

Transitory response of a myelodysplastic syndrome with deletion of chromosome 5q to thalidomide.

Report of one case

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ABSTRACT

Myelodysplastic syndrome with deletion of chromosome 5q (5q-syndrome) has a favorable prognosis and a low risk of transformation to acute myeloid leukemia, when treated with lenalidomide. Azacitidine leads to complete remission even as second-line therapy and in patients with clonal evolution. We report a 70 years old female without previous exposure to myelotoxic drugs, presenting with three weeks with fatigue and dyspnea. She had anemia with normal white blood cell and platelet count. Bone marrow biopsy showed 50% cellularity and the karyotype analysis revealed a (5) (q33q34) deletion in 22% of the metaphases. A diagnosis of 5q-syndrome with low risk calculated using the Revised International Prognostic Scoring System (IPSS-R), was made. Since lenalidomide was not affordable, thalidomide 100 mg/day was initiated, achieving transfusion independence for three years. Afterwards, she developed pancytopenia and a bone marrow biopsy showed erythroid and megakaryocyte dysplasia with a complex karyotype, which worsened prognosis (IPSS-R of five points). Therefore, azacitidine (by donation) was administered. She achieved complete remission with a normal karyotype and completed 12 cycles of treatment. Thereafter, she relapsed and received only supportive care for a year. She suffered an ischemic stroke and died two weeks later.

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Key words: Azacitidine; Lenalidomide; Myelodysplastic Syndromes.

Respuesta transitoria de un síndrome mielodisplásico con delección del cromosoma 5q a talidomida. Informe de un caso

El síndrome mielodisplásico con delección del cromosoma 5q (síndrome 5q) tiene un pronóstico favorable y riesgo bajo de transformación a leucemia aguda en pacientes que son tratados con lenalidomida (tratamiento estándar). El uso Azacitidina tiene respuestas completas incluso como segunda línea de tratamiento en pacientes con evolución clonal. Presentamos una mujer de 71 años, sin exposición a mielotóxicos que debutó con un síndrome anémico. Se realizó biopsia de medula ósea que mostró celularidad del 50% y en el análisis citogenético se

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detectó una deleción del cromosoma 5 en 22% de las metafases analizadas, lo que llevó al diagnóstico de Síndrome 5q- de riesgo bajo de acuerdo con el puntaje IPSS-R (Revised International Prognostic Scoring System). Ya que no se pudo costear lenalidomida, se trató con talidomida (100 mg/día). Permaneció tres años sin requerir soporte transfusional. Posteriormente, presentó pancitopenia y en el nuevo aspirado de médula ósea se observó displasia de la serie roja y megacariocitos, con cariotipo complejo y peor pronóstico (IPSS-R 5 puntos). Se trató con 12 ciclos de azacitidina con lo que logró respuesta completa. Recayó 12 meses después y continuó manejo de soporte por un año. Finalmente falleció debido a un accidente vascular cerebral.

Palabras clave: Azacitidina; Lenalidomida; Síndromes Mielodisplásicos.

Myelodysplastic disorders (MDS) constitute a heterogeneous group of primary bone clonal hematopoietic diseases that are characterized by ineffective hematopoiesis associated with dysplasia, which leads to chronic cytopenia and a variable progression to Acute Myeloid Leukemia (AML)¹.

Chromosomal abnormalities have been described in approximately 50% of this group of patients; interstitial deletion of the long arm of chromosome 5 [5q- or del(5q)] accounts for approximately 10- 15% of primary MDS. The three most prevalent types of cytogenetic deletion reported include: del(5)(q13q31), del(5)(q13q33), and del(5)(q22q35), and being an heterozygous deletion, it has been related to haploinsufficiency for one or more genes located in this chromosome region².

Clinically, 5q- syndrome is associated with favorable prognosis and a low risk of transformation to acute myeloid leukemia if receiving lenalidomide, the standard treatment³. Thalidomide could have adequate response (up to 20%) as an alternative with lower cost. Low-risk cancers that do not receive target therapy have bad prognosis and low survival rates. Additionally, azacitidine shows complete remission even as second-line therapy and in patients with clonal evolution.

Herein, we report the case of a female with 5q-syndrome, without access to target therapy do to its cost so she received thalidomide, later on she developed clonal evolution and got an excellent, although transitory, response with azacitidine.

Case Presentation

A seventy-one-year-old Mexican female, with no family cancer history, and with personal history

of type 2 diabetes and high blood pressure, without previous exposure to myelotoxics, referred three weeks with fatigue and dyspnea (Figure 1). The blood tests showed hemoglobin 5.5g/dL, hematocrit 17.5%, MCV 107.2fL, platelet count 318000/mm³ WBC 4.4/mm³, granulocytes 3.1/mm³, iron 150 mcg/dL, iron saturation 40.7%, ferritin 1593 ng/ml, B12 vitamin 660 pg/dL, HIV and hepatitis (A, B and C) were negative. Bone marrow biopsy showed 50% cellularity and the karyotype analysis revealed del(5)(q33q34) in 22% of the metaphases. The diagnosis of 5q- syndrome with low risk by IPSS-R (2.5 points) was established. Since lenalidomide was not affordable, thalidomide 100 mg daily was initiated. Within the first two months of treatment, the patient required 2 units of red blood cells every 3 to 4 weeks. At the third month, she achieved transfusion independence. In terms of adverse events, she only developed paresthesia grade 1 (CTCAE v4.0) in hands during all her treatment with thalidomide⁴. After 3 years with hematological complete response, pancytopenia was documented: leukocyte count decreased slowly to 1.9/mm³, with granulocytes 800/mm³, hemoglobin 7.8 g/dL and platelet count 85 000/mm³. A new bone marrow biopsy showed erythroid and megakaryocyte dysplasia; no increase in blasts and no myelofibrosis were documented. Cytogenetic analysis showed clonal evolution with complex karyotype: 45XX, -8[2]/43XX, -11,-14-22[1]/46XX, -16, mar[1]/46XX[5]÷36-41(2n),XX[10], which worsened prognosis (IPSS-R 5.5 points). She required transfusion therapy monthly during 2 months again so with these findings, azacitidine (100 mg SC daily during 7 days every 28 days) was administered; our patient had access to this therapy by donation. She achieved not only transfusion independence, but

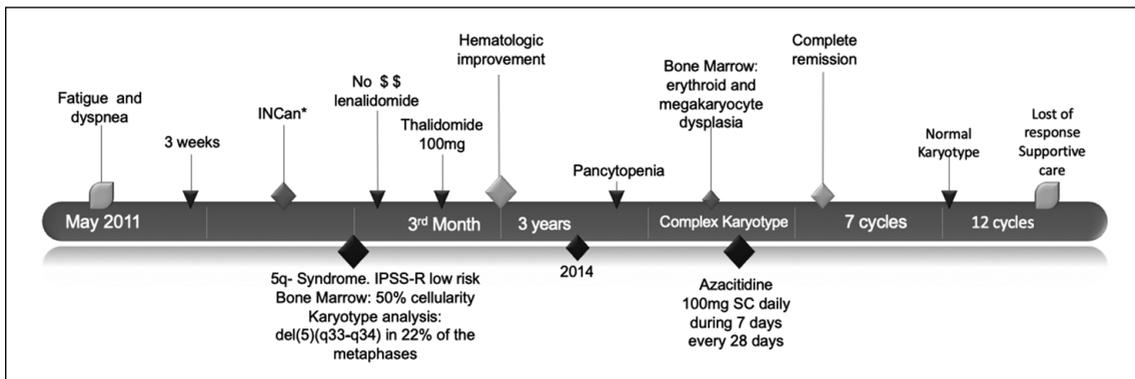


Figure 1. Timeline of the patient's evolution. Abbreviations: INCan: Instituto Nacional de Cancerología; IPSS-R: Revised International Prognostic Scoring System; SC: Subcutaneous.

also hematologic improvement. After 7 cycles, a bone marrow biopsy revealed 10% of erythroid and megakaryocyte dysplasia with no increase in blasts cells, neither myelofibrosis was found. New cytogenetic analysis showed a normal karyotype. The patient completed 12 cycles of azacitidine and thereafter, she lost the hematologic response, required transfusion therapy every 2-3 months again and was maintained only with supportive care during one year. She suffered an ischemic stroke and died two weeks later.

Discussion

The 5q- syndrome was first described with the presence of macrocytic anemia, normal or high platelet count, and hypolobulated megakaryocytes, with female predominance, and only 10% of patients developing clonal evolution that leads to an AML transformation¹.

The commonly deleted region (CDR) includes 1.5 megabases comprising 41 genes located at or near the 5q32-33.4 region. Genes in 5q associated with the MDS pathogenesis include: RPS14 (erythroid phenotype of 5q- syndrome), microRNAs miR-145 and miR-146 (causes elevated platelet counts and selective advantage to the 5q- clone), EGR1 (increases stem-cell self-renewal), CTNNA1 (hypermethylation of the remaining allele is associated with progression to AML), SPARC gene (probably haploinsufficiency could increase adhesion of the clone to the bone marrow)^{2,3}.

Lenalidomide is by far, the first line of treatment for this disease, even though access to lenalidomide may have economic limitations, however an analogue as thalidomide (with lower but documented responses in MDS), may be an option, as depicted in this case. In fact, this patient had clinical benefit, with transfusion independence for 3 years with mild neurologic toxicity. Pellagatti et al. studied the effects of lenalidomide in isolated erythroblast cultures from patients with del(5q) MDS, concluding that lenalidomide inhibited the growth of differentiated erythroblasts without affecting cytogenetically normal cells³. The presence of cell cycle-regulating phosphatases CDC25C and PP2A (encoded on 5q) are associated with favorable response to lenalidomide². Lenalidomide inhibits CDC25C dephosphorylation and suppresses the catalytic domain activity of PP2A, leading the MDM2 hyperphosphorylation and the consequent p53 degradation in erythroid progenitors^{2,6}. Patients with del(5q) MDS who fail to lenalidomide treatment have an increased risk for clonal evolution and progression to AML, with cumulative incidence at 5 years as high as 60%¹.

In MDS, hematopoietic cells not only have an increased proliferation rate, but also undergo excessive apoptosis mediated by cytokines (TNF- α , TGF- β , IL-1B, IL-6)⁷. Thalidomide selectively inhibits TNF- α production by enhancing the degradation of TNF- α mRNA⁷, it also inhibits angiogenesis induced by basic fibroblast growth factor⁸, as well as having immune modulatory effects. Thalidomide as monotherapy, was effective to achieve hematologic response in 19% of

erythropoietin non-responders, dose escalation was limited by its neurotoxicity⁶.

As described, clonal evolution constitutes part of the natural history of this disease group. In the presented case, progressive cytopenia appeared, and a complex karyotype was documented. As reported in the literature, patients with del(5q) syndrome without cytogenetic remission after treatment even with lenalidomide have a high risk of clonal evolution, and this risk might be even higher for patients treated with thalidomide as seen in our patient⁹. According with IPSS-R¹⁰ risk score, this patient evolved into a high risk category, where demethylating agents constitute the treatment of choice. The hypomethylating agents (HMAs) as azacitidine and decitabine have been shown to improve survival or delay disease progression in patients with higher-risk MDS¹¹. Azacitidine was initiated, attempting to get transfusion independence again and decrease the risk of AML transformation in our patient.

The case presented is particularly interesting since an initial suboptimal treatment with thalidomide, even though achieved hematologic response, later it allowed clonal evolution in this patient, who later, got an excellent response with the use of a demethylating agent.

Benefit with azacitidine has been demonstrated in clinical trials^{10,11}, including the reduction in risk of death. It is known that treatment with azacitidine increases survival in 26.2-50.8% in 1 year, as well as the mean time to AML transformation from 11.5 to 17.8 months. These benefits are widely accepted and therefore, it constitutes the first line of treatment in high risk MDS. Although the cost of treatment may not be affordable for all patients in developing countries, a pharmacoeconomic study showed that benefits of azacitidine are cost-effective in patients with MDS, even as a second line treatment as in our patient¹².

Conclusion

In the case presented, we demonstrate how thalidomide as single agent therapy may achieve transfusion independence in patients with 5q-syndrome, even for long periods of time which could be of particular interest for countries with low income; however there is no effect over genomics, noting in our patient that it worked only as a

support agent without modifying the progression of the disease, while azacitidine, on the other hand, remains as the standard therapy even with clonal evolution.

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