

Severe Hypoxemia in a Healthy Donor for Allogeneic Hematopoietic Stem Cell Transplantation after Only the First Administration of Granulocyte-Colony Stimulating Factor

Keita Yamamoto^a Noriko Doki^a Yasushi Senoo^a Yuho Najima^a Takeshi Kobayashi^a
Kazuhiko Kakihana^a Kyoko Haraguchi^b Yoshiki Okuyama^b Hisashi Sakamaki^a
Kazuteru Ohashi^a

^aHematology Division, Tokyo Metropolitan Cancer and Infectious Diseases Center, Komagome Hospital, Tokyo, Japan;

^bDivision of Transfusion and Cell Therapy, Tokyo Metropolitan Cancer and Infectious Diseases Center, Komagome Hospital, Tokyo, Japan

Keywords

Severe hypoxemia · Healthy donor ·
Allogeneic hematopoietic stem cell transplantation ·
Allo-HSCT · Peripheral blood stem cells · PBSCs ·
Granulocyte-colony stimulating factor · G-CSF

Summary

Background: Granulocyte-colony stimulating factor (G-CSF) is widely used to mobilize peripheral blood stem cells (PBSCs) in healthy donors. A few reports have shown that some healthy donors developed acute respiratory distress syndrome or capillary leak syndrome after more than several rounds of G-CSF administration or leukapheresis. **Case Report:** We report the case of a healthy donor for allogeneic stem cell transplantation who developed severe hypoxemia 1 h after only the first administration of G-CSF. The donor was administered 10 µg/kg G-CSF (lenograstim) subcutaneously for PBSC mobilization. 1 h after the first administration of G-CSF, the donor suddenly presented with dry cough and dyspnea. The oxygen saturation by pulse oximetry (SpO₂) in the room air was 88%. An electrocardiogram and chest radiography revealed no abnormalities. We excluded other causes of severe hypoxemia and diagnosed the donor with hypoxemia due to G-CSF administration, which was subsequently terminated. The donor was administered 2 l/min oxygen via a nasal cannula and 100 mg hydrocortisone intravenously. He subsequently recovered, and

SpO₂ in the room air returned to 98% 10 h after hypoxemia. **Conclusion:** These respiratory symptoms might be related to anaphylactoid or hypersensitivity reaction. The donors should be observed for at least 1 h after the first administration of G-CSF.

© 2016 S. Karger GmbH, Freiburg

Introduction

Granulocyte-colony stimulating factor (G-CSF) has been widely used to mobilize peripheral blood stem cells (PBSCs) in healthy donors [1, 2]. Many reports have described well-recognized transient adverse effects, including bone pain, headache, fatigue, nausea, fever, insomnia, anorexia, and myalgias [1–3]. Regarding pulmonary events, interstitial pneumonitis, pulmonary edema, and lung fibrosis are very rare [2]. However, a few cases of acute respiratory distress syndrome (ARDS) [3–6] and capillary leak syndrome [7] after administration of G-CSF have been reported in healthy donors. These cases developed ARDS or capillary leak syndrome after more than several rounds of G-CSF administration or leukapheresis [3–7]. We here report the case of a healthy donor for allogeneic hematopoietic stem cell transplantation (allo-HSCT) who developed severe hypoxemia 1 h after only the first administration of G-CSF.

Case Report

A 50-year-old man was admitted as a related donor for allo-HSCT. He did not have a medical or allergy history. Physical examination, chest radiography, and laboratory examinations were normal, and his body mass index (BMI) was 23.8 kg/m². Spirometry on admission demonstrated normal data with 126.2% vital capacity and 78 forced expiratory volume in 1 s. The oxygen saturation by pulse oximetry (SpO₂) in the room air was 98%. The donor was administered 10 µg/kg G-CSF (lenograstim) subcutaneously for PBSC mobilization. 1 h after the first administration of G-CSF, the donor suddenly presented with dry cough and dyspnea, but developed neither fever nor rash. On physical examination, he did not show wheezes, crackles, pain, abdominal symptoms, lymphadenopathy, or pharyngeal abnormalities. Although the SpO₂ in the room air was 88%, the donor was found to have stable observations: body temperature 36.5 °C, pulse rate 66 min/regular, and blood pressure 99/66 mm Hg. An electrocardiogram revealed no abnormalities. Chest radiography demonstrated no infiltration, but slight cardiac dilatation was observed. 2 l/min oxygen administration via a nasal cannula was started. The laboratory findings demonstrated a white blood cell count of 10,100/µl, aspartate aminotransferase of 22 U/l, alanine transaminase of 31 U/l, lactate dehydrogenase of 145 U/l (normal range 115–245 U/l), alkaline phosphatase of 386 IU/l, creatine kinase of 88 U/l, C-reactive protein of 0.15 mg/dl, sialylated carbohydrate antigen KL-6 of 25 IU/ml (normal range 0–499 IU/ml), and pulmonary surfactant protein-D of 32.8 ng/ml (normal range 0–109.9 ng/ml). We excluded the possibility of acute infection. No new medications had been introduced other than G-CSF. These results suggest that severe hypoxemia may have developed after exposure to G-CSF, and thus, G-CSF administration was terminated. The donor was administered 100 mg hydrocortisone intravenously after hypoxemia. He subsequently recovered, and SpO₂ in the room air returned to 98% 10 h after hypoxemia. Computed tomography of the chest on day 5 after administration of G-CSF showed no significant abnormalities. The donor was discharged from the hospital in good condition 5 days after hypoxemia. He fully recovered and showed a normal complete blood cell count, normal SpO₂, and normal chest radiography 2 months after administration of G-CSF. The patient to whom the donor had planned to donate PBSCs underwent emergent cord blood transplantation, and engraftment was achieved.

Discussion

In this case, we were able to exclude other causes of hypoxemia aside from the administration of G-CSF.

In patients receiving chemotherapy, the reported pulmonary side effects of G-CSF include cough, dyspnea, and interstitial or alveolar infiltrates with mild to severe blood gas deterioration [3]. Lung toxicity in allogeneic stem cell donors has been reported in only a few cases [3–6]. The present donor did not demonstrate bilateral infiltrates and interstitial pneumonitis at hypoxemia. The values of sialylated carbohydrate antigen KL-6, and pulmonary surfactant protein-D were normal. These findings do not meet the diagnostic criteria for acute lung injury [8], ARDS [8], and drug-induced pneumonitis [9]. On the other hand, anaphylactic reactions including lung involvement due to G-CSF application are well known, and several cases are reported [10–13] as well as hypersensitivity reaction mimicking anaphylaxis [14]. Although these

cases showed acute anaphylactic reactions within 15 min after the administration of G-CSF, an acute reaction was not observed in the current case. However, as the donor recovered from hypoxemia rapidly after a single dose of 100 mg hydrocortisone, these respiratory symptoms might be related to an anaphylactoid or hypersensitivity reaction.

A previous report on healthy donors showed that gas exchange is significantly disturbed during G-CSF administration and is reversible on discontinuation of G-CSF [15]. Because levels of both partial pressure of CO₂ in arterial blood and alveolar-arterial oxygen difference are significantly higher after G-CSF administration, G-CSF may induce an increase in the physiologic dead space and result in a decreased gas exchange capacity of alveoli [15]. Furthermore, G-CSF leads to induction of serum IL-6 and polymorphonuclear leukocyte elastase, which are important mediators of acute lung injury [15]. On the other hand, apoptosis plays an important role in the regulation of several biological processes, including inflammatory response [16]. Several inflammatory mediators such as G-CSF and granulocyte-macrophage colony stimulator factor (GM-CSF) inhibit apoptosis and prolong neutrophil survival in vitro, which leads to neutrophilic alveolitis [16]. These mechanisms may be associated with hypoxemia after exposure to G-CSF.

Regarding other factors associated with hypoxemia under G-CSF use, human leukocyte antigen (HLA) phenotypes such as HLA-B51 or HLA-B52 have also been associated with the onset of G-CSF-related pulmonary toxicity in patients receiving chemotherapy or stem cell transplant [17]. Yoshida et al. [15] reported two donors with a BMI of more than 28 kg/m² who experienced respiratory symptoms with only a slight reduction of PaO₂. In our present case, the donor did not show the HLA-B51 or HLA-B52 phenotype, and his BMI was less than 28 kg/m².

Conclusion

G-CSF is a widely used agent for inducing mobilization of PBSCs in donors. This case report describes acute hypoxemia after the first G-CSF application. Acute lung injury or acute respiratory distress syndrome were not confirmed by the findings, and hypoxemia due to an anaphylactoid reaction cannot be excluded. The donors should be observed for at least 1 h after giving the initial dose of G-CSF.

This case also emphasizes the need for clinical awareness when administering G-CSF for mobilization of PBSCs.

Disclosure Statement

The authors declare no conflict of interest.

References

- 1 Pulsipher MA, Chitphakdithai P, Logan BR, Shaw BE, Wingard JR, Lazarus HM, Waller EK, Seftel M, Stronck DF, Lopez AM, Maharaj D, Hematti P, O'Donnell PV, Loren AW, Leitman SF, Anderlini P, Goldstein SC, Levine JE, Navarro WH, Miller JP, Confer DL: Acute toxicities of unrelated bone marrow versus peripheral blood stem cell donation: results of a prospective trial from the National Marrow Donor Program. *Blood* 2013;121:197–206.
- 2 Hölig K: G-CSF in healthy allogeneic stem cell donors. *Transfus Med Hemother* 2013;40:225–235.
- 3 D'Souza A, Jaiyesimi I, Trainor L, Venuturumili P: Granulocyte colony-stimulating factor administration: adverse events. *Transfus Med Rev* 2008;22:280–290.
- 4 Azoulay E, Attalah H, Harf A, Schlemmer B, Delclaux C: Granulocyte colony-stimulating factor or neutrophil-induced pulmonary toxicity: myth or reality? Systematic review of clinical case reports and experimental data. *Chest* 2001;120:1695–1701.
- 5 Arimura K, Inoue H, Kukita T, Matsushita K, Akimot M, Kawamata N, Yamaguchi A, Kawada H, Ozak A, Arima N, Te C: Acute lung injury in a healthy donor during mobilization of peripheral blood stem cells using granulocyte-colony stimulating factor alone. *Haematologica* 2005;90:e27–e29.
- 6 Wetzko K, Blechschmidt M, Hölig K, Poppe-Thiede K, Ganepola S, Fischbach R, Ordemann R, Laniado M, Schulte-Hubbert B, Schuler M, Cotta L, Braumann D, Ehninger G, Kroschinsky F: Pulmonary adverse events in unrelated donors of peripheral blood stem cells. *Transfus Med* 2013;23:69–71.
- 7 de Azevedo AM, Goldberg Tabak D: Life-threatening capillary leak syndrome after G-CSF mobilization and collection of peripheral blood progenitor cells for allogeneic transplantation. *Bone Marrow Transplant* 2001;28:311–312.
- 8 Bernard GR, Artigas A, Brigham KL, Carlet J, Falke K, Hudson L, Lamy M, Legall JR, Morris A, Spragg R: The American-European Consensus Conference on ARDS. Definitions, mechanisms, relevant outcomes, and clinical trial coordination. *Am J Respir Crit Care Med* 1994;149:818–824.
- 9 Ohnishi H, Yokoyama A, Yasuhara Y, Watanabe A, Naka T, Hamada H, Abe M, Nishimura K, Higaki J, Ikezoe J, Kohno N: Circulating KL-6 levels in patients with drug induced pneumonitis. *Thorax* 2003;58:872–875.
- 10 Jaiyesimi I, Giralt SS, Wood J: Subcutaneous granulocyte colony-stimulating factor and acute anaphylaxis. *N Engl J Med* 1991;325:587.
- 11 Batel-Copel L, Mommeja-Marin H, Oudard S, Chauvenet L, Pujade-Lauraine E, Coupier J, Bernadou A: Anaphylactic reaction after a first filgrastim (G-CSF) injection. *Eur J Cancer* 1995;31A:13–14.
- 12 Keung YK, Suwanvecho S, Cobos E: Anaphylactoid reaction to G-CSF used in mobilization of peripheral blood stem cells. *Bone Marrow Transplant* 1999;23:200–201.
- 13 Tulpule S, Shaw BE, Makoni P, Little AM, Madrigal JA, Goldman JM: Severe allergic reaction with anaphylaxis to G-CSF (lenograstim) in a healthy donor. *Bone Marrow Transplant* 2009;44:129–130.
- 14 Tholpady A, Chiosea I, Lyons JJ, Baird K, Leitman SF: Systemic hypersensitivity reaction mimicking anaphylaxis after first filgrastim administration in a healthy donor. *Transfusion* 2013;53:1146–1147.
- 15 Yoshida I, Matsuo K, Teshima T, Hashimoto D, Tanimoto Y, Harada M, Tanimoto M: Transient respiratory disturbance by granulocyte-colony-stimulating factor administration in healthy donors of allogeneic peripheral blood progenitor cell transplantation. *Transfusion* 2006;46:186–192.
- 16 Barros de Souza A, Brandão dos Santos F, Negri EM, Zin WA, Rocco PRM: Lung tissue remodelling in the acute respiratory distress syndrome. *J Pneumologia* 2003;29:235–245.
- 17 Takatsuka H, Takemoto Y, Mori A, Okamoto T, Kanamaru A, Kakishita E: Common features in the onset of ARDS after administration of granulocyte colony-stimulating factor. *Chest* 2002;121:1716–1720.