudes des Agranulocytoses médicamenteuses* (GREAT) des *Hôpitaux Universitaires de Strasbourg* (HUS), Strasbourg, France). After rigorous selection, only 15 papers were selected and analyzed. The latter was used to write this paper in the form of a short narrative review.

American Society of Hematology educational books, textbooks of Hematology and Internal medicine, and information gleaned from international meetings were also used.

3. Etiologies of severe neutropenia

In adults, the diagnosis of acute and severe neutropenia (neutrophil count of $<0.5 \times 10^9/L$) includes a limited number of conditions [1]. In fact, the main differential diagnoses outside the context of treatment of cancer with chemotherapy (e.g., alkylating agents, antimetabolites, etc.) or radiotherapy, include myelodysplastic syndromes, especially in elderly patients, and acute leukemia.

All other conditions induced moderate neutropenia, with an absolute neutrophil count between 1.5 and $0.5 \times 10^9/L$. These conditions mainly include: neutropenia secondary to sepsis, particularly viral infections or bacterial infections (severe Gram-negative infections with *Salmonella* sp., tuberculosis, *Brucella* sp.); and neutropenia associated with

hypersplenism [2]. Other rarer differential diagnoses include neutropenia secondary to alcoholism, nutritional deficiencies (folic acid, vitamin B12, cooper, etc.), Felty's syndrome, systemic lupus erythematosus or Sjögren's syndrome, and lastly aplastic anemia or paroxysmal nocturnal hemoglobinuria [2].

In the literature, acute and severe neutropenia has been shown to be attributable to drugs in 70–90% of cases [2]. Thus, in practice, idiosyncratic drug-induced neutropenia or agranulocytosis should be discussed routinely (considered in first) even if there is a context moving toward another condition.

4. Definition

To date, drug-induced, or drug associated, severe neutropenia, or agranulocytosis is defined at least by a neutrophil count of $<0.5 \times 10^9/L$, which occurs as a result of exposure to drugs [3]. The presence of fever and sepsis signs is usual, even required, for some authors. In the majority of patients, the neutrophil count is under $0.1 \times 10^9/L$.

All drugs may be the causative agents, particularly: chemotherapy, immune modulator agents or biotherapies. Other daily drugs may also be more rarely incriminated. Such event is called "idiosyncratic" drug-induced neutropenia and agranulocytosis [2, 3]. Either the drug itself or one of its metabolites may be the causative agent.

Currently, the recommended criteria for diagnosing blood cytopenias and for implicating a drug as a causative agent in neutropenia are derived from an international consensus meeting [2, 4]. These criteria are outlined in **Table 1**. As idiosyncratic severe neutropenia and agranulocytosis are life-threatening conditions, no patient was re-challenged with the incriminated drug ("theoretical method of reference").

Definition of agranulocytosis	Criteria of drug imputability
Neutrophil count $<0.5 \times 10^9/L$ ± existence of a fever and/or any signs of infection	Onset of agranulocytosis during treatment or within 7 days of exposure to the drug, with a complete recovery in neutrophil count of more than $1.5 \times 10^9/L$ within one month of discontinuing the drug Recurrence of agranulocytosis upon re-exposure to the drug (this is rarely observed, as the high risk of mortality contra-indicates new administration of the drug) Exclusion criteria: history of congenital neutropenia or immune mediated neutropenia, recent infectious disease (particularly recent viral infection), recent chemotherapy and/or radiotherapy and/or immunotherapy* and existence of an underlying hematological disease

*Immunoglobulins, interferon, anti-TNF antibodies, anti-CD20 (rituximab).

Table 1. Criteria for idiosyncratic drug-induced agranulocytosis.

5. Epidemiology and causative drugs

Idiosyncratic agranulocytosis is a rare disorder. In Europe, the annual incidence of such events is between 1.6 and 9.2 cases per million populations [2, 4]. In the USA, reported ranges from 2.4 to 15.4 per million per year. In our experience, the incidence remains unchanged, despite the withdrawn of incriminated drugs (which carry a high-risk), and increased levels of medical awareness and pharmacovigilance [5]. Older patients are thought to be at greater risk for to drug-induced neutropenia, probably because of increased medication use.

Almost all classes of drugs have been implicated as “causative,” but for the majority, the risk appears to be very small (**Table 2**) [2, 5]. However, for drugs such as antithyroid drugs, ticlopidine, clozapine, phenothiazines, sulfasalazine, trimethoprim-sulfamethoxazole (cotrimoxazole), and dipyron or sulfasalazine, the risk may be higher. For antithyroid drugs (propyl-thiouracil and méthimazole), a risk of 3 per 10,000 users has been reported. For

Family drug	Drugs
Analgesics and nonsteroidal anti-inflammatory drugs:	Acetaminophen, acid acetylsalicylic (aspirin), aminopyrine, benoxaprofen, diclofenac, diflunisal, dipyron, fenoprofen, indomethacin, ibuprofen, naproxen, phenylbutazone, piroxicam, sulindac, tenoxicam, tolmetin
Antipsychotics, hypnotosedatives and antidepressants:	Amoxapine, chlomidamine, chlorpromazine, chlordiazepoxide, clozapine, diazepam, fluoxetine, haloperidol, levopromazine, imipramine, indalpin, meprobamate, mianserin, olanzapine, phenothiazines, risperidone, tiapride, ziprasidone
Antiepileptic drugs:	Carbamazepine, ethosuximide, phenytoin, trimethadione, valproic acid (sodium valproate)
Antithyroid drugs:	Carbimazole, methimazole, potassium perchlorate, potassium thiocyanate, propylthiouracil
Cardiovascular drugs:	Acid acetylsalicylic, amiodarone, aprindine, bepridil, captopril, coumarins, dipyridamole, digoxin, flurbiprofen, furosemide, hydralazine, lisinopril, methyldopa, nifedipine, phenindione, procainamide, propafenone, propranolol, quinidine, ramipril, spironolactone, thiazide diuretics, ticlopidine, vesnarinone
Anti-infective agents:	Abacavir, acyclovir, amodiaquine, atovaquone, cephalosporins, chloramphenicol, chloroguanine, chloroquine, ciprofloxacin, clindamycin, dapson, ethambutol, flucytosine, fusidic acid, gentamicin, hydroxychloroquine, isoniazid, levamisole, lincomycin, linezolid, macrolids, mebendazole, mepacrine, metronidazole, minocycline, nitrofurantoin, norfloxacin, novobiocin, penicillins, pyrimethamine, quinine, rifampicin, streptomycin, terbinafine, tetracycline, thioacetazone, tinidazole, trimethoprim-sulfamethoxazole (cotrimoxazole), vancomycin, zidovudine
Miscellaneous drugs:	Acetazolamide, acetylcysteine, allopurinol, aminoglutethimide, arsenic compounds, benzafibrate, brompheniramine, calcium dobesilate, chloropheniramine, cimetidine, colchicine, dapson, deferiprone, famotidine, flutamide, gold, glucocorticoids, hydroxychloroquine, mesalazine, metapyrilène, methazolamide, metoclopramide, levodopa, olanzapine, omeprazole, oral hypoglycemic agents (glibenclamide), mercurial diuretics, penicillamine, ranitidine, riluzole, sulfasalazine, most sulfonamides, tamoxifen, thenalidine, tretinoid, tripeleminamine

Table 2. Drugs implicated in the occurrence of idiosyncratic agranulocytosis.

ticlopidine, the risk is more than 100-fold higher. Clozapine induces agranulocytosis in almost 1% of patients, particularly in the first three months of treatment, with older patients and females being at a higher risk [2, 5].

In our single-center cohort from the GREAT team (n = 203), the most frequent causative drugs are: antibiotics (49.3%), especially β -lactams and cotrimoxazole; antithyroid drugs (16.7%); neuroleptic and anti-epileptic agents (11.8%); antiviral agents (7.9%); and platelet aggregation inhibitors (6.9%), especially ticlopidine [5]. Since 1990–2000, no case of noramidopyrine- and ticlopidine-induced agranulocytosis is reported in the literature. Recently, several new drugs have been listed as causative agents for severe neutropenia and agranulocytosis, for example, acyclovir, ganciclovir, lamotrigine, terbinafine or deferiprone [2, 5].

6. Mechanisms of idiosyncratic drug-induced neutropenia

The pathogenesis of drug-induced neutropenia is a heterogeneous process, which is not yet fully understood [2, 3]. Clinical observations, studies in volunteers and laboratory experiments have suggested that this disorder is mediated by immune allergic and toxic mechanisms. In many cases, neutropenia occurs after prolonged drug exposure, resulting in decreased granulocyte production by hypoplastic bone marrow. In other cases repeated, intermittent exposure is implicated. This suggests an immune mediated mechanism, although this hypothesis is not entirely confirmed.

Direct damage, either to the microenvironment of the bone marrow or myeloid precursors, plays a significant role in most other cases [3]. Complex metabolic pathways that metabolize drugs and other chemicals are regulated by genetic factors. Genetic polymorphism results in heterogeneity of expression of the various enzymes, which generate or destroy intermediate toxic compounds [3].

Other mechanisms, involving cytotoxic T cells, haptens, auto-immunity, and oxidative modification of the drug have also been considered [3]. The impact of myeloperoxidase and NADPH-oxidase polymorphism in drug-induced neutropenia and agranulocytosis have also been studied. Clozapine appears to accelerate the process of apoptosis, thought to be due to depletion of ATP and reduced glutathione, which renders the neutrophils highly susceptible to oxidant-induced apoptosis [3].

7. Clinical manifestations

Initially, symptomatic patients with idiosyncratic drug-induced severe neutropenia or agranulocytosis usually present with fever, which often is the earliest and sometimes the only sign during evolution. This later is often associated with general malaise, often including chills [2, 3]. In this setting, symptoms may appear either immediately or insidiously, depending on the time course of neutropenia development. Symptomatic patients are commonly present at discovery

a non-specific sore throat, acute tonsillitis or sinusitis. More rarely, patients have first, as a not expected and brutal event, a severe deep and potentially life-threatening infection [2].

It is important to note that without medical intervention, particularly immediate antibiotics administration, natural history of agranulocytosis include severe and potentially life-threatening infections with often signs of general sepsis and septicemia (fever, chills, hypotension, etc.). During the evolution, documented pneumonia as well as anorectal, skin or oropharyngeal infections and septic shock were the most reported infections [2, 3]. To date, classical manifestations as necrotic tonsillitis and perinea gangrene or are exceptional.

In our experience (203 patients), the clinical manifestations include: isolated fever (unknown origin) (26.3%); septicemia (13.9%); documented pneumonia (13.4%); sore throat and acute tonsillitis (9.3%); and septic shock (6.7%) [5]. While in hospital 19.2% of the patients worsened clinically and exhibited features of severe sepsis, septic shock, or systemic inflammatory response syndrome (SIRS).

However, besides these “loud” clinical manifestations, clinicians must keep in mind that the signs of these infections may be sometimes crude and atypical because of the neutropenia (**Figure 1**). For practitioners, it is to note that pneumonia is often asymptomatic because of the lack of neutrophil cells. In this situation, thoracic CT-scan may be proposed with much better results than X-ray (**Figure 2**). Similarly, when antibiotics are administered prophylactically, or at the beginning of this adverse event, both the patient’s complaints and the physical findings may be “masked,” and fever is often the only clinical sign detected [2].



Figure 1. Chest radiography in a patient with absolute neutrophil count $<0.1 \times 10^9/L$: “Masked” pneumonia.

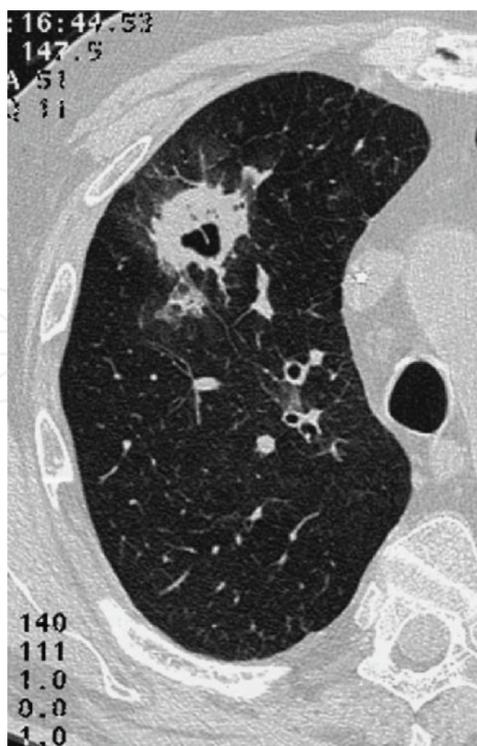


Figure 2. CT-scan in a patient with absolute neutrophil count $<0.1 \times 10^9/L$: Lung aspergillosis.

8. Biological data

Theoretically, acute neutropenia is classically diagnosed in a blood sample, resulting in a neutrophil count of $<0.5 \times 10^9/L$ [3, 5]. In this setting, monocyte and basophile counts may be increased. In the majority of patients, the neutrophil count is under $0.1\text{--}0.2 \times 10^9/L$.

In this setting, bone marrow examination may not be required in for all patients but is pivotal to exclude an underlying pathology, particularly in the elderly to rule out myelodysplastic disorders and malignant hematological diseases [1, 2]. Bone marrow examination may be particularly required in case of associated anemia, thrombocytopenia or abnormal blood cells. In such patients with idiosyncratic drug-induced agranulocytosis, the bone marrow typically shows a lack of mature myeloid cells, whereas in other cases, immature cells from the myelocyte stage are preserved. This latter appearance is described as “myeloid maturation arrest” [2, 3].

In severe neutropenia, multiple microbiological specimens should be taken, as in the case of post-chemotherapy neutropenia. With such multiple microbial samples, a causative pathogen, typically Gram-negative bacilli or Gram-positive cocci (mainly *Staphylococcus* spp.), was isolated in 30% of cases [3]. Fungi are also involved as secondary infective agents ($>10\%$), however, in a few percent of cases regarding neutropenia related to chemotherapy. To date, modern molecular techniques have further facilitated identification of microbial pathogens, allowing for aggressive interventions that appear to improve patient outcomes as documented later in the paper.

9. Prognosis and mortality rate

Idiosyncratic drug-induced severe neutropenia usually resolves over time, with supportive care and management of infection [2, 3]. The time to neutrophil recovery has typically been reported to range from 4 to 24 days.

In our aforementioned cohort study (n = 203), the mean duration of hematological recovery (neutrophil count $\geq 1.5 \times 10^9/L$) is 7.8 days (range: 2–20) [5]. The median duration for neutrophil count $\geq 0.5 \times 10^9/L$ is 6.8 days (range: 1–24).

In this context, the mortality rate for idiosyncratic agranulocytosis has recently fallen from 10 to 16 to 5% (range 2.5–10%) [2, 3]. This is likely due to improved recognition, management, and treatment of the condition. The highest mortality rate is observed in “frailty” patients: older patients (>65 years), with poor performance status, as well as those with several comorbidities as renal failure (defined as serum creatinine level $> 120 \mu\text{mol/L}$), chronic heart failure; bacteremia septicemia at diagnosis; or shock at diagnosis (**Table 3**); or low neutrophil count levels [2, 6].

Previously, we have found demonstrated that several variables were significantly associated with a longer neutrophil recovery time ($> 1.5 \times 10^9/L$), as: that an absolute neutrophil count of $< 0.1 \times 10^9/L$ at diagnosis, as well as septicemia and/or shock [7], were variables that were significantly associated with a longer neutrophil recovery time. In our cohort, bone marrow showing a lack of myeloid cells was not found to be associated with a delayed recovery (using uni- and multivariate analysis) [5].

It is worth noting, that in elderly patients, clinical manifestations were generally more severe, with septicemia or septic shock in at least two-thirds of patients, as we have previously published [8]. It is also the case in patients with associated morbidities as chronic cardiac failure, chronic obstructive pulmonary disease, renal failure and immune disorders. In our experience, the depth of the neutropenia impacts the severity of the clinical, manifestations [7].

Age > 65 years	Negative impact on duration of hematological recovery**, duration of hospitalization and antibiotherapy
Neutrophil count at diagnosis: $\leq 0.1 \times 10^9/L$	Negative impact on duration of hematological recovery, duration of hospitalization and antibiotherapy
Clinical status: Deep severe infections or bacteremia or septic shock (versus isolated fever)	Negative impact on duration of hospitalization and antibiotherapy and of mortality
Severe underlying disease or severe co-morbidity: Renal failure, cardiac or respiratory failure, systemic auto-inflammatory diseases	Negative impact on duration of hematological recovery and hospitalization
Management with pre-established procedures and hematopoietic growth factor for use in severe conditions	Positive impact on duration of hematological recovery, duration of hospitalization and of mortality

*Prognosis: hematological recovery, duration of hospitalization and antibiotherapy, mortality).

**Hematological recovery: absolute neutrophil count $> 1.5 \times 10^9/L$.

Table 3. Impact factors for the prognosis* of idiosyncratic drug-induced agranulocytosis.

At the opposite side, some patients (<20%) (not-well identified characteristics or profile) remained asymptomatic [3]. This supports the case for routine monitoring of blood counts in individuals receiving high-risk medications such as, for example, antithyroid drugs [2, 3]. This also supports not consensual home management of such an event in certain patients (young, without medical history, and with fever as the sole sign) [3].

10. General management

The management of idiosyncratic drug-induced severe neutropenia and agranulocytosis begins with the immediate withdrawal of any medications, which may potentially be responsible [2, 3]. Thus, the patient's medication history must be carefully obtained in chronological order so that the suspected agent(s) may be identified.

For experts, routine monitoring for agranulocytosis is required in some high-risk drugs, such as clozapine, ticlopidine, and antithyroid drugs [2, 3]. All cases of drug-induced neutropenia must be notified to the pharmacovigilance center. All febrile patients should be admitted to hospital, without any delay [2, 3].

Concomitant measures include realization of multiple microbial samples (blood, urine, stool, and sputum cultures) and aggressive treatment of confirmed or potential sepsis, as well as the prevention of secondary infections. It should be noted that as a result of neutrophil deficiency, both the patient's symptoms and the physical findings may be altered, and fever may be the only clinical sign [3]. Preventive measures include good hygiene and infection control, paying particular attention to high-risk areas such as the mouth, skin, and perineum [2, 3].

Patients with a low-risk of infection, and good performance status may be managed in home with intensive supervision and monitoring! The occurrence of sepsis requires prompt management, without any delay, including the administration of broad-spectrum intravenous antibiotic therapy [2, 3].

In case of fever or for "frailty" patients, prompt hospitalization without delay may be required [2, 3]. In this setting, patient isolation and the use of prophylactic antibiotics (e.g., for the gastrointestinal tract) have been proposed, but their usefulness in limiting the risk of infection has not been documented or at least, has not been clinically proven [3].

11. Antimicrobial therapy

In case of sepsis, we commonly combine in first-line therapy, new cephalosporins and quinolones or aminoglycosides. It is important to note that a great part of these recommendations is adapted from the evidence-based medicine recommendations for the management of chemotherapy-induced neutropenia (field of oncology) [3]. Of course ureidopenicillins beta-lactam/beta-lactamase inhibitor combinations, as carbapenems, or imipenem can be safely used in these antibiotic combinations. The addition of intravenous vancomycin or teicoplanin

is considered in patients at high-risk of serious Gram-positive infections or after 48 hours of continued fever despite first-line of antibiotics with at least cephalosporins [2, 3].

In patients with persistent fever despite broad-spectrum antibiotics against Gram-negative bacilli or Gram-positive cocci or systematically after 1 week of persistent fever, the addition of empirical antifungal agents should be considered, as amphotericin B or related derivatives (e.g., liposomal preparation of amphotericin), and voriconazole or caspofungin [2, 3].

12. Hematopoietic growth factors (HGF)

Since 1985, two-thirds of reported cases of idiosyncratic agranulocytosis have been treated with HGF, especially *granulocyte-colony stimulating factor* (G-CSF) [9]. The most recent, major studies on hematopoietic growth factors (HGF) use in drug-induced agranulocytosis are described in **Table 4** [2, 5, 10–15]. In our aforementioned cohort, a faster hematological non-significantly recovery (neutrophil count $>1.5 \times 10^9/L$) was observed in the HGF group: 2.1 days

Type of study and target population	Main results
Systematic review of all published cases (n = 492); all patients with idiosyncratic drug-induced agranulocytosis [2]	Treatment with hematopoietic growth factors was associated with a statistically significantly lower rate of infectious and fatal complications, in cases with a neutrophil count $<0.1 \times 10^9/L$
Meta-analysis (n = 118); all patients with idiosyncratic drug-induced agranulocytosis [10]	G-CSF or GM-CSF (100 to 600 $\mu g/day$) reduced the mean time to neutrophil recovery (neutrophil count $>0.5 \times 10^9/L$) from 10 to 7.7 days, in cases with a neutrophil count $<0.1 \times 10^9/L$, and reduced the mortality rate from 16 to 4.2%
Case control study, retrospective analysis (n = 70); all patients with idiosyncratic drug-induced agranulocytosis [11]	G-CSF and GM-CSF (100 to 600 $\mu g/day$) reduced the recovery of neutrophil count from 7 to 4 days, particularly in patients with a neutrophil count $<0.1 \times 10^9/L$
Cohort study, retrospective analysis (n = 54); patients with idiosyncratic drug-induced agranulocytosis >65 years of age, with poor prognostic factors [12]	G-CSF (300 $\mu g/day$) significantly reduced the mean duration for hematological recovery from 8.8 to 6.6 days ($p < 0.04$). G-CSF reduced the global cost
Cohort study, retrospective analysis (n = 20); patients with antithyroid drug-induced agranulocytosis and poor prognostic factors [13]	G-CSF (300 $\mu g/day$) significantly reduced the mean durations of hematological recovery, antibiotic therapy and hospitalization from: 11.6 to 6.8 days, 12 to 7.5 days and 13 to 7.3 days, respectively ($p < 0.05$ in all cases). G-CSF reduced the global cost
Cohort study, retrospective analysis (n = 145); all patients with idiosyncratic drug-induced agranulocytosis [14]	G-CSF shortens time to recovery in patients with agranulocytosis
Cohort study, retrospective analysis (n = 201); all patients with idiosyncratic drug-induced agranulocytosis [5]	G-CSF (300 $\mu g/day$) reduced the mean durations of hematological recovery for 2.1 days ($p = 0.057$).
Prospective randomized study (n = 24); all patients with antithyroid drug-induced agranulocytosis [15]	G-CSF (100 to 200 $\mu g/day$) did not significantly reduce the mean duration for hematological recovery

G-CSF: Granulocyte-Colony Stimulating factor; GM-CSF: Granulocyte-Macrophage-Colony Stimulating factor

Table 4. Recent studies on the use of hematopoietic growth factors in idiosyncratic drug-induced agranulocytosis.

($p = 0.057$) [5]. Thus, for certain hematologist, the usefulness of HGF remains controversy in such patients. To support this view, the only available prospective randomized study (based on 24 patients with antithyroid-related agranulocytosis) did not confirm the benefit of G-CSF [10]. Nevertheless, this negative result may be related to inappropriate G-CSF doses (100–200 $\mu\text{g}/\text{day}$).

To date, no data is available on the use of pegfilgrastim (a long-acting recombinant G-CSF) in idiosyncratic drug-induced neutropenia [2, 3].

In this setting, it is important to keep in mind that transfusion of granulocyte concentrates should only be used in exceptional circumstances, and only then for the control of life-threatening infections with antibiotic resistance such as perineal gangrene [2].

13. Conclusions

In conclusion, it is important to keep in mind that idiosyncratic drug-induced or drug-associated, severe neutropenia and agranulocytosis remains a potentially serious adverse event due to the frequency of severe sepsis, with severe deep tissue infections (e.g., pneumonia), life-threatening infections, septicemia, and septic shock in two-thirds of all hospitalized patients. In this setting, several poor prognostic factors, impacting the hematological recovery, the duration of hospitalization, and the outcome have been documented: old age, poor performance status, septicemia or shock, comorbidities such as renal failure, and a neutrophil count below $0.1 \times 10^9/\text{L}$. In this situation, modern management, with broad-spectrum antibiotics in case of any sepsis sign and HGF is likely to improve the prognosis, with a currently mortality rate around 5%.

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