**Lenalidomide Followed by Decitabine Combined with HAG Regimen Treatment of an Older MDS-EB-1 Patient with Deletion 5q and ETNK1 Mutation: Case Report and Literature Review**

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**Citation:** Tao S, Deng Y, Chen Y, Gan Y, Ding B, et al (2022) Lenalidomide Followed by Decitabine Combined with HAG Regimen Treatment of an Older MDS-EB-1 Patient with Deletion 5q and ETNK1 Mutation: Case Report and Literature Review. Ann Case Report 7: 906. DOI: 10.29011/2574-7754.100906

**Received:** 04 August 2022, **Accepted:** 08 August 2022, **Published:** 10 August 2022

**Abstract**

Objective: Myelodysplastic syndromes (MDS) is a very heterogeneous disorder and high risk of transformation to acute leukemia. Diagnosis of MDS is based on cytopenia, morphological evidence of dysplasia and bone marrow cytogenetic analysis. Treatment options were depended on prognostic risk, transfusion needs, and percent of blasts, cytogenetic and mutational profiles, and comorbidities. The prognosis of higher risk MDS patients are poor and the goal of therapy is to prolong survival. Lenalidomide can decrease transfusion requirements and improve cytogenetic and cytologic abnormalities in MDS patients with the deletion 5q. However, lenalidomide is not currently used for patients with deletion 5q and bone marrow blasts more than 5%. Method: The present study we report an older MDS patient with deletion 5q and excess blasts (9%) who was treated with decitabine combined with HAG regimen, after one cycle, the bone marrow blasts decreased to 5.5%, then lenalidomide monotherapy was administered to maintenance therapy due to the patient refused to continue chemotherapy. Result: Patients adhere to regular outpatient follow-up; the patient’s blood cell counts were basically normal and no drug-related adverse reactions occurred. By the follow-up date of June 30, 2021, the patient had been disease-free survival for 2 years. Conclusion: lenalidomide alone therapy followed by decitabine combined with HAG regimen may be an effective treatment in elderly MDS patients with 5q deletion and excess blasts who cannot tolerate chemotherapy. Further studies and larger sample groups are needed to validate the effectiveness of this treatment option.
Keywords: Lenalidomide; Myelodysplastic syndromes; Excess blasts type 1; Deletion 5q; ETNK1 mutation

Introduction

Myelodysplastic syndromes (MDS), a kind of clonal hematopoietic stem cell disorder predominating in the elderly patients, which is characterized by myelodysplasia, recurrent genetic abnormalities, ineffective hematopoiesis, and blood cytopenia and by a high risk of evolution to acute myeloid leukemia (AML) [1]. According to the 2016 World Health Organization (WHO) classification, on the basis of morphologic and cytogenetic abnormalities, MDS are categorized into MDS with dysplasia, MDS with isolated deletion 5q, and MDS with excess blasts type 1 or type 2 [1,2]. The specific MDS subtype of isolated deletion 5q abnormality, a favorable subtype, which is response to lenalidomide therapy alone with a particular disease phenotype and biology [2]. However, lenalidomide is not currently recommended for patients with deletion 5q and bone marrow blasts > 5%, complex cytogenetic abnormalities in addition to deletion 5q, patients with TP53 gene mutation [3]. There has been no relevant report on maintenance therapy with lenalidomide after demethylating drugs combined with low-dose chemotherapy to reduce the bone marrow blasts burden. In this study, we report an older MDS patient with deletion 5q and excess blasts (9%) (EB-1) who was treated with lenalidomide followed by decitabine combined with HAG regimen (composed of homoharringtonine, cytarabine and granulocyte colony stimulating factor), then lenalidomide therapy alone was used for maintenance therapy. By the follow-up date, the patient had been disease-free survival for 2 years.

Figure 1: Morphologic features of a myelodysplastic syndrome patient with deletion 5q and excess blasts-1. (Wright-Giemsa-stained bone marrow smear, × 1000). A. The morphologic features were at newly diagnosis stage, which showed 8% blasts. B. The morphologic features were 14 days after treatment with decitabine combined with HAG regimen. The bone marrow smear shown 9.0% blasts, suggesting no remission. C and D shown the morphologic features of the patient’s bone marrow after three and twelve cycles of lenalidomide, respectively. Bone marrow hyperplasia was active and the proportion of blasts was less than 5%.
Figure 2: Flow cytometry dot plots showing immunotype of abnormal populations in a patient with myelodysplastic syndrome. A. CD45 labeled the gate and circled a group of abnormal cells. B. MPO expression and CD3 not expression. C. HLA-DR expression but CD34 not expression. D. CD19 and CD10 were both negative. E. CD13 and CD33 were both positive. F. CD56 and CD16 were both negative.

Figure 3: Karyotype of a myelodysplastic syndrome patient deletion 5q and excess blasts-I. G-banded karyotype showing 46, XX, del (11) (q22) in 4/20 and 46, XX, del (5) (q15q33), del (11) (q22) in 9/20 analyzed metaphases, the arrows are indicated 5q- and 11q- respectively.
Case presentation

A 66-year-old female patient with weakness and fatigue was admitted to our hospital of hematology department. The peripheral blood counts revealed the white blood cell counts of 4.45×10⁹/L, hemoglobin level of 76.0 g/dl and the platelet counts of 843×10⁹/L. The morphology of bone marrow showed active proliferation of granulocytes. The ratio of granulocytes to erythrocytes was 2.71:1, binucleated granulocytes and small megakaryocytes were observed, and the proportion of blasts were 8% (Figure 1). The immunophenotype analysis shown that 9% of the blasts were abnormal, and positive labeling for MPO, CD13, CD33, and HLA-DR (Figure 2). The karyotype was 46, XX, del (11) (q22) in 4/20 and 46, XX, del (5) (q15q33), del (11) (q22) in 9/20 analyzed metaphases (Figure 3). Recurrent somatic mutation in Ethanolamine-Kinase-1 (ETNK1) was identified, the mutant type was heterozygous missense mutation [c.731A>G (p.Asn244Ser)], the variant allele fraction was 27.35% (Figure 4). Fluorescence in situ hybridization (FISH) was performed on 400 interphase cells using dual-color translocation probes, deletion 5q was detected in 108/400 analyzed interphase cells (Figure 5). According to the 2016 WHO classification and diagnostic
criteria, the patient was diagnosed MDS with excess blasts type 1. Refer to the Revised International Prognostic Scoring System (R-IPSS) scoring system, the patient scored 4.5 points and was in the intermediate risk group. Decitabine was started at a daily dose of 20 mg/m² 1-5 days. After one cycle, bone marrow aspiration showed blasts ration of 9%. The decitabine (20 mg/m²/day for 5 days) combined with HAG regimen [homoharringtonine (2 mg/day for 7 days), cytarabine (40 mg/day for 14 days), and granulocyte colony-stimulating factor (GCSF; 300 μg/day until WBC count was >20×10⁹/L)] was administered as reinduction chemotherapy. The patient suffered from myelosuppression and transient ischemic attack after chemotherapy. After two weeks of chemotherapy, her hematologic parameters were as follows: white blood cell counts of 5.04×10⁹/L, hemoglobin level of 91.0 g/dl and the platelet counts of 166×10⁹/L. A third BM smear showed 5.5% blasts. The patient refused to continue chemotherapy due to poor tolerance and personal will. Considering the presence of deletion 5q, therefore, the patient was received lenalidomide therapy alone at a daily dose of 10 mg/d for 21 days in one month. Blood routine, liver function and renal function were regularly monitored in the outpatient department and bone marrow punctures were performed every six months. After 3 cycles of lenalidomide treatment, deletion 5q was not detected, however, deletion 5q was detected again after 12 cycles (264/400 analyzed interphase cells) and 18 cycles (304/400 analyzed interphase cells) of lenalidomide treatment, respectively (Figure 5). By the follow-up date of June 30, 2021, the patient had been disease-free survival for 2 years with normal white blood cell counts, hemoglobin and platelet counts (Figure 6).

Discussion

According to the 2016 WHO classification, the diagnosis and classification of MDS are based on cytogenetics and morphology. The molecular biology and cytogenetic abnormalities are an important feature of MDS, and have been widely implemented in the stratification of MDS prognosis and guidance of treatment [4]. Next-generation sequencing (NGS), as a fast, efficient, and informative sequencing technology, which revealed a landscape of genetic alterations [5,6]. Previous studies shown that more than 90% of MDS patients have been found to have a somatic mutation in at least one gene with this method [5]. Each of these mutations is associated with distinct clinical subtypes of MDS and their own unique correlation with other driver mutations [6]. Currently, according to the mutated genes found in MDS, these genes are involved in biological processes including splicing factors, DNA methylation, histone modification, signal transduction and p53 signaling pathway, etc. [5]. Del (5q) is one of the most common cytogenetic abnormalities in MDS due to the deletion of the long arm of chromosome 5[6]. About 20% of MDS patients have del(5q), and accounting for approximately 15% patients with excess of bone marrow blasts and/or other cytogenetic abnormalities have a poor prognosis [7]. Some genes including CSNK1A1, RPS12, EGR1, miR-145, and miR-146a located on 5q, in addition, TP53 mutation is the most common gene mutations that affects the prognosis of del(5q) MDS patients, TP53 mutated patients shown inferior outcome [8]. Lenalidomide, an immunomodulatory drug, which displays remarkable efficacy in multiple myeloma (MM), also induces impressive responses, reduces transfusion requirements and suppresses the abnormal del(5q) clone cells specifically in MDS patients with isolated deletion 5q [9-11]. However, lenalidomide is not currently recommended for patients with deletion 5q and bone marrow blasts > 5%, complex cytogenetic abnormalities in addition to deletion 5q, patients with TP53 gene mutation [3]. Therefore, how to choose the appropriate treatment regimen for the elderly MDS patients with del(5q) and excess blasts who cannot tolerate chemotherapy? This is a real-world problem for clinicians.

The therapeutic options of MDS require individualized treatment mainly according to risk stratification such as conventional prognostic scores (R-IPSS) [12]. In higher risk MDS patients, the aim is to delay disease progression and prolong survival, allogeneic stem cell transplantation (allo-SCT) is the potential curative treatment for these patients [12]; however, most patients cannot receive allo-SCT due to age, physical condition, no suitable donors and other factors. Decitabine, 5-azacitidine, intensive chemotherapy and lower dose chemotherapy are considered to recommend for the treatment in higher risk MDS old patients who are not eligible for allo-SCT and intensive chemotherapy [3,12,13]. A retrospective study shown that decitabine priming prior to low-dose chemotherapy could improve therapeutic responses in patients with MDS-EB [14]. Lenalidomide represents selective and possible disease modifying activity in MDS with isolated del (5q) or one additional abnormality, the role of lenalidomide in non-del (5q) higher risk MDS patients need to be explored [11]. Combing lenalidomide with induction chemotherapy in higher risk MDS with del(5q) and complex karyotype represented a hematological and cytogenetic response [7]. Moreover, a recent case report shown that treatment with lenalidomide combined with decitabine for a MDS patient with del(5q) and excess blasts significantly prolonged survival [15]. In our case, the old intermediate risk MDS-EB-1 patient was with del(5q) and other cytogenetic or molecular abnormalities including the deletion of the long arm of chromosome 11 and ETNK1 mutation. Recurrent somatic ETNK1 mutations were identified for the first-time evidence in the context of myeloproliferative/myelodysplastic disorders [16]. It can encode an ethanolamine kinase catalyzed the de novo phosphatidylethanolamine biosynthesis pathway. The presence of ETNK1 mutants in atypical chronic myeloid leukemia (aCML) and chronic myelomonocytic leukemia (CMML) were confirmed, all ETNK1 variants were heterozygous and dominant clone. The catalytic activity of the kinase may be inhibited by
ETNK1 mutations [16]. It was reported that ETNK1 mutations were detected in about 10% aCML and 3% CML patients [17,18]. Mutated ETNK1 caused ROS production, DNA damage, and mitochondrial hyperactivation [19]. There is no evidence that ETNK1 mutation has not been reported in MDS until now. It is reported that an older MDS-EB-1 patient with deletion 5q and ETNK1 mutation, she was first received a cycle of decitabine, which showed no significant decrease in bone marrow blasts, suggesting that decitabine alone was not effective. The patient was treated with decitabine combined with HAG regimen as the second cycle, and the bone marrow blasts decreased to 5.5%. And then lenalidomide therapy alone was used for her at a daily dose of 10 mg/d for 21 days in one month. During the treatment of lenalidomide, the patient’s blood cell counts were in the normal range, the del(5q) clones were not detected after 3 courses of lenalidomide, nonetheless, the del(5q) clones were examined again after 12 and 18 cycles, respectively. The reappearance of del(5q) clones may be related to lenalidomide resistance. In del(5q) MDS, lenalidomide can induce ubiquitination and degradation of casein kinase 1A1 (CK1α), CK1α is a negative regulator of p53 [20]. TP53 mutations are involved in primary resistance of del(5q) MDS to lenalidomide, acquired resistance to lenalidomide is associated with protein phosphatase 2A catalytic domain alpha (PP2Acα) overexpression [11,20]. Genomic analysis shown that lenalidomide resistance in non-del(5q) MDS was related to variety of genetic abnormalities including mutation in SF3B1, TET2, and WNT3A amplification [21]. Unfortunately, genome analysis was not performed when the del(5q) clones appeared again in our patient, and we will further complete NGS in the follow-up.

In conclusion, lenalidomide alone therapy followed by decitabine combined with HAG regimen may be an effective treatment in elderly MDS patients with del(5q) and excess blasts who cannot tolerate intense chemotherapy. However, Prospective studies with lager samples are needed to validate the effectiveness of this treatment option.

Acknowledgements: Not applicable.

Funding: The present study was supported by the Science and Technology Fund of Jiangsu Commission of Health (grant no. H2019082).

Availability of data and materials: The data that support the findings of the present study are available from Kindstar Global Medical Laboratory Center (https://www.kindstar.com.cn/platform.html).

Authors’ contributions: ST and YD collected patient data and drafted the initial manuscript. CW conceived and designed the present study. ST revised the manuscript along with, YC, ZD, YG, BD, ZH and CW, and these individuals were responsible for the treatment of the patients. All authors have read and approved the final manuscript.

Ethics approval and consent to participate: The present study was approved by the Institutional Review Board of the Affiliated Huai’an No. 1 People’s Hospital of Nanjing Medical University. Written informed consent was provided by the patient prior to the study start.

Competing interests: The authors declare that they have no competing interests.

References


