

## Letter

## OPEN ACCESS

# Alteration of chromosome 13 abnormalities after therapeutic hematopoiesis recovery in myelodysplastic syndrome

*Tadashi Nagai<sup>1</sup>, Takahiro Suzuki<sup>1</sup>, Norio Komatsu<sup>2</sup>, Kohei Hosokawa<sup>3</sup>, Shinji Nakao<sup>3</sup>, Keiya Ozawa<sup>1</sup>*

<sup>1</sup> Division of Hematology, Jichi Medical University, Tochigi, Japan

<sup>2</sup> Department of Hematology, Juntendo University School of Medicine, Tokyo, Japan

<sup>3</sup> Cellular Transplantation Biology, Kanazawa University Graduate School of Medical Science, Kanazawa, Japan

### Corresponding Author & Address:

*Tadashi Nagai\**

Associate Professor, Jichi Medical University, 3311-1 Yakushiji, Shimotsuke, Tochigi 329-0498, Japan; Tel.: +81-285-58-7353; Fax: +81-285-44-5258; Email address: [t-nagai@jichi.ac.jp](mailto:t-nagai@jichi.ac.jp)

Published: 27<sup>th</sup> December, 2012

Accepted: 27<sup>th</sup> December, 2012

Received: 27<sup>th</sup> November, 2012

Open Journal of Hematology, 2012, 3-7

© Nagai et al.; licensee Ross Science Publishers

ROSS Open Access articles will be distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/3.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided that the original work will always be cited properly.

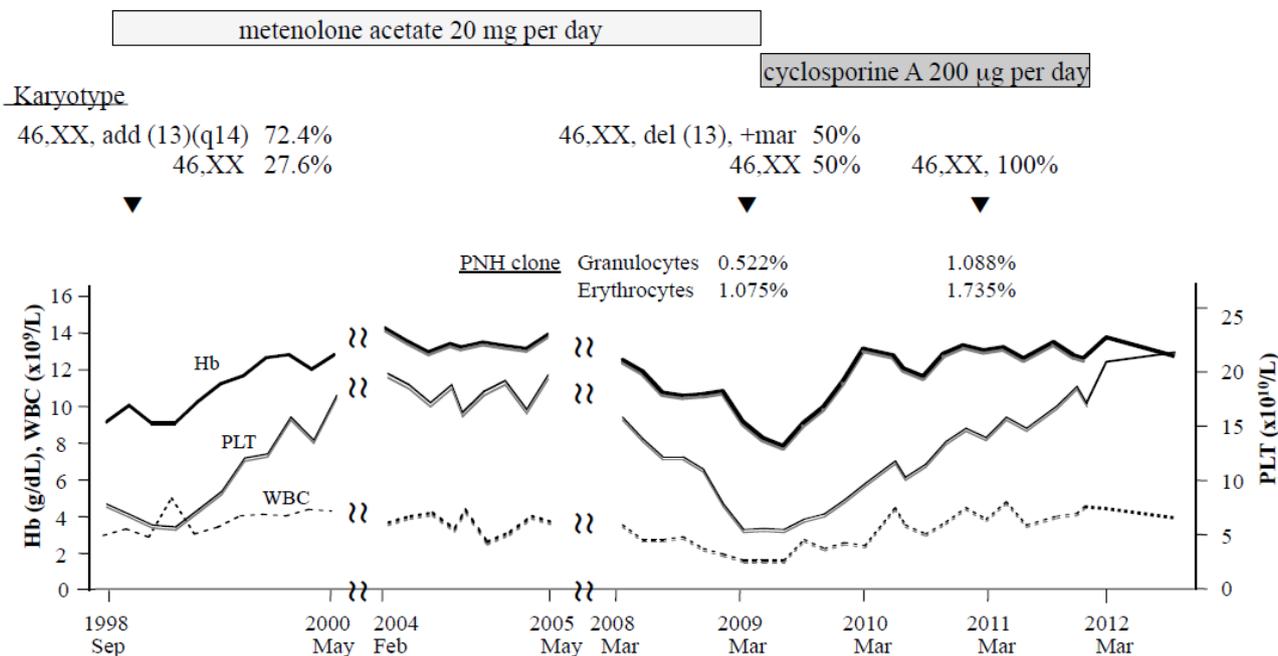
**Keywords:** myelodysplastic syndrome, karyotype, paroxysmal nocturnal hemoglobinuria, cyclosporine A

As with aplastic anemia, it is thought that immunological stimulation suppresses normal hematopoiesis in myelodysplastic syndrome (MDS) patients [1-2]. Therefore, immunosuppressive reagents such as cyclosporine A may abrogate this effect, and improve cytopenia [3-4]. The presence of small populations of CD55- and CD59-negative paroxysmal nocturnal hemoglobinuria (PNH) clone portends a good response to immunosuppressive therapy in patients with low-risk MDS [5-6]. Recently, Hosokawa et al. analyzed clinical features of 22 MDS patients with del (13q), and found a high prevalence of PNH phenotype and good response to immunosuppressive therapy [7]. Interestingly, del (13q) disappeared with immunosuppressive therapy in some patients; whereas, in others it was persistently detected despite the recovery of hematopoiesis [7-8]. The mechanisms underlying this disparity remain unknown. However, it is

hypothesized that the del (13q) clone acquires survival advantages over normal hematopoietic stem cells due to a lack of the 13q region that determines the sensitivity to inhibitory cytokines; but the fate of this clone after immunosuppressive therapy may depend on the primary life span of the del (13q) stem cells [7].

We present a case of MDS, one of 22 cases reported by Hosokawa et al, in which an initial abnormal clone with add (13)(q14) disappeared while a different clone with -13, +mar emerged during the clinical course; and finally, the abnormal clone with -13, +mar was undetectable after two years of cyclosporine A treatment. In this case, it is speculated that each clone with a chromosome 13 abnormality acquired survival advantages due to a loss of sensitivity to inhibitory cytokine-mediated immunological attack; but it had sequentially expanded and disappeared due to the limited life span of mutant stem cells.

Figure 1. Clinical course.



A 57-year-old woman visited our hospital in September 1998. Hematological examination revealed a decrease in white blood cell count ( $2.9 \times 10^9/L$ ), hemoglobin concentration (9.1 g/dl), and platelet count ( $75 \times 10^9/L$ ). A bone marrow aspiration disclosed hypercellular bone marrow with dysplasia in erythroid lineage. Furthermore, an abnormal karyotype of add (13)(q14) (21/29 cells: 72.4%) was simultaneously observed. Based on these results, we diagnosed this case as MDS-U (unclassifiable). The patient was given 20 mg per day metenolone acetate as an initial treatment. After therapy commenced, pancytopenia gradually improved (Figure 1). At seven months, all blood cell counts had improved to normal levels, and these levels had been maintained for eight years thereafter. However, since May 2008 the pancytopenia had gradually recurred; therefore, bone marrow examination was performed in March 2009. Although the bone marrow feature had not obviously changed since 1998, an abnormal karyotype of -13, +mar (10/20 cells: 50%) was found; whereas, the add (13)(q14) abnormality, which had been observed at the time of diagnosis, could not be detected. At this time, we tested for the presence of PNH clone using flow cytometry analysis. The result showed that the patient had 0.522% and 1.075% of PNH clone in granulocytes and erythrocytes, respectively. We

therefore started cyclosporine A administration; whereupon, blood cell counts markedly increased, and have stabilized at normal levels thereafter. Two years later, we performed another bone marrow examination to follow the status of MDS. Surprisingly, it showed normocellularity with no dysplasia. Furthermore, chromosomal analysis demonstrated no abnormal karyotype; and FISH analysis was negative for -13 (0.6%) (normal value: 0-1.3 %). In contrast, the PNH clone slightly increased (Figure 1). Thereafter, no recurrence of MDS has been observed.

Consistent with the previous observations, the present patient, who had -13 clone as well as PNH clone, showed remarkable recovery of hematopoiesis by cyclosporine A treatment [5-6, 9]. Importantly, the change in percentages of PNH clone was not correlated with that of the -13-possessing cells. This fact suggests that the -13-possessing MDS clone and the PNH clone did not share an identical phenotype. A previous report also described that del (13q) clone is not derived from PNH stem cells [7].

Unfortunately, we did not perform SKY analyses, which may have clearly identified the 13 anomaly, on the present case; however, our chromosomal analysis detected two independent clones involving chromosome 13 abnormalities,

add (13)(q14) or -13, +mar. The striking feature of this case is that two different abnormal clones possessing chromosome 13 abnormalities emerged and disappeared at different times. The expansion of these clones involving 13q strongly supports the hypothesis that some genes in the 13q region mediate sensitivity to immunological attack. It is possible that MDS stem cells possessing either add (13)(q14) or -13, +mar in the patient were short-lived; therefore, those chromosomal abnormalities disappeared during the clinical course. In contrast, PNH stem cells in the patient might have emerged in long-lived stem cells.

## REFERENCES

- [1] Hamblin TJ. Immunological abnormalities in myelodysplastic syndromes. *Semin Hematol.* **1996**; 33: 150-62.
- [2] Calado RT. Immunologic aspects of hypoplastic myelodysplastic syndrome. *Semin Oncol.* **2011**; 38: 667-72.
- [3] Ishikawa T, Tohyama K, Nakao S, Yoshida Y, Teramura M, Motoji T, Takatoku M, Kurokawa M, Mitani K, Uchiyama T, Omine M. A prospective study of cyclosporine A treatment of patients with low-risk myelodysplastic syndrome: presence of CD55(-)CD59(-)blood cells predicts platelet response. *Int J Hematol.* **2007**; 86: 150-7.
- [4] Sloand EM, Wu CO, Greenberg P, Young N, Barrett J. Factors affecting response and survival in patients with myelodysplasia treated with immunosuppressive therapy. *J Clin Oncol.* **2008**; 26: 2505-11.
- [5] Wang H, Chuhjo T, Yasue S, Omine M, Nakao S. Clinical significance of a minor population of paroxysmal nocturnal hemoglobinuria-type cells in bone marrow failure syndrome. *Blood.* **2002**; 100: 3897-902.
- [6] Sugimori C, Chuhjo T, Feng X, Yamazaki H, Takami A, Teramura M, Mizoguchi H, Omine M, Nakao S. Minor population of CD55-CD59- blood cells predicts response to immunosuppressive therapy and prognosis in patients with aplastic anemia. *Blood.* **2006**; 107: 1308-14.
- [7] Hosokawa K, Katagiri T, Sugimori N, Ishiyama K, Sasaki Y, Seiki Y, Sato-Otsubo A, Sanada M, Ogawa S, Nakao S. Favorable outcome of patients who have 13q deletion: a suggestion for revision of the WHO 'MDS-U' designation. *Haematologica.* **2012**; 97: 1845-9.
- [8] Kasahara I, Nishio M, Endo T, Fujimoto K, Koike T, Sugimori N, Katagiri T, Nakao S. Sustained trilineage hematopoietic recovery in a patient with refractory anemia, del(13)(q12q22), and paroxysmal nocturnal hemoglobinuria-type cells treated with immunosuppressive therapy. *Leuk Res.* **2011**; 35: e147-8.
- [9] Ishiyama K, Karasawa M, Miyawaki S, Ueda Y, Noda M, Wakita A, Sawanobori M, Nagai H, Nakao S. Aplastic anaemia with 13q-: a benign subset of bone marrow failure responsive to immunosuppressive therapy. *Br J Haematol.* **2002**; 117: 747-50.

## CONFLICT OF INTEREST

We declare no financial interest or relationships in the present report.

## ACKNOWLEDGMENTS

We wish to thank Ms. E. Yamakawa for preparation of the manuscript and Mr. Gary Baley for academic editing.



Publish with **ROSS Science Publishers** and every scientist can easily read your work for free!

Your research papers will be:

- available for free to the entire scientific community
- peer reviewed and published immediately after acceptance
- cited in renowned open repositories upon indexation of the journal
- owned by yourself — author keeps the copyright