




Efficacy of lenalidomide in the treatment of myelodysplastic/myeloproliferative neoplasms, unclassifiable (MDS/MPN-U) with the presence of deletion 5q– and trisomy 8+

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Abstract

Myelodysplastic/myeloproliferative neoplasms (MDS/MPN) are very rare clonal myeloid characterized by the simultaneous presence of both of erythrocytic and/or granulocytic dysplasia with myeloproliferative features. The etiology of the disease remains unknown. The MDS/MPN group is made up of five disorders: chronic myelomonocytic leukemia, atypical chronic myeloid leukemia, juvenile myelomonocytic leukemia, MDS/MPN ring sideroblasts with thrombocytosis and MDS/MPN, unclassifiable (MDS/MPN-U). MDS/MPN-U remains the least characterized entity. It accounts less than 5% of all myeloid disorder. The reare currently no well-established diagnostic criteria. The disease is heterogeneous with unclear management strategies.

The aim of this paper is to present a case of a 59-year-old female patient diagnosed with MDS/MPN-U with deletion 5q– and trisomy 8+, whom lenalidomide 10 mg daily has been used as monotherapy. The disease has initially manifested as severe cytopenias, multiple transfusions of blood preparations were required. Currently patient is in the 9th month of treatment. Hemoglobin, platelets and white blood cells returned to normal. The patient completely became independent of transfusion of red blood cell concentrates. No adverse events were observed.

Key words: myelodysplastic/myeloproliferative neoplasm, unclassifiable, MDS/MPN-U, deletion 5q–, trisomy 8+, lenalidomide

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Introduction

Myelodysplastic/myeloproliferative neoplasms (MDS/MPN) are a group of rare clonal disorders of the myeloid lineage, characterized by bone marrow failure and coexistence of dysplasia with signs of myeloproliferative features. Their clinical picture is remarkably heterogeneous. The etiology of the disease remains unclear. According to the current

classification of the World Health Organization (WHO) of bone marrow neoplasms, MDS/MPN include chronic myelomonocytic leukemia (CMML), atypical chronic myelogenous leukemia (aCML), juvenile myelomonocytic leukemia (JMML), MDS/MPN with ring sideroblasts and thrombocytosis and MDS/MPN unclassifiable (MDS/MPN-U, myelodysplastic/myeloproliferative neoplasm, unclassifiable) (Table 1) [1, 2].

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Table 1. Classification of myelodysplastic/myeloproliferative neoplasms according to World Health Organization (2016) (source [2])

Chronic myelomonocytic leukemia (CMML):
• CMML-0
• CMML-1
• CMML-2
Atypical chronic myelogenous leukemia, <i>BCR-ABL1</i> -negative (aCML <i>BCR-ABL1</i> -)
Juvenile myelomonocytic leukemia (JMML)
Myelodysplastic/myeloproliferative neoplasm with ring sideroblasts and thrombocytosis (MDS/MPN-RS-T)
Myelodysplastic/myeloproliferative neoplasm, unclassifiable (MDS/MPN-U)

Case report

A 59-year-old female patient with observed from July 2018 anemia requiring numerous transfusions of red blood cells (RCC), periodically with markers of hemolysis, with hepatosplenomegaly, was undergoing diagnostics in Hemato-oncology and Bone Marrow Transplantation University Department from October 2018. The patient had cardiologic co-morbidities including single vessel ischemic heart disease, after successful left anterior descending (LAD) angioplasty with implantation of anti-proliferative drug-eluting stent (DES) in July 2018, on dual antiplatelet therapy (acetylsalicylic acid + clopidogrel); she was admitted to hospital due to severe macrocytic anemia [hemoglobin concentration (Hb) 5.6 g/dL, mean corpuscular volume (MCV) 101 fL] with hemolysis markers [haptoglobin 0.12 g/dL, lactate dehydrogenase (LDH) 603 IU/L, total bilirubin 1.38 mg/dL, reticulocyte count 2.82%], ferritin 527 ng/mL. Folic acid concentration [12.09 ng/mL (norm: > 5.38 ng/mL)] and vitamin B₁₂ concentration [285 pg/mL (norm: 211–911 pg/mL)] were measured. Hepatomegaly (197 mm in CC dimension) and splenomegaly (size 133 × 78 mm) were present on abdominal ultrasound. On blood group examination antibodies were detected; their specificity was not determined. Direct antiglobulin test (DAT) was negative. The patient had transfusions of phenotypically compatible red blood cell concentrate (RBCC). The patient had a hematology consultation; based on the results of the investigations carried out according to the consultant's recommendations [protein electrophoresis, urine analysis, ultrasound (USG) of the abdominal cavity, chest X-ray] no obvious cause of hemolysis was identified. In addition, a positive test result for gastric parietal cell antibodies was received. Endoscopy of the upper gastrointestinal tract showed features of atrophic gastritis, biopsies

were taken for histopathology, *Helicobacter pylori* stool antigen test was requested. Intramuscular vitamin B₁₂ supplementation was given.

In the following months, the patient was hospitalized again due to severe anemia requiring RBCC transfusion. The patient was sent again for hematology consultation and had further tests to rule out paroxysmal nocturnal hemoglobinuria (PNH) — no clone of cells with PNH defect was confirmed. As the patient was on dual antiplatelet therapy, a bone marrow biopsy was put on hold.

During another admission to the Hemato-oncology Department, steroid therapy was administered — dexamethasone 4 mg/day. After a few days of treatment, episodes of hyperglycemia were observed as well as increased blood pressure and mental disturbance — the patient was aggressive, agitated and refused any medical procedures, she presented with delusional symptoms. Treatment with steroids was stopped. The patient was transferred to a psychiatric ward; antipsychotics (olanzapine, quetiapine) were given resulting in an improvement of the observed symptoms.

During her next inpatient stay, a full blood count showed pancytopenia — grade 2 neutropenia, grade 2 thrombocytopenia and grade 4 anemia. Olanzapine and quetiapine were discontinued and treatment with lithium carbonate initiated — as prescribed by the psychiatrist. After discontinuation of antipsychotic drugs, neutrophil and platelet count (PLT) returned to normal values [neutrophil count (NEU) 4.5 G/L, white blood cells (WBC) 6.8 G/L, PLT 156 G/L]. The patient still had severe anemia (Hb 5 g/dL) and required multiple transfusions of RBCC.

The patient was under the care of a hematology outpatient clinic, received azathioprine 50 mg orally (p.o., *per os*) and danazol 400 mg p.o. Despite treatment, the patient remained transfusion-dependent.

Given the unclear etiology of the patient's persistent severe anemia and ineffectiveness of the immunosuppressive treatment, further in-depth diagnostic investigations were carried out during hospitalization in June 2019. Due to the reoccurrence of grade 2 thrombocytopenia (PLT count approximately 50 G/L) treatment with azathioprine and danazol was stopped. Diagnostic bone marrow trephine biopsy was done, 2 days before the procedure clopidogrel was withheld. The procedure was uneventful. However, no bone marrow aspirate was obtained (so-called dry tap). In addition, a molecular test for *JAK2* mutation was requested on peripheral blood, which was found to be negative. Due to positive anti-nuclear

antibodies (ANA) titer diagnostics were extended with a full antibody panel, showing positive anti-smooth muscle antibodies (anti-SMA).

The trephine biopsy reported significantly increased bone marrow cellularity considering the patient's age, comprising about 80% of bone marrow spaces. Erythroid lineage was reduced and represented by infrequent large erythroid islands, some of the para-trabecular location. Granulocytic lineage (CD34+ in < 1% of cells) was well represented with preserved maturation. Megakaryocytes were located by tens in trabecule, scattered and located in small and large loose and compact clusters; the cells varied in size from large to small, most of them were hypolobated and monolobated. Lymphocytes small, scattered and forming a single lymphoid follicle constituted about 15% of marrow cells. Reticulin pattern was emphasized (MF2). The diagnosis of myelodysplastic-myeloproliferative disorder unclassifiable (MDS/MPN-U) was made.

Due to the persistence of anemia requiring transfusion of blood products, grade 2 thrombocytopenia, new onset of grade 4 neutropenia (NEU < 1000 G/L), lack of response to current treatment, lack of indication to hypomethylating therapy (< 1% immature cells in bone marrow) a decision of trial of treatment with thalidomide 50 mg was made. The patient's informed consent to therapy was obtained. The patient was also informed about the need for an urgent cardiac assessment as to the continuation of dual antiplatelet therapy (PLT count remained around 50 G/L).

The second trial of aspiration was performed, successfully. The interstitial deletion was detected in the long arm of chromosome 5 [del(5)(q13q33)] as well as an additional copy of chromosome 8. Normal female karyotype was present in only 3 metaphases. Karyotype: 46~47,XX,del(5)(q13q33),8[cp16]/46,XX [3].

The patient has been qualified to the intermediate-risk category according to the revised International Prognostic Scoring System (R-IPSS). It was then decided to undertake a treatment trial with lenalidomide. The drug was possessed on the grounds of compassionate use by the Celgene pharmaceutical company.

In September 2019 the patient commenced treatment with lenalidomide 10 mg/day on days 1–21 of a 28-day cycle. During 1st treatment cycle due to the reduction of PLT count below the value allowing to continue treatment with lenalidomide — the therapy was held until blood count parameters improved. After 2 weeks PLT count returned

to values above 25 G/L and the treatment with lenalidomide 10 mg on alternate days was restarted. Iron chelation therapy was commenced.

The patient is in the 9th month of therapy. A gradual increase in hemoglobin level has been observed as well as the return of PLT, WBC and NEU to normal figures. Hb is around 14.5 g/dL. The patient is RBCC transfusion independent. No complications of therapy have been observed.

Discussion

Unclassifiable myelodysplastic-myeloproliferative neoplasm is characterized by the coexistence of features of dysplasia in erythroid and/or myeloid lineage with less than 20% blasts in peripheral blood and bone marrow and myeloproliferative features in patients without preceding therapy with cytotoxics or growth factor, without the Philadelphia chromosome, fusion genes *BCR-ABL1*, *PDGFRA*, *PDGFRB* or isolated del(5q), t(3;3)(q21;q26) or inv(3)(q21q26). Myeloproliferative features in principle are characterized by thrombocytosis (PLT count ≥ 450 G/L) linked with megakaryocyte proliferation and leukocytosis (WBC count ≥ 13 G/L) with or without splenomegaly. Currently, MDS/MPN-U is referred to as a temporary subgroup of MDS/MPN, which includes disorders not meeting diagnostic criteria for CMML, JMML or aCML. There are no clearly defined diagnostic and therapeutic recommendations for this disease entity [3].

In the case of the presented patient, apart from morphological features of myelodysplastic syndrome (MDS), i.e., anemia with features of erythroid lineage dysplasia, bone marrow fibrosis as well as hepatosplenomegaly were present. The presence of molecular abnormalities — del(5q) with coexisting trisomy 8+ — is not characteristic of any other disease entity.

Treatment of MDS/MPN-U is a major clinical challenge. Due to poor disease characteristics, lack of defined prognostic model and treatment guidelines, the management of patients in clinical practice is most often based on models relating to MDS. Treatment choice should be individualized [4].

DiNardo et al. [3] in so far the largest published study on the efficacy of therapy in patients with MDS/MPN-U (n = 85) showed that the majority of patients with cytopenias requiring transfusions of blood products were treated with hypomethylating drugs. The authors observed that these allow longer overall survival periods compared to other drugs [interferon-alpha (IFN- α), thalidomide,

lenalidomide or anti-thymocyte globulin] (16.4 vs. 11.5 months, $p = 0.57$). They further stressed that the choice of therapy should be based on characteristic cytogenetic and molecular abnormalities present in individual patients. In the case of *JAK2* V617F mutation, treatments with JAK2 inhibitors have been attempted [3]. Therefore, in the presence of del (5q), it seems appropriate to apply a therapeutic strategy known to be effective in MDS, i.e., lenalidomide monotherapy.

Interstitial deletions of the long arm of chromosome 5 (5q) are the most common cytogenetic abnormalities in MDS. They occur in 10–15% of cases, both as an isolated anomaly — the so-called 5q- syndrome, and as a component of more complex abnormalities. The significance of del (5q) in MDS is very important. The long arm of chromosome 5 contains many genes involved in the regulation of hematopoiesis, including genes coding cytokines and their receptors, regulatory proteins of the cell cycle, transcription factors and signal transmitting molecules [5].

5q- syndrome has a relatively good prognosis with a low frequency of transformation to acute myeloid leukemia (AML). The prognosis is significantly worsened by RBCC transfusion dependence and the presence of additional cytogenetic abnormalities and/or increased percentage of bone marrow blasts over 5% [6].

Among new drugs used these days in MDS 5q- therapy — best rated is lenalidomide — a drug with an immunomodulatory mechanism of action, thalidomide analogue, showing the complex influence on the bone marrow microenvironment. It can overcome the negative impact of the 5q deletion on cell differentiation and signal transmission pathways. It has an anti-angiogenic effect, which can inhibit the expansion of the clone of cells with 5q deletion by reducing the density of the blood vessel network. It inhibits the effect of many pro-inflammatory cytokines, including tumour necrosis factor alpha (TNF- α), resulting in a reduction of progenitor cell apoptosis in the bone marrow. It has a costimulatory effect on T lymphocytes and has a direct anti-neoplastic effect. In animal models, it has been shown to enhance cellular immunity through inducing the production of interleukin 1 (IL-1) and interferon-gamma (IFN- γ) and increasing the response of cytotoxic T lymphocytes and cells of natural cytotoxicity (NK, natural killers) [7, 8].

Lenalidomide was approved on 27th December 2005 by the American Food and Drug Administration (FDA) for patients with low or intermediate-1 risk MDS with 5q deletion with or without addition-

al cytogenetic abnormalities. On 17th June 2013, it was approved by the European Medicines Agency (EMA) for treatment of low or intermediate-1 risk MDS patients with 5q deletion without additional cytogenetic abnormalities, RBCC transfusion-dependent for whom other treatment methods turned out to be inadequate or inappropriate [9].

The use of lenalidomide for the treatment of patients with MDS with 5q31 deletion and coexisting additional cytogenetic abnormalities remains the subject of discussion.

Arcioni et al. [9] for the study evaluating the drug efficacy in MDS 5q- recruited 190 patients, of which 2 (~1.3%) had a complex karyotype, and 25 (~16.8%) had one additional aberration. Complete response in the erythroid lineage was achieved in 92.8% and cytogenetic in 22.6% of cases. Interestingly, the study showed that hematological and cytogenetic responses to the treatment were similar among patients with both the isolated 5q deletion and with one additional chromosomal abnormality [9].

Giagounidis et al. [6] presented a case of a 78-year-old female patient with MDS 5q- and complex karyotype, with less than 5% blasts. The patient received lenalidomide 10 mg/day for 5 months. Then due to side effects (nausea, vomiting, skin itchiness), its dose was reduced to 5 mg/day. Histopathological examination of the bone marrow carried out after 6 months of treatment showed erythroid hyperplasia and normalization of megakaryocyte morphology and conversion of the karyotype to normal on cytogenetic testing. Fluorescent *in situ* hybridization (FISH) technique study did not reveal any persistent metaphases with 5q deletion. An increase in Hb concentration to 12.4 g/dL was observed [6].

Summary

There are no clear treatment algorithms for patients diagnosed with MDS/MPN with del(5q) either as an isolated aberration or a component of complex molecular abnormalities. The literature describes case studies of patients with features of a myelodysplastic/myeloproliferative neoplasm with ring sideroblasts and thrombocytosis (MDS/MPN-RS-T) and MDS with del (5q) in whom lenalidomide is highly effective [10, 11]. To the best of the authors' knowledge, however, there is a lack of reports on lenalidomide use in MDS/MPN-U therapy.

Despite frequent classification updates of hematological diseases, there are still disorders

that do not fit into any of the categories and present a big challenge for practising hematologists. Considering the example of the presented clinical case, the authors emphasize that a trial of the use of lenalidomide should be considered in the treatment of patients with MDS/MPN-U 5q — with coexisting additional chromosomal abnormality.

Conflict of interests

None.

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Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/EU for animal experiments; Uniform Requirements for manuscripts submitted to Biomedical journals.

References

1. Sochacki AL, Fischer MA, Savona MR. Therapeutic approaches in myelofibrosis and myelodysplastic/myeloproliferative overlap syndromes. *Onco Targets Ther.* 2016; 9: 2273–2286, doi: [10.2147/OTT.S83868](https://doi.org/10.2147/OTT.S83868), indexed in Pubmed: [27143923](https://pubmed.ncbi.nlm.nih.gov/27143923/).
2. Arber DA, Orazi A, Hasserjian R, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. *Blood.* 2016; 127(20): 2391–2405, doi: [10.1182/blood-2016-03-643544](https://doi.org/10.1182/blood-2016-03-643544), indexed in Pubmed: [27069254](https://pubmed.ncbi.nlm.nih.gov/27069254/).
3. DiNardo CD, Daver N, Jain N, et al. Myelodysplastic/myeloproliferative neoplasms, unclassifiable (MDS/MPN, U): natural history and clinical outcome by treatment strategy. *Leukemia.* 2014; 28(4): 958–961, doi: [10.1038/leu.2014.8](https://doi.org/10.1038/leu.2014.8), indexed in Pubmed: [24492324](https://pubmed.ncbi.nlm.nih.gov/24492324/).
4. Talati C, Padron E. An exercise in extrapolation: clinical management of atypical CML, MDS/MPN-unclassifiable, and MDS/MPN-RS-T. *Curr Hematol Malig Rep.* 2016; 11(6): 425–433, doi: [10.1007/s11899-016-0350-1](https://doi.org/10.1007/s11899-016-0350-1), indexed in Pubmed: [27664113](https://pubmed.ncbi.nlm.nih.gov/27664113/).
5. Giagounidis AAN, Germing U, Aul C. Biological and prognostic significance of chromosome 5q deletions in myeloid malignancies. *Clin Cancer Res.* 2006; 12(1): 5–10, doi: [10.1158/1078-0432.CCR-05-1437](https://doi.org/10.1158/1078-0432.CCR-05-1437), indexed in Pubmed: [16397017](https://pubmed.ncbi.nlm.nih.gov/16397017/).
6. Giagounidis AAN, Germing U, Strupp C, et al. Prognosis of patients with del(5q) MDS and complex karyotype and the possible role of lenalidomide in this patient subgroup. *Ann Hematol.* 2005; 84(9): 569–571, doi: [10.1007/s00277-005-1054-0](https://doi.org/10.1007/s00277-005-1054-0), indexed in Pubmed: [15891887](https://pubmed.ncbi.nlm.nih.gov/15891887/).
7. List A, Kurtin S, Roe DJ, et al. Efficacy of lenalidomide in myelodysplastic syndromes. *N Engl J Med.* 2005; 352(6): 549–557, doi: [10.1056/NEJMoa041668](https://doi.org/10.1056/NEJMoa041668), indexed in Pubmed: [15703420](https://pubmed.ncbi.nlm.nih.gov/15703420/).
8. List A, Ebert BL, Fenau P. A decade of progress in myelodysplastic syndrome with chromosome 5q deletion. *Leukemia.* 2018; 32(7): 1493–1499, doi: [10.1038/s41375-018-0029-9](https://doi.org/10.1038/s41375-018-0029-9), indexed in Pubmed: [29445113](https://pubmed.ncbi.nlm.nih.gov/29445113/).
9. Arcioni F, Roncadori A, Di Battista V, et al. MORE Study Centres. Lenalidomide treatment of myelodysplastic syndromes with chromosome 5q deletion: Results from the National Registry of the Italian Drug Agency. *Eur J Haematol.* 2018; 101(1): 78–85, doi: [10.1111/ejh.13067](https://doi.org/10.1111/ejh.13067), indexed in Pubmed: [29569278](https://pubmed.ncbi.nlm.nih.gov/29569278/).
10. Ziarkiewicz M, Dwilewicz-Trojaczek J, Pastwińska A, et al. Refractory anaemia with ringed sideroblasts associated with marked thrombocytosis (RARS-T) with superimposed 5q-syndrome. *Pol J Pathol.* 2010; 61(2): 105–109, indexed in Pubmed: [20924996](https://pubmed.ncbi.nlm.nih.gov/20924996/).
11. Alshaban A, Padilla O, Philipovskiy A, et al. Lenalidomide induced durable remission in a patient with MDS/MPN-with ring sideroblasts and thrombocytosis with associated 5q- syndrome. *Leuk Res Rep.* 2018; 10: 37–40, doi: [10.1016/j.lrr.2018.08.001](https://doi.org/10.1016/j.lrr.2018.08.001), indexed in Pubmed: [30186759](https://pubmed.ncbi.nlm.nih.gov/30186759/).