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REVIEW ARTICLE

State of Art on Idiosyncratic Drug-Induced Severe Neutropenia and Agranulocytosis

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ABSTRACT

In this paper, we report and discuss the clinical impact of severe and acute neutropenia with the example of idiosyncratic drug-induced severe neutropenia and agranulocytosis (neutrophil count of <0.5 x 109/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 includes: old age, poor performance status, septicemia or shock, comorbidities such as renal failure, and a neutrophil count below 0.1×109/L. recovery In this situation, modern management, with broad-spectrum antibiotics in case of any sepsis sign and hematopoietic growth factors (particularly G-CSF), is likely to improve the prognosis, with a currently mortality rate around 5%.

Introduction

White blood cells, 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, or leukocytes, constitute only 1% of the total blood volume. They originate in the bone marrow and circulate throughout the lymphoid tissues of the body. They include: the granulocytes with neutrophils (55-65%), eosinophils (1-4%, basophils (0-1%); the lymphocytes (20-40%); and the monocytes (3-8%).The term neutropenia describes an absolute decrease in neutrophil numbers [1]. Neutropenia is defined by a neutrophil count <1.5 x 10^9/L (<1.2 x 10^9/L in black people).

The degree of neutropenia predicts the risk of serious bacterial infections. Severe neutropenia are characterized by a profound decrease of circulating neutrophils, also called agranulocytosis in case of an absolute lack of circulating neutrophils, classically resulting in a neutrophil count of <0.5 x 10^9/L (associated or not with fever) [2]. The acute onset of severe neutropenia is frequently associated with a high risk of infection, particularly severe infections.

In the present paper, we report and discuss the clinical impact of idiosyncratic drug-induced, or drug-associated, severe neutropenia and agranulocytosis.

Search Strategy

A literature search was performed on the *PubMed* database of the *US National Library of Medicine* and on *Scholar Google*. We searched for articles published between January 2010 and February 2018, using the following key words or associations: "*neutropenia*", "*drug-induced neutropenia*", "*drug-induced agranulocytosis*", "*idiosyncratic neutropenia*" and "*idiosyncratic agranulocytosis*"; restrictions included: English- or French-language publications; published from Jan. 1, 2010, to Feb. 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 (*GRoupesd'Etudes des AgranulocytosesMédicamenteuses* [GREAM] des *Hôpitaux Universitaires de Strasbourg* [HUS], Strasbourg, France).

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

Definition

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 with drug intake*" [2]. To date, "drug-induced", also called "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 0.1×10^9/L.

All drugs may be the causative agents, particularly: chemotherapy; immune modulator agents or biotherapies. Other daily drugs may be also 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").

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 practice, acute and severe neutropenia has been shown to be attributable to drugs in 70 to 90% of cases [2]. In this setting, the main differential diagnoses outside the context oftreatment of cancer with chemotherapy (e.g., alkylating agents, antimetabolites, etc.) or radiotherapy, include acute leukemiaandmyelodysplastic syndromes, especially in elderly patients.

All other conditions induced moderate neutropenia, with an absolute neutrophil count between 1.5 to 0.5×10^9/L. These conditions mainly includes: neutropenia secondary to sepsis, particularly viral infections (quiet all viruses) 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 anemiaor paroxysmal nocturnal hemoglobinuria [2].

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 population [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.

Table 1: Criteria for idiosyncratic drug-induced agranulocytosis.

Definition of agranulocytosis:	Criteria of drug imputability:
▪ Neutrophil count <0.5 x 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 x 10^9/L within one month of discontinuingthedrug ▪ Recurrence of agranulocytosis upon re-exposure to the drug (this is rarely observed, as the high risk of mortality contra-indicates new administrationof 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 2: Drugs implicated in the occurrence of idiosyncratic agranulocytosis [3].

Family drug:	Drugs:
▪ Analgesics and nonsteroidal anti-inflammatory drugs:	▪ Acetaminophen, acid acetylsalicylic (aspirin), aminopyrine, benoxaprofen, diclofenac, diflunisal, dipyrone, fenoprofen, indomethacin, ibuprofen, naproxen, phenylbutazone, piroxicam, sulindac, tenoxicam, tolmetin
▪ Antipsychotics, hypnosedatives and antidepressants:	▪ Amoxapine, chlomipramine, 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, propanolol, quinidine, ramipril, spironolactone, thiazide diuretics, ticlopidine, vesnarinone
▪ Anti-infective agents:	▪ Abacavir, acyclovir, amodiaquine, atovaquone, cephalosporins, chloramphenicol, chloroguanine, chloroquine, ciprofloxacin, clindamycin, dapsone, ethambutol, flucytosine, fusidic acid, gentamicin, hydroxychloroquine, isoniazid, levamizole, lincomycin, linezolid, macrolids, mebendazole, mepacrine, metronidazole, minocycline, nitrofurantoin, norfloxacin, novobiocin, penicillins, pyrimethamine, quinine, rifampicin, streptomycin, terbinafine, tetracycline, thioacetazone, tinidazole, trimethoprim-sulfametoxazole (cotrimoxazole), vancomycin, zidovudine
▪ Miscellaneous drugs:	▪ Acetazolamide, acetylcysteine, allopurinol, aminoglutethimide, arsenic compounds, benzafibrate, brompheniramine, calcium dobesilate, chloropheniramine, cimetidine, colchicine, dapsone, 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, tripelennamine

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

Age >65 years	Negative impact on duration of hematological recovery**, duration of hospitalization and antibiotherapy
Neutrophil count at diagnosis: ≤0.1 x 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 x 10^9/L.

Almost all classes of drugs have been implicated as "causative", but for the majority the risk appears to be very small [2,5]. However for drugs such as antithyroid drugs, ticlopidine, clozapine, phenothiazines, sulfasalazine, trimethoprim-sulfametoxazole (cotrimoxazole), and dipyrone 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 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 (n=203), the most frequent causative drugs are: antibiotics (49.3%), especially ß-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] (Table 2). Since 1990 and 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, e.g. acyclovir, ganciclovir, lamotrigine, terbinafine or deferiprone [2,5].

Mechanisms of Idiosyncratic Drug-Induced Neutropenia

The pathogenesis of drug-induced neutropenia is a heterogeneous process which is not yet fully understood [2]. Clinical observations, studies in volunteers and laboratory experiments have suggested that this disorder is mediated by two main mechanisms: toxic mechanismsand immune allergic mechanism. In first case, neutropenia occurs after prolonged drug exposure, resulting in decreased granulocyte production by hypoplastic bone marrow. In the second case, 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 to 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]. For example, this is the case for clozapine with HLA. Two loci in the major histocompatibility complex are independently associated: a single amino acid in HLA-DQB1 (126Q) ($P=4.7 \times 10(-14)$, odds ratio [OR]=0.19, 95% confidence interval [CI]=0.12-0.29) and an amino acid change in the extracellular binding pocket of HLA-B (158T) ($P=6.4 \times 10(-10)$, OR=3.3, 95% CI=2.3-4.9) [2].

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 has 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].

Clinical Manifestations

Initially, symptomatic patients with idiosyncratic drug-induced agranulocytosis usually present with fever, which often is the earliest and sometimes the only sign during evolution ("fever of unknown origin" [FUO]). This later is often associated with general malaise, often including chills, myalgia [2,3]. Symptoms may appear either immediately or insidiously, depending on the time course of neutropenia development. Symptomatic patients 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, e.g; pneumonia [2]. It's important to note that without medical intervention, particularly immediate antibiotics administration, natural history of agranulocytosis includes severe and potentially life-threatening infections, with often severe signs of sepsis and septicemia (fever, chills, hypotension…).

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 beside 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). It is notable that 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].

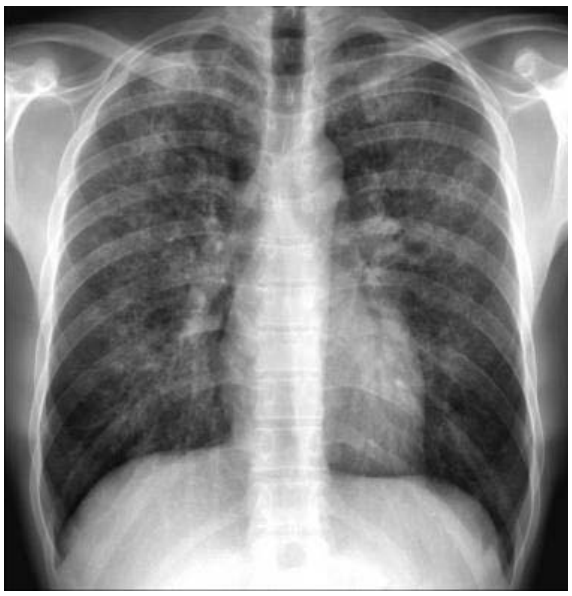

Figure 1: Chest radiography in a patient with absolute neutrophil count <0.1 x 10^9/L: "masked" pneumonia.

With 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 per cent of cases in regard to 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.

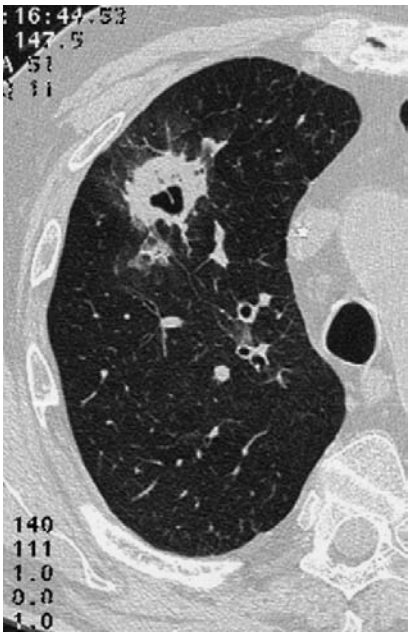

Figure 2: CT-scan in a patient with absolute neutrophil count <0.1 x 10^9/L: lung aspergillosis.

Clinical Manifestations

Theoretically, acute neutropenia is classically diagnosed in a blood sample, resulting in a neutrophil count of <0.5 x 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 to 0.2 x 10^9/L.it is important to note that after nadir, the increase of monocytes is the first sign of medullary regeneration.

In idiosyncratic agranulocytosis, 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, malignant hematological diseases or extensive

solid carcinomas [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].

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 10-16% to 5% (range, 2.5 to 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 µmol/L), chronic heart failure; bacteremia septicemia at diagnosis; or shock at diagnosis (Table 3); or low neutrophil count levels [2,6]. Previously, we have 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 co-morbidities as Chronic Heart Failure (CHF), Chronic Obstructive Pulmonary Disease (COPD), renal failure and autoimmune disorders. In our experience, the depth of the neutropenia impacts the severity of the clinical, manifestations [7].

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 antithyroid drugs or ticlopidine [2,3]. This also supports a not consensual home management of such an event in certain patients (young, without medical history, with fever as the sole sign, particularly in the setting of antithyroid drug-induced agranulocytosis) [3].

Management

1. General measures

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.

Patients with a low risk of infection, and good performance status, may be managed in home with intensive supervision and monitoring! However 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. To our knowledge, laboratory parameters

such as C Reactive Protein (CRP), procalcitonin, or other acute phase reactants have been of few utility in clinical practice, especially to differentiate the neutropenic fever and 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].

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].

2. Antimicrobial therapy

The occurrence of sepsis requires prompt management, without any delay, including the administration of broad-spectrum intravenous antibiotic therapy [2,3]. It's important to note that these recommendations are adapted from the evidence based-medicine recommendations for the management of chemotherapy-induced neutropenia (field of oncology) [3].

In case of sepsis, we commonly combine in first line therapy, new cephalosporins and quinolones or aminoglycosides [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 a 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 derivates (e.g. liposomal preparation of amphotericin) and voriconazol or caspofungin [2,3].

3. Hematopoietic growth factors

Since 1985, two-thirds of reported cases of idiosyncratic agranulocytosis have been treated with Hematopoietic Growth Factors (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 [5,9]. In our aforementioned cohort, a faster hematological non significantly recovery (neutrophil count >1.5 x 109/L) was observed in the HGF group: 2.1 days (p=0.057) [5]. Thus, for certain Hematologist the usefulness of hematopoietic growth factors 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 µg/day).

In this setting, it's 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].

Conclusion

In conclusion, it is important to keep in mind that severe and acute neutropenia as in the case of idiosyncratic 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 0.1×10^9/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%.

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

Type of study and target population	Main results
Systematic review of all published cases (n=492); All patients with idiosyncratic drug-induced agranulocytosis	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 x 10^9/L
Meta-analysis (n=118); All patients with idiosyncratic drug-induced agranulocytosis	*G-CSF* or *GM-CSF* (100 to 600 µg/day) reduced the mean time to neutrophil recovery (neutrophil count >0.5 x 10^9/L) from 10 to 7.7 days, in cases with a neutrophil count <0.1 x 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	*G-CSF* and *GM-CSF* (100 to 600 µg/day) reduced the recovery of neutrophil count from 7 to 4 days, particularly in patients with a neutrophil count <0.1 x 10^9/L
Cohort study, retrospective analysis (n=54); Patients with idiosyncratic drug-induced agranulocytosis >65 years of age, with poor prognostic factors	*G-CSF* (300 µg/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	*G-CSF*(300 µg/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	*G-CSF* shortens time to recovery in patients with agranulocytosis
Cohort study, retrospective analysis (n=201); All patients with idiosyncratic drug-induced agranulocytosis	*G-CSF* (300 µg/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	*G-CSF* (100 to 200 µg/day) did not significantly reduce the mean duration for hematological recovery

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

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