Case Report

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Disappearance of Trisomy +8 In A Case with Myelodysplastic Syndrome After Azacitidine Therapy Followed by Lenalidomide Treatment

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ABSTRACT

Myelodysplastic Syndrome (MDS) is clonal hematopoietic stem cell disorders with a variety of molecular and cytogenetic abnormalities that subclassify it into different genomic subgroups with specific clinic- pathological features including prognosis and therapeutic response. The aim of this case report is to describe an unusual case with MDS in which has been observed disappearance of the clone carrying both 5q- and +8 after treatment with azacitidine followed by lenalidomide administration.

Keywords: Myelodysplastic Syndrome; 5q- Syndrome; Lenolidomide

Abbreviations: MDS: Myelodysplastic Syndrome; Hg: Hemoglobin; BM: Bone Marrow; PLT: Platelets; IPSS: International Prognosis Scoring System; FISH: Fluorescent in Situ Hybridization

Introduction

Myelodysplastic syndrome (MDS) is clonal hematopoietic stem cell disorders characterized clinically by ineffective hematopoiesis as a consequence of abnormalities in proliferation, differentiation, and apoptosis of hematopoietic precursors and their progeny [1]. MDS is associated with a variety of molecular and cytogenetic abnormalities that subclassify it into different genomic subgroups with specific clinic- pathological features including prognosis and therapeutic response [2,3]. The most defined entity is the so-called MDS with "5q- syndrome" which is characterized by isolated refractory anemia, older age, female predominance, normal or elevated platelet count, megakaryocytic dysplasia, low risk of leukemia progression and good prognosis [4]. Patients with "5 syndrome" successfully respond to treatment with lenalidomide [5-8]. In contrast, treatment of MDS with lenalidomide in cases that have 5q- with additional anomalies particular +8 is less effective [7,8]. Here we describe an unusual case with MDS in which has been observed disappearance of the clone carrying both 5q- and +8 after treatment with azacitidine followed by lenalidomide administration.

Case Report

At Nov 2016, a 61 years old woman presented at the Clinic of Hematology with a history of etiology unknown macrocytic anemia for 1 years, hemoglobin (Hg) level 81 g/l, (WBC) 7.6 x 10^9/l and platelets (PLT) 242 x 10^9/l. Screening panel disclaimed iron deficiency or other alimentary associated anemia, negative test for hemolytic anemia. Peripheral blood smear revealed absence of blast population. The bone marrow aspiration revealed hypercellular bone marrow (BM) with 2% blasts and dysplastic features of all the three cell lines, the most prominent dysplasia was found in erythroblasts presented mainly with multinuclear cell nuclei. The test for ring sideroblasts was negative. Conventional cytogenetics revealed clone with isolated trisomy of chromosome 8 in 67% of the examined cells - 47,XX,+8[16]/46,XX[8]. The diagnosis of myelodysplastic syndrome refractory cytopenia with

multilineage dysplasia was concluded [1]. Based on these finding, the risk stratification as intermediate-1 risk group according to International prognosis scoring system (IPSS) for MDS [2] and the defined serum erythropoietin level more than 500 mU/ml, best supported care was accepted as treatment strategy. Eighteen months (July 2018) after start of best supported care the transfusion needs increased significantly, and disease reassessment was performed with bone marrow aspiration showing blast 4% population. Conventional cytogenetics of BM revealed the following karyotype: 47,XX,+8[24]/47,XX,del(5)(q13q33),+8[3]/46,XX[2].

The Fluorescent in Situ Hybridization (FISH) with satellite enumeration DNA probe for chromosome 8 conformed the +8 clone and the 5q- specific DNA probe demonstrated that the 5q- anomaly is presented in 21% of the cells (100 cells examined). New therapy strategy with azacytidine was start at July 2018. After two cycles with hypomethylating agent therapy was discontinued due to severe anemia (Hb nadir 51 g/L). At October 2018 2nd with lenalidomide was started with documented erythroid response, which is still preserved, but progressive thrombocytopenia was seen. Hereof bone marrow reassessment was done October 2019 showing at conventional cytogenetics that a new clone carrying only the 5q- was arisen - 46,XX,del(5)(q13q33)[3]/46,XX[22] and metaphases with +8 or combination of +8 with 5q- was not presented. FISH study with 5q- specific DNA probe conformed the 5q- anomaly in 20% of the cells (100 cells examined) and the satellite enumeration DNA probe for chromosome 8 did not find cells with trisomy of chromosome 8.

Discussion

Trisomy 8 is a common cytogenetic abnormality associated with intermediate cytogenetic risk according to IPSS and Reverse IPSS [2,3]. The use of Antithymocyte Globulin (ATG) for this subgroup of MDS show response rates up to 67%, [9]. However, Solan et al. [10] demonstrated that younger age and HLA-DR15 positivity were the most significant factors favoring response to immunosuppressive treatment (IST, ATG plus cyclosporine (CsA), or CsA alone). Based on this study IST is recommended for patients ≤60 years old and ≤5%blast in bone marrow or those with hypocellular bone marrow, PNH clone positivity or STAT-3 mutant cytotoxic T clone positivity [11]. For all other cases with/witout del(5q) symptomatic anemia low/int -1 MDS azacytidine therapy is recommended as is in the presented clinical case. In accordance with the already known hematological and nonhematological adverse events associated with azacytidine use is the discontinuation of therapy in our patients [12]. However, the reassessment of bone marrow before starting azacytidine treatment showed new clone with del(5q) which allow us to start treatment with lenalidomide. The therapeutic effectiveness of lenalidomide in 5q- low/int-1 IPSS MDS is proved in two randomized studies where most of the patients were with isolated del(5q) or del(5q) plus ≥1 cytogenetic abnormality [6,7]. Erythroid hematological improvement was achieved in approximately 60% of patients. There were no data if additional cytogenetic abnormality influences the therapeutic effect. Other studies showed that additional cytogenetic abnormality including trisomy 8 significantly decreased overall survival [8] and cytogenetic response was not achieved in patients with 5q syndrome with additional aberration hereofexcept of trisomy 21 or t(1;22)q(21p11.2) [6].

Contrary in the presented case we found complete clearance of cytogenetic clone with trisomy 8, which is unique considering the known intermediate risk associated with +8 and lower response rate. It should be noted, however that the patients were treated also with hypomethylating agent in the course of the disease, which could influence the observed clearance of +8 MDS clone. Some data from clinical studies phase II showed synergic effect from the combination of azacytidine with lenalidomide in patients with MDS int-1/int-2/high risk IPSS [12]. The effectiveness of the same combination was also investigated in the setting of acute myeloid leukemia with contradictory results [13-15]. We suppose that the hypomethylating effect of the azacytidine had initiated genomic reorganization that have been led to the activation of pro-apoptotic genes .and that the subsequent cytotoxic influence of the lenalidomide of the pro-apoptotic cells had resulted in eradication of the clones caring +8.

Conclusion

The presented clinical case raises the question for consecutive therapy of azacytidine and lenalidomide in the case of low/int-1 IPSS risk MDS with del(5q) with +8 additional aberration. Lenalidomide mediated its immunomodulating effect by altering cytokine production, regulating T cell co- stimulation and augmenting the NK cell cytotoxicity. The biological mechanism of action of azacytidine is based on its hypomethylating effect and direct cytotoxic effect [12]. It could be purposed that combination or consecutive of these two different therapeutic strategies could have synergic effect in such cases 5q- syndrome with additional trisomy 8, but prospective clinical trials are necessary for conclusions.

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