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CASE REPORT

Myeloid leukemoid reaction after initial azacitidine therapy for chronic myelomonocytic leukemia

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Abstract

The development of myeloid leukocytosis in leukemia patients during antileukemic treatment requires a differential diagnosis between myeloid leukemoid reaction and leukemia progression. We herein report the case of an 80-year-old Japanese man with chronic myelomonocytic leukemia (CMML) who developed marked myeloid leukocytosis (36.3×10^9/L) with 32.5% monocytes and 48% neutrophils about 4 weeks after the initial 5-azacitidine (AZA) treatment. The leukocytosis was unlikely to be attributed to infection and adverse drug reaction. As it resolved in a few days without any interventions, the transient myeloid leukocytosis was confirmed to be a myeloid leukemoid reaction. After four cycles of AZA treatment, leukemic blasts in the bone marrow decreased and the patient became transfusion-independent. Interestingly, levels of serum G-CSF showed a similar trend to the myeloid leukocytosis, while those of serum GM-CSF and IL-17 were undetectable throughout the clinical course, suggesting that a differentiation response to AZA treatment might lead to the myeloid leukemoid reaction. Our case implies that a marked but transient myeloid leukemoid reaction mimicking CMML progression can develop during AZA treatment, which requires careful clinical monitoring and differential diagnosis.

Keywords Chronic myelomonocytic leukemia · Azacitidine · Myeloid leukemoid reaction · Granulocyte colony-stimulating factor (G-CSF)

Introduction

Chronic myelomonocytic leukemia (CMML) is a clonal stem cell disorder which possesses overlapping features of myeloproliferative neoplasm (MPN) and myelodysplastic syndrome (MDS) [1]. Its rate of transformation to acute myeloid leukemia (AML) is reported to be 15–30% [2–9]. Treatment with 5-azacitidine (AZA), a kind of hypomethylating agent, can be applied to patients with MDS [10, 11] and CMML [12]. While CMML patients show poor response to conventional chemotherapy, AZA treatment can achieve a response in 30–60% and complete response in < 15% of CMML patients [13]. We report an 80-year-old Japanese man with CMML that developed a marked myeloid leukocytosis after the initial AZA treatment. The situation required careful clinical monitoring and differential diagnosis of myeloid leukemoid reaction versus CMML progression.

Case report

An 80-year-old Japanese man with a past history of hypertension, dyslipidemia, atrial fibrillation, myocardial infarction, and congestive heart failure was referred to our hospital due to anemia (hemoglobin 7.0 g/dL) and thrombocytopenia (platelet count 30.0×10^9/L). At that time, his peripheral white blood cell (WBC) count was 6.5×10^9/L with 22.5% monocytes and 0% blasts. The initial bone marrow (BM) aspiration showed 2.8% blasts, more than 10% dysplastic cells with pseudo-Pelger–Huët anomaly or agranular cytoplasm out of the total granulocytic lineage cells, and more than 50% multinucleated megakaryocytes out of the total megakaryocytes, which was consistent with CMML.

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He had no hepatosplenomegaly, and cytogenetic analysis revealed a normal karyotype. Thus, the ambulatory patient was diagnosed with CMML-0 according to the WHO diagnostic criteria [14]. Afterwards, he exhibited a poor response to treatment with recombinant human erythropoietin and became transfusion dependent. As the subsequent BM aspiration showed 5% blasts, the diagnosis was revised to CMML-1. Six weeks later, AZA treatment (75 mg/m^2/day subcutaneously for 7 consecutive days per 28-day treatment cycle) was initiated (Fig. 1). The complete blood count on the day before the first AZA cycle revealed WBC count of 10.7×10^9/L (35% monocytes, 35% neutrophils, 3% eosinophils, 0.5% basophils, 26.5% lymphocytes, 0% blasts), hemoglobin at 6.5 g/dL, and platelet count of 45×10^9/L. Unexpectedly, the patient showed a marked myeloid leukocytosis (WBC count of 36.3×10^9/L with 32.5% monocytes, 48% neutrophils, 2.5% eosinophils, 0% basophils, 0.5% blasts, 3% myelocytes, and 8% promyelocytes) on day 25. However, the myeloid leukocytosis resolved in a few days without any interventions, and the BM aspiration on day 27 showed 3.8% blasts, indicating a response to AZA. He never developed fever, had no signs and symptoms of infections, and his serum C-reactive protein levels were within a normal range (below 2 mg/L) throughout the first cycle. Except for AZA and ramosetron hydrochloride that were newly started, no changes in medication took place; his regular medications consisted of rabeprazole, carvedilol, atorvastatin**,** imidafenacin, L-carbocisteine, finasteride, and heavy magnesium oxide. A total score of 5 (probable) was obtained using the Naranjo adverse drug reaction probability scale [15], suggesting that adverse drug reaction was unlikely to be a primary cause of the leukocytosis. As no other causes seemed to be attributed to the myeloid leukocytosis, the transient leukocytosis was confirmed to be a myeloid leukemoid reaction, which allowed the next cycle to be started. On day 32, just after the second AZA cycle was initiated, his anemia showed improvement (hemoglobin 9.6 g/dL) while his monocytosis (WBC count of 11.5×10^9/L with 25.5%

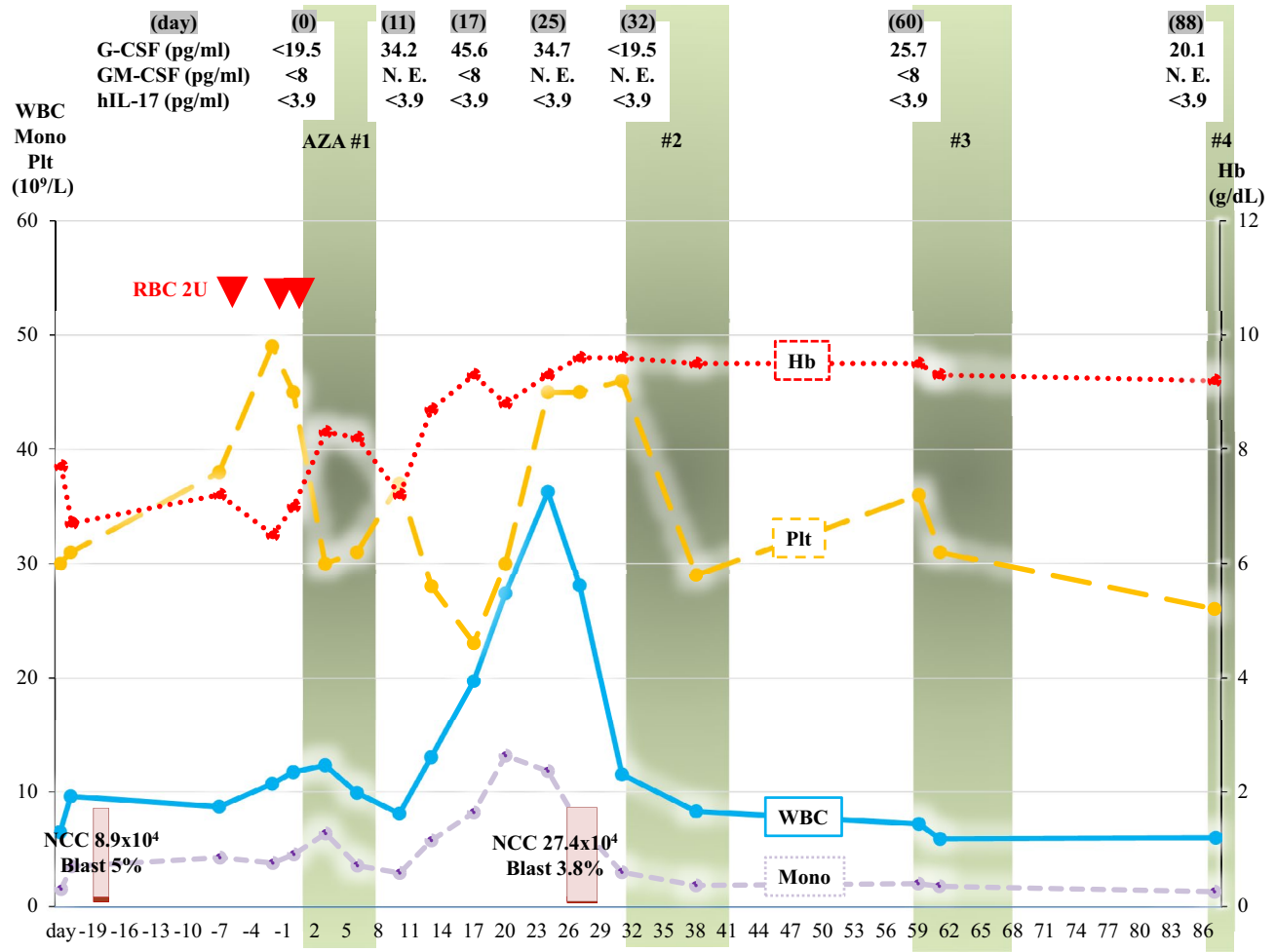

Fig. 1 The clinical course of the patient. AZA: azacitidine; RBC: red blood cells; G-CSF: granulocyte colony-stimulating factor; GM-CSF: granulocyte-macrophage colony-stimulating factor; NCC: nucleated cell count; N.E.: not examined

monocytes, 53.0% neutrophils, 5.0% eosinophils, 0.5% basophils, 0% blasts, 0% promyelocytes, and 16.0% lymphocytes) and thrombocytopenia (platelet count 46.0×10^9/L) persisted. Despite a slight reduction of BM blasts, his response after the first AZA cycle was evaluated as 'clinical benefit' (erythroid response), according to the criteria of the MDS/MPN International Working Group [16]. While receiving 3 more AZA cycles at our hospital, the patient became transfusion independent without CMML progression. He was transferred to another hospital for unspecified personal reasons. Afterwards, it was reported that the patient developed progressive anemia and recurrent pneumonia after receiving a total of 13 cycles of AZA treatment, possibly indicating CMML progression. He died about two years after the initial diagnosis of CMML.

For investigating the cause of the unanticipated and transient myeloid leukocytosis, we retrospectively examined pro-inflammatory cytokine levels in this patient during the first four AZA cycles (Fig. 1). Levels of serum granulocyte colony-stimulating factor (G-CSF), granulocyte–macrophage colony-stimulating factor (GM-CSF), interleukin (IL)-17 before initiating AZA treatment were undetectable (< 19.5, < 8, and < 3.9 pg/mL, respectively). While GM-CSF and IL-17 levels remained undetectable throughout the treatment course, G-CSF levels increased after 7-day AZA administration. The G-CSF levels peaked at 45.6 pg/mL on day 17 and decreased to the undetectable range on the starting day of the second AZA treatment cycle (day 32), showing a similar trend to the myeloid leukocytosis. Slightly increased G-CSF levels were observed at the start of the third and fourth cycles (25.7 and 20.1 pg/mL, respectively). Additionally, next-generation sequencing (NGS) of unsorted peripheral WBCs before AZA treatment detected mutations in ASXL, EZH2, NRAS, ETV6, and TP53, with variant allele fractions of 42.1, 79.7, 35.2, 40.4, and 41.3%, respectively. These genetic profiles suggested an unfavorable prognosis for this patient.

Discussion

To the best of our knowledge, this is the first report of myeloid leukemoid reaction in CMML upon initial AZA treatment. During the treatment, the patient developed a marked myeloid leukocytosis accompanied with monocytosis (Fig. 1), which required diagnostic distinction between benign and malignant leukocytosis. Finally, the leukocytosis was confirmed to be a myeloid leukemoid reaction, reflecting a possible differentiation response by AZA. Although inflammatory cytokine and gene mutation profiles could not contribute to the treatment plan of this patient due to the limited access at that time, the rapid increase of G-CSF levels could retrospectively support our differential diagnosis.

We selected no treatment for the leukocytosis in our case because the preceding BM aspiration found no increase in blast count and he was afebrile after initiating the first AZA cycle. Accordingly, hydroxycarbamide was not administered, even though a previous report showed its effectiveness in controlling transient leukocytosis after initiating AZA treatment in a patient with MDS (RAEB-2) [17]. For differentiating myeloid leukemoid reaction from CMML progression in our case, flow cytometry analysis of $CD14^+$/$CD16^-$ monocyte subset [18] could have been helpful, although flow cytometry was not routinely performed in our hospital. Moreover, the coinciding increases in WBC and platelet counts during days 17–25 (Fig. 1) might support the diagnosis of myeloid leukemoid reaction.

As for clinical effect of AZA treatment for CMML, it has been reported that improved overall survival in CMML patients is associated with an absolute monocyte count below 10.0×10^9/L and $< 5\%$ peripheral blood blasts at the start of AZA treatment [19]. Another study reported inferior survival in AZA-treated CMML patients with palpable splenomegaly or over 10% BM blasts; however, mutation status had no impact on overall survival [20]. According to the MD Anderson prognostic score (MDAPS) [21], this patient had intermediate-1 risk. If the NGS data were available in advance, his risk could have been revised as intermediate-2, using the CMML-specific prognostic scoring system (CPSS) [4].

From in vitro studies, it has been reported that AZA can exert antileukemic effects by DNA hypomethylation and cytotoxicity [22]. The previous clinical study involving patients with AML or MDS indicated that decitabine, another kind of hypomethylating agent, can induce differentiation before the reduction of leukemic blasts; DNA hypomethylation can precede cytotoxicity [23]. The sequence of events can partly explain the situation of our case.

It is known that AZA can derepress chromatin structure of a key hematopoietic transcription factor PU.1 in MDS [24], leading to upregulations of PU.1 and its target C/EBPα. Subsequently, PU.1 and C/EBPα upregulate their targets G-CSF receptor and GM-CSF receptor [25, 26], suggesting an indirect mechanism of AZA to promote myeloid differentiation. It is also known that AZA-treated patients with advanced AML or MDS have a significant increase of peripheral IL-17A-secreting $CD4^+$ T cells [27], and that IL-17 can regulate granulopoiesis through G-CSF [28]. These reports led us to retrospectively investigate serum G-CSF, GM-CSF, and IL-17 levels in our case. In addition, previous reports showed that exogenous G-CSF administration in post-chemotherapy patients can cause transient atypical monocytosis mimicking myelomonocytic leukemia, which resolved after discontinuation of G-CSF [29–31]. Although the reason why only G-CSF levels showed a transient increase in our case is still unclear, it was suspected that the intra-individual

endogenous G-CSF increase and decrease could contribute to the transient myeloid leukocytosis. Considering the trend of G-CSF levels during the AZA treatment, it was also suspected that our case could have shown transient leukocytosis after the second and third AZA cycles; however, frequent monitoring of WBC count and differential could not be performed for the patient's personal reasons. A previous report showed that an AZA-treated MDS patient developed transient and fully reversible leukocytosis in all ten cycles, among which hydroxycarbamide was administered in the first and second cycles [17].

Although clinical efficacy of AZA is limited in transfusion-dependent and erythropoiesis-stimulating agent-resistant, low and intermediate-1 risk MDS [32], our case actually showed a 1.2% reduction in BM blast counts after the first AZA cycle, and became transfusion independent, indicating the cytotoxic effect of AZA. Mutations in ASXL1, EZH2, and NRAS have been reported to be correlated with higher risk features and shorter overall survival and progression-free survival in CMML [33]. Interestingly, TP53-mutated AML or MDS patients can have temporal but better clinical responses to initial decitabine therapy than those with wild-type TP53 [24] although TP53 VAF > 40% was an independent factor of poor prognosis in MDS patients [34]. Thus, it is possible to assume that TP53 mutation in our case might contribute to a temporal response to the initial AZA treatment.

In conclusion, when AZA treatment is initiated, a marked but transient myeloid leukemoid reaction mimicking CMML progression can be developed, which requires careful clinical monitoring and differential diagnosis.

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Declarations

Conflict of interest None declared.

Patient consent for publication Written informed consent was obtained from the patient for the publication of this case report.

References

1. Patnaik MM, Wassie EA, Lasho TL, Hanson CA, Ketterling R, Tefferi A. Blast transformation in chronic myelomonocytic leukemia: risk factors, genetic features, survival, and treatment outcome. Am J Hematol. 2015;90(5):411–6.
2. Merlevede J, Droin N, Qin T, Meldi K, Yoshida K, Morabito M, et al. Mutation allele burden remains unchanged in chronic myelomonocytic leukaemia responding to hypomethylating agents. Nat Commun. 2016;7:10767.
3. Itzykson R, Kosmider O, Renneville A, Gelsi-Boyer V, Meggendorfer M, Morabito M, et al. Prognostic score including gene mutations in chronic myelomonocytic leukemia. J Clin Oncol. 2013;31(19):2428–36.
4. Elena C, Gallì A, Such E, Meggendorfer M, Germing U, Rizzo E, et al. Integrating clinical features and genetic lesions in the risk assessment of patients with chronic myelomonocytic leukemia. Blood. 2016;128(10):1408–17.
5. Patnaik M, Parikh SA, Hanson CA, Tefferi A. Chronic myelomonocytic leukaemia: a concise clinical and pathophysiological review. Br J Haematol. 2014;165:273–86.
6. Benton CB, Nazha A, Pemmaraju N, Garcia-Manero G. Chronic myelomonocytic leukemia: forefront of the field in 2015. Crit Rev Oncol Hematol. 2015;95:222–42.
7. Such E, Germing U, Malcovati L, Cervera J, Kuendgen A, Porta MGD, et al. Development and validation of a prognostic scoring system for patients with chronic myelomonocytic leukemia. Blood. 2013;121:3005–15.
8. Breccia M, Latagliata R, Mengarelli A, Biondo F, Mandelli F, Alimena G. Prognostic factors in myelodysplastic and myeloproliferative types of chronic myelomonocytic leukemia: a retrospective analysis of 83 patients from a single institution. Haematologica. 2004;89:866–8.
9. Nösslinger T, Reisner R, Grüner H, Tüchler H, Nowotny H, Pittermann E, et al. Dysplastic versus proliferative CMML—a retrospective analysis of 91 patients from a single institution. Leuk Res. 2001;25:741–7.
10. Silverman LR, Demakos EP, Peterson BL, Kornblith AB, Holland JC, Odchimar-Reissig R, et al. Randomized controlled trial of azacitidine in patients with the myelodysplastic syndrome: a study of the cancer and leukemia group B. J Clin Oncol. 2002;20(10):2429–40.
11. Musto P, Maurillo L, Spagnoli A, Gozzini A, Rivellini F, Lunghi M, et al. Azacitidine for the treatment of lower risk myelodysplastic syndromes: a retrospective study of 74 patients enrolled in an Italian named patient program. Cancer. 2010;116(6):1485–94.
12. Fenaux P, Mufti GJ, Hellstrom-Lindberg E, Santini V, Finelli C, Giagounidis A, et al. Efficacy of azacitidine compared with that of conventional care regimens in the treatment of higher-risk myelodysplastic syndromes: a randomised, open-label, phase III study. Lancet Oncol. 2009;10(3):223–32.
13. Patnaik MM, Tefferi A. Chronic myelomonocytic leukemia: 2018 update on diagnosis, risk stratification and management. Am J Hematol. 2018;93(6):824–40.
14. Arber DA, Orazi A, Hasserjian R, Thiele J, Borowitz MJ, Le Beau MM, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. Blood. 2016;127(20):2391–405.
15. Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, et al. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther. 1981;30(2):239–45.
16. Savona MR, Malcovati L, Komrokji R, Tiu VR, Mughal IT, Orazi A, et al. An international consortium proposal of uniform response criteria for myelodysplastic/myeloproliferative neoplasms (MDS/MPN) in adults. Blood. 2015;125(12):1857–65.
17. Feldmann G, Brossart P, von Lilienfeld-Toal M. Transient and fully reversible leukocytosis in a myelodysplastic syndrome patient upon initiation of azacitidine treatment. Ann Hematol. 2013;92(11):1577–9.
18. Selimoglu-Buet D, Wagner-Ballon O, Saada V, Bardet V, Itzykson R, Bencheikh L, et al. Characteristic repartition of monocyte subsets as a diagnostic signature of chronic myelomonocytic leukemia. Blood. 2015;125:3618–26.
19. Fianchi L, Criscuolo M, Breccia M, Maurillo L, Salvi F, Musto P, et al. High rate of remissions in chronic myelomonocytic leukemia

treated with 5-azacytidine: results of an Italian retrospective study. Leuk Lymphoma. 2013;54(3):658–61.
20. Adès L, Sekeres MA, Wolfromm A, Teichman ML, Tiu RV, Itzykson R, et al. Predictive factors of response and survival among chronic myelomonocytic leukemia patients treated with azacitidine. Leuk Res. 2013;37(6):609–13.
21. Onida F, Kantarjian HM, Smith TL, Ball G, Keating MJ, Estey EH, et al. Prognostic factors and scoring systems in chronic myelomonocytic leukemia: a retrospective analysis of 213 patients. Blood. 2002;99(3):840–9.
22. Kimura S, Kuramoto K, Homan J, Naruoka H, Ego T, Nogawa M, et al. Antiproliferative and antitumor effects of azacitidine against the human myelodysplastic syndrome cell line SKM-1. Anticancer Res. 2012;32(3):795–8.
23. Welch JS, Petti AA, Miller CA, Fronick CC, O'Laughlin M, Fulton RS, et al. TP53 and decitabine in acute myeloid leukemia and myelodysplastic syndromes. N Engl J Med. 2016;375(21):2023–36.
24. Curik N, Burda P, Vargova K, Pospisil V, Belickova M, Vlckova P, et al. 5-azacitidine in aggressive myelodysplastic syndromes regulates chromatin structure at PU.1 gene and cell differentiation capacity. Leukemia. 2012;26(8):1804–11.
25. Smith LT, Hohaus S, Gonzalez DA, Dziennis SE, Tenen DG. PU.1 (Spi-1) and C/EBP alpha regulate the granulocyte colony-stimulating factor receptor promoter in myeloid cells. Blood. 1996;88(4):1234–47.
26. Hohaus S, Petrovick MS, Voso MT, Sun Z, Zhang DE, Tenen DG. PU.1 (Spi-1) and C/EBP alpha regulate expression of the granulocyte-macrophage colony-stimulating factor receptor alpha gene. Mol Cell Biol. 1995;15(10):5830–45.
27. Frikeche J, Clavert A, Delaunay J, Brissot E, Grégoire M, Gaugler B, et al. Impact of the hypomethylating agent 5-azacytidine on dendritic cells function. Exp Hematol. 2011;39(11):1056–63.
28. Stark MA, Huo Y, Burcin TL, Morris MA, Brissot E, Grégoire M, Gaugler B, et al. Phagocytosis of apoptotic neutrophils regulates granulopoiesis via IL-23 and IL-17. Immunity. 2005;22(3):285–94.
29. Liu CZ, Persad R, Inghirami G, Sen F, Amorosi E, Goldenberg A, Ibrahim S. Transient atypical monocytosis mimic acute myelomonocytic leukemia in post-chemotherapy patients receiving G-CSF: report of two cases. Clin Lab Haematol. 2004;26(5):359–62.
30. Ranaghan L, Drake M, Humphreys MW, Morris TC. Leukaemoid monocytosis in M4 AML following chemotherapy and G-CSF. Clin Lab Haematol. 1998;20(1):49–51.
31. Reykdal S, Sham R, Phatak P, Kouides P. Pseudoleukemia following the use of G-CSF. Am J Hematol. 1995;49(3):258–9.
32. Tobiasson M, Dybedahl I, Holm MS, Karimi M, Brandefors L, Garelius H, et al. Limited clinical efficacy of azacitidine in transfusion-dependent, growth factor-resistant, low- and Int-1-risk MDS: results from the nordic NMDSG08A phase II trial. Blood Cancer J. 2014;4: e189.
33. Palomo L, Garcia O, Arnan M, Xicoy B, Fuster F, Cabezón M, et al. Targeted deep sequencing improves outcome stratification in chronic myelomonocytic leukemia with low risk cytogenetic features. Oncotarget. 2016;7(35):57021–35.
34. Sallman DA, Komrokji R, Vaupel C, Cluzeau T, Geyer SM, McGraw KL, et al. Impact of TP53 mutation variant allele frequency on phenotype and outcomes in myelodysplastic syndromes. Leukemia. 2016;30(3):666–73.