

CASE REPORT

GM-CSF as successful salvage therapy of metamizole (dipyrone)-induced agranulocytosis with Fournier's gangrene and severe septic shock in an adolescent

Annegret Winkler¹, Silke Kietz², Hagen Bahlmann¹, Gunel Jafarzade³, Holger N. Lode² & Matthias Heckmann¹

¹Division of Neonatology and Pediatric Intensive Care, Department of Pediatrics and Adolescent Medicine, Medical University of Greifswald, Greifswald, Germany

²Division of Pediatric Hematology and Oncology, Department of Pediatrics and Adolescent Medicine, Medical University of Greifswald, Greifswald, Germany

³Division of Pediatric Surgery, Department of Pediatrics and Adolescent Medicine, Medical University of Greifswald, Greifswald, Germany

Correspondence

Annegret Winkler, Division of Neonatology and Pediatric Intensive Care, Department of Pediatrics and Adolescent Medicine, Medical University of Greifswald, Ferdinand-Sauerbruch-Straße, 17475 Greifswald, Germany. Tel: +49-3834-866421; Fax: +49-3834-866422; E-mail: annegret.winkler@uni-greifswald.de

Key Clinical Message

This case report describes the successful use of granulocyte and macrophage colony-stimulating factor as salvage therapy and an alternative to hematopoietic stem cell transplantation in a 14-year-old adolescent with metamizole (dipyrone)-induced agranulocytosis and severe septic shock.

Keywords

Agranulocytosis, filgrastim, metamizole (dipyrone), sargramostim, septic shock.

Funding Information

No sources of funding were declared for this study.

Received: 21 July 2015; Revised: 13 April 2016; Accepted: 17 May 2016

Clinical Case Reports 2016; 4(8): 816–819

doi: 10.1002/ccr3.616

Introduction

Metamizole (dipyrone)-induced agranulocytosis (neutrophil granulocytes $<0.5 \times 10^9/L$) is a rare severe adverse reaction ($<1/10,000$) [1, 2]. In Europe, 10 per 1 million inhabitants per year are affected by drug-induced agranulocytosis, and metamizole-induced agranulocytosis represents only part of this incidence [1]. However, if agranulocytosis is associated with severe sepsis and necrotic wounds, an adequate level of neutrophil granulocytes is crucial. Due to the rare occurrence, there are no common treatment guidelines regarding how to best re-establish granulopoiesis. Available treatment interventions include recombinant human growth factors and blood stem cell transplantation as a last resort [3]. Here, we report a case where granulocyte and macrophage

colony-stimulating factor (GM-CSF) was successfully used as a second-line treatment to re-establish bone marrow function.

Case Report

A 14-year-old adolescent in severe septic shock was admitted to the hospital by ambulance. She had undergone an elective resection of a pilonidal fistula 4 weeks previously and was then treated with analgesic metamizole (dipyrone) frequently with 3 g/day (40 mg/kg body weight in three single doses, maximum 5 g/day) for pain due to progressive wound healing failure.

Upon arrival, the adolescent presented with hypotension (60/30 mmHg), tachycardia, acute renal failure (serum creatinine 238 $\mu\text{mol/L}$), liver failure with

cholestasis and dysfunctional plasma coagulation (Quick 29%, INR 2.4), and signs of systemic inflammation (CRP max. 155 mg/L). She was drowsy, but fully oriented. Although fluid was administered (40 mL/kg in 1 h), dopamine (up to 17.5 $\mu\text{g}/\text{kg}/\text{min}$) was required to maintain blood pressure. There were extensive necrotic areas and purulent lesions in the sacral and genital areas (Fig. 1). The wound swab and blood culture identified a mixture of aerobes and anaerobes, including *Pseudomonas aeruginosa*.

We initiated broad-spectrum antibiotic therapy with meropenem (3 g/day), clindamycin (20 mg/kg/day), and metronidazole (30 mg/kg/day), and surgical infectious source control. The adolescent was intubated straightly before the first surgery, ventilator settings were PIP 26 cmH₂O, Peep 12 cmH₂O, maximum FiO₂ 0.45 after surgery.

The initial blood counts were leukocytes $0.6 \times 10^9/\text{L}$ with absolute neutropenia ($0.01 \times 10^9/\text{L}$) and moderate lymphopenia ($0.56 \times 10^9/\text{L}$), normal platelets ($150 \times 10^9/\text{L}$), decreased erythrocytes ($2.5 \times 10^{12}/\text{L}$), and anemia with a hemoglobin level of 4.2 mmol/L. The bone marrow was characterized by a complete absence of granulopoiesis with no myeloid progenitor cells, consistent with the diagnosis of a metazolone-induced agranulocytosis. Due to the severe sepsis and extensive necrotic areas, we started therapy with granulocyte colony-stimulating factor (G-CSF, filgrastim, Neupogen®: Hexal AG, Holzkirchen, Germany) at a dose up to 18 $\mu\text{g}/\text{kg}/\text{day}$ for 8 days. Neutrophil granulocytes did not increase with G-CSF treatment. Between days 10 and 17, the patient received four granulocyte concentrates, which provided the bridging during the switch from G-CSF to GM-CSF.

Granulocyte concentrates (containing a total of $>1 \times 10^{10}$) were collected from two different ABO blood donors after stimulation with G-CSF at a dose of 5 $\mu\text{g}/\text{kg}$ body weight [4]. Tissue typing was performed to initiate the search for a matched, unrelated blood stem cell donor. The patient's treatment was changed to GM-CSF (sargramostim, Leukine®: Sanofi Aventis, Bridgewater, New Jersey, USA), 250 $\mu\text{g}/\text{day}$ for 7 days. Neutrophil granulocytes increased (after 6 days: $0.11 \times 10^9/\text{L}$, after 7 days: $1.19 \times 10^9/\text{L}$), as well as the monocyte count (Fig. 2).

Once granulopoiesis was restored, the patient's overall condition improved over time. Inotropic support was stopped on day 14. The patient was weaned from mechanical ventilation on day 17 and then received respiratory support with a high-flow nasal cannula, which was applied for 3 weeks (flow 25 L/min, FiO₂ around 0.30). The wound healing improved slowly with repetitive surgeries which include debridements and vacuum-assisted closure therapy (a total of 41 surgeries). Clearly visible granulation tissue was reported by the surgeon 11 days after starting GM-CSF. Discharge from the hospital was possible after 5 months.

While in the hospital, a second episode of agranulocytosis occurred due to an accidental application of metazolone during surgery. Administration of GM-CSF was able to restore neutrophil granulocytes again (Fig. 2).

Discussion

Our patient presented with life-threatening, severe septic shock, induced by *Pseudomonas* spp., as a result of isolated agranulocytosis in the blood and bone marrow following a 4-week exposure to a high dose of metazolone



Figure 1. Intraoperative findings on day 1. Left – the vulva and inguinal region after first debridement, right – sacral area with a lesion (10 cm × 5 cm × 5 cm) that extends down to the sacrum.

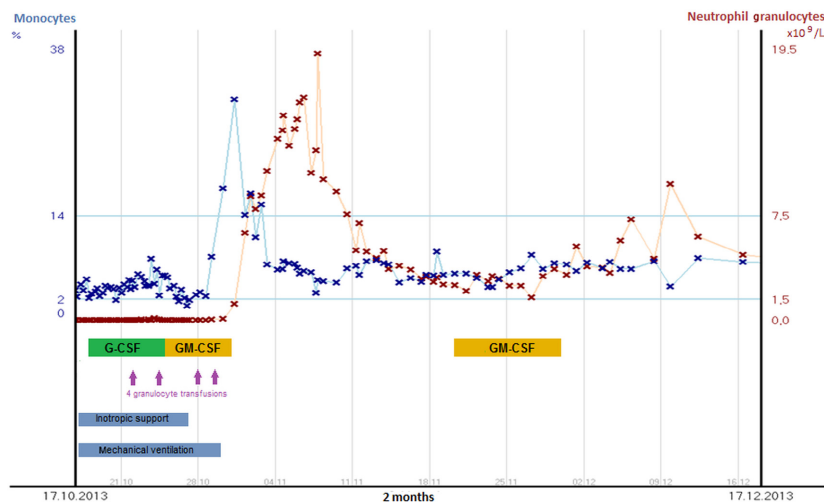


Figure 2. The counts of neutrophil granulocytes and monocytes over time in a 14-year-old adolescent with metamizole-induced agranulocytosis and severe septic shock, treated with granulopoiesis-stimulating factors.

(dipyrrone). The options to treat the underlying problem are limited and include the use of growth factors and blood stem cell transplantation. Given the septic condition of this patient, blood stem cell transplantation would have been associated with extremely high treatment-related mortality. Even if a genotypical sibling donor is available, the aplasia during pre- and posttransplantation period would make the survival highly unlikely. Therefore, the first choice treatment was to use granulopoiesis stimulating factors. Both G-CSF and GM-CSF are known to stimulate granulopoiesis to approximately the same extent, and are equally used for this purpose [1, 5]. One prospective study showed neutrophils recovered 1 day faster with G-CSF compared with GM-CSF after chemotherapy-induced neutropenia [6]. However, in acute leukemia for example there are no real benefits reported regarding the reduction in incidence and severity of infections and overall survival with less time in neutropenia. [7]. Both agents have been used for the same indications in different countries, based on country-specific drug approval conditions. Both agents were also reported to successfully treat agranulocytosis induced by drugs others than chemotherapy [8]. For this indication too, a reduction in the duration of agranulocytosis, antibiotic therapy, and length of hospital stay is reported, whereas clear data on the reduction of mortality is lacking [1]. Reports comparing both agents in metamizole-induced agranulocytosis are not available. Furthermore, dose-dependent side effects of GM-CSF like hypoxia and hypotension as a first-dose reaction following doses above 10 $\mu\text{g}/\text{kg}$ should be taken into account particularly in the critical care setting [9]. In our patient, a dose of 5 $\mu\text{g}/\text{kg}$ (250 $\mu\text{g}/\text{day}$) was effective and well tolerated.

In Germany, G-CSF is approved for chemotherapy-induced neutropenia; therefore, we first selected G-CSF. After 5 days without a response, granulocytes were transfused to rescue the critical situation. Three days later, the G-CSF was switched to GM-CSF. The monocytes increased after 3 days followed by neutrophils after two more days (Fig. 2). The GM-CSF was well tolerated and no acute side effects were noted [10]. However, both the neuroprotective and neurotoxic properties of GM-CSF were reported in animal experiments [11, 12]. The selection of GM-CSF was also based on its broader effect, compared with G-CSF, on the stimulation of myelopoiesis. GM-CSF acts on more immature myeloid progenitor cells and it stimulates the monocyte/macrophage compartment; in contrast, G-CSF stimulates the proliferation and differentiation of neutrophils [13]. We cannot prove that the failure of G-CSF in our patient was overcome by using GM-CSF. However, G-CSF did not restore granulopoiesis within the expected response time. In contrast, administration of GM-CSF, with its broader spectrum of activity and recruitment of primitive hematopoietic progenitors, resulted in an immediate response. Therefore, GM-CSF should be started directly in such a patient in whom a delay of 8 days of ineffective therapy might be life threatening. Furthermore, as outlined before, stem cell transplantation in such a critical patient is highly questionable.

The fact that the patient is an adolescent is probably one of the main reasons for the favorable outcome. The young, 14 years old patient was healthy without any pre-existing conditions, before she became septic. Fournier's gangrene is rare in adolescents. Epidemiologic data and scoring systems are only available for adults, especially

older male patients with pre-existing diseases. However, age seemed to be an important factor as shown in the population-based study by Sorensen *et al.* [14]. They found an increasing mortality with higher age of the patient (odds ratio 4.0 until 15.0) compared to patients <40 years. Furthermore, young patients are probably better responders to growth factors compared to elderly patients [15].

Conclusion

We report successful rescue of myelopoiesis with second-line GM-CSF therapy in an adolescent with metamizole (dipyrone)-induced agranulocytosis. This provides a new treatment option for patients who fail to respond to G-CSF to avoid hematopoietic stem cell transplantation.

Ethics Statement

Informed consent has been documented.

Acknowledgment

We especially thank Prof. Tamam Bakchoul for the information about preparation of granulocyte concentrates.

Conflict of Interest

None declared.

References

- Andrès, E., F. Maloisel, and J. Zimmer. 2010. The role of haematopoietic growth factors granulocyte colony-stimulating factor and granulocyte-macrophage colony-stimulating factor in the management of drug-induced agranulocytosis. *Br. J. Haematol.* 150:3–8.
- Product instruction Novalgine® (metamizole), product instruction service Germany Available at <http://www.fachinfo.de/suche/fi/014708>. Published May 2014, (accessed April 17, 2015).
- Beauchesne, M.-F., and S. J. Shalansky. 1999. Nonchemotherapy drug-induced agranulocytosis: a review of 118 patients treated with colony-stimulating factors. *Pharmacotherapy* 19:299–305.
- Price, T. H., M. Boeckh, R. W. Harrison, J. McCullough, P. M. Ness, R. G. Strauss, *et al.* 2015. Efficacy of transfusions with granulocytes from G-CSF/dexamethasone treated donors in neutropenic patients with infection. *Blood* 126:2153–2161.
- Garbe, E. 2007. Non-chemotherapy drug-induced agranulocytosis. *Expert. Opin. Drug Saf.* 6:323–335.
- Beveridge, R. A., J. A. Miller, A. N. Kales, R. A. Binder, N. J. Robert, J. H. Harvey, *et al.* 1998. A comparison of sargramostim (yeast-derived RhuGM-CSF) and filgrastim (bacteria-derived RhuG-CSF) in the therapeutic setting of chemotherapy-induced myelosuppression. *Cancer Invest.* 16:366–373.
- Wadleigh, M., and R. M. Stone. 2009. The role of myeloid growth factors in acute leukemia. *J. Natl. Compr. Canc. Netw.* 7:84–91.
- Andersohn, F., C. Konzen, and E. Garbe. 2007. Systematic review: agranulocytosis induced by nonchemotherapy drugs. *Ann. Intern. Med.* 146:657–665.
- Stern, A. C., and T. C. Jones. 1992. The side-effect profile of GM-CSF. *Infection* 20(Suppl. 2):S124–S127.
- Vial, T., and J. Descotes. 1995. Clinical toxicity of cytokines used as haemopoietic growth factors. *Drug Saf.* 13:371–406.
- Franzen, R., D. Bouhy, and J. Schoenen. 2004. Nervous system injury: focus on the inflammatory cytokine ‘granulocyte-macrophage colony stimulating factor’. *Neurosci. Lett.* 361:76–78.
- Zhu, F., Y. Liu, J. Zhao, and Y. Zheng. 2014. Minocycline alleviates behavioral deficits and inhibits microglial activation induced by intrahippocampal administration of granulocyte-macrophage colony stimulating factor in adult rats. *Neuroscience* 266:275–281.
- Barreda, D. R., P. C. Hanington, and M. Belosevic. 2004. Regulation of myeloid development and function by colony stimulating factors. *Dev. Comp. Immunol.* 28:509–554.
- Sorensen, M. D., J. N. Krieger, F. P. Rivara, M. B. Klein, and H. Wessells. 2009. Fournier’s gangrene: management and mortality predictors in a population based study. *J. Urol.* 182:2742–2747.
- Tortorella, C., O. Simone, G. Piazzolla, I. Stella, and S. Antonaci. 2007. Age-related impairment of GM-CSF-induced signaling in neutrophils: role of SHP-1 and SOCS proteins. *Ageing Res. Rev.* 6:81–93.