

Long-Term Response in a Patient with del(5q) Myelodysplastic Syndrome Who Discontinued Lenalidomide and Obtained a Good Response and Tolerance to Rechallenge

Francesco Pisani^a Giulia Orlandi^b Roberta Merola^b

Departments of ^aHematology and ^bClinical Pathology, Regina Elena National Cancer Institute, Rome, Italy

Key Words

Myelodysplastic syndromes · 5q– myelodysplastic syndrome · Lenalidomide

Abstract

Background: The introduction of the immunomodulatory drug lenalidomide has revolutionized the treatment of patients with myelodysplastic syndromes (MDS) and deletion of the long arm of chromosome 5. Treatment with lenalidomide results in transfusion independence in the majority of patients, but some questions remain unresolved, among them the duration of treatment. Moreover, a number of unexpected long-term remissions in patients who stopped lenalidomide for various reasons have been observed. **Case Report:** We report the case of a 60-year-old Caucasian male with deletion of the long arm of chromosome 5 and International Prognostic Scoring System (IPSS)-defined low-risk MDS who was treated with lenalidomide, achieving complete cytogenetic remission and erythroid response. After tapering off and interrupting the treatment, the patient relapsed and showed a new response by lenalidomide retreatment. Six years after the initial treatment, we registered a durable erythroid long-term response and good tolerance, but there was no evidence of a very profound cytogenetic response compared to using lenalidomide as a first-line treatment. Cytogenetic and fluorescence in situ hybridization together with hemoglobin level, mean corpuscular volume (MCV) and vitamin B₁₂ level helped us to monitor the patient response; during the various phases of lenalidomide treatment, MCV and vitamin B₁₂ normalization correlated with good response. **Conclusion:** Lenalidomide interruption and rechallenge in

Francesco Pisani
Department of Hematology
Regina Elena National Cancer Institute
Via Elio Chianesi, 53, IT-00128 Rome (Italy)
E-Mail fr.pisani@tiscali.it

some 5q⁻ MDS patients, with low risk according to the IPSS, is safe and feasible but does not result in a profound cytogenetic response.

© 2014 S. Karger AG, Basel

Introduction

Myelodysplastic syndromes (MDS) are clonal bone marrow disorders characterized by ineffective bone marrow hematopoiesis, peripheral blood cytopenias and risk of transformation to acute myeloid leukemia (AML). Patients are stratified according to the International Prognostic Scoring System (IPSS) into low-, intermediate-1-, intermediate-2- and high-risk categories [1]. Among cytogenetic abnormalities, partial or complete deletion of the long arm of chromosome 5 [del(5q)] is the most common cytogenetic abnormality found in MDS patients, occurring in 10–15% of all de novo MDS patients [2, 3] and in up to 30% of cases with abnormal karyotype. The prognosis of MDS cases with del(5q) worsens with additional cytogenetic changes and increase in blast percentages [4]. Treatment with the immunomodulatory drug lenalidomide has set a new standard for the management of low/intermediate-1-risk MDS with 5q⁻ in transfusion-dependent patients [5]. Lenalidomide suppresses the growth of MDS progenitors harboring 5q⁻, giving rise to a high frequency of transfusion independence (TI) and cytogenetic response and promotes erythroid lineage competence and colony-forming capacity [6]. Lenalidomide may restore transcriptional response to endogenous erythropoietin in MDS progenitors, suggesting that lenalidomide enhances cellular responsiveness to erythropoietin stimulation; moreover, p53 expression in erythroid precursors decreased in lenalidomide responders but is upregulated upon the emergence of resistance to lenalidomide [7].

The current treatment recommendation is to treat 5q⁻ with lenalidomide until relapse or transfusion dependence or progressive disease [8]. Consequences of the long-term effects of continuous immunomodulation with lenalidomide are unknown, and the question whether interruption of lenalidomide treatment is beneficial for patients in remission has never been formally addressed [9].

We herein report a patient with MDS with isolated 5q deletion and IPSS-defined low-risk MDS, who was treated with lenalidomide, achieving complete cytogenetic remission and erythroid response, and who after tapering off and interrupting the treatment relapsed. A new response was observed after re-exposure to lenalidomide, showing durable erythroid long-term response and good tolerance, but cytogenetic response was not very profound.

Case Report

A 60-year-old Caucasian male was first seen for the evaluation of macrocytic anemia, weakness and easy fatigue. Laboratory analyses confirmed the macrocytic anemia: hemoglobin (Hb) 10.6 g/dl; mean corpuscular volume (MCV) 109 fl with a normal reticulocyte count; white blood cell count (WBC) was $3.34 \times 10^9/l$; absolute neutrophil count (ANC) was $1.87 \times 10^9/l$, and platelet count was $215 \times 10^9/l$. Bone marrow aspirate and biopsy were performed revealing hypoplastic bone marrow with dyserythropoiesis, no ring sideroblasts were present, and micromegakaryocytes with single eccentric nuclei were also observed. Cytogenetic analysis showed 5q⁻ with no other abnormalities; at least 10 metaphases and whenever possible 20–25 metaphases were analyzed by the classical cytogenetic method. The karyotype was written as 46,XY,del(5)(q31). A diagnosis of MDS with isolated 5q⁻ was established, corresponding to the IPSS low-risk category. The serum erythropoietin level

Pisani et al.: Long-Term Response in a Patient with del(5q) Myelodysplastic Syndrome Who Discontinued Lenalidomide and Obtained a Good Response and Tolerance to Rechallenge

was ≤ 200 IU/l and the patient was transfusion-independent; therefore, we observed him periodically.

After 11 months, he showed a decline in the Hb level: Hb was 9.8 g/dl, MCV 112 fl and the serum erythropoietin level was less than 200 IU/l. We then treated the patient with 40,000 IU of erythropoietin α biweekly for 6 months. Despite erythropoietin support the patient had a continuous decline in Hb levels. After 7 months of this treatment, Hb was 7.9 g/dl, MCV was 110 fl, vitamin B₁₂ was 930 pg/ml (range 191–663), the bone marrow showed an increased dyserythropoiesis, and the fluorescence in situ hybridization (FISH) analysis, using LSI5q31 (EGR1)/D5S23, D5S721 probe (Abbott, Molecular Inc., Des Plaines, Ill., USA) on 200 interphase nuclei, permitted to detect a higher percentage of cells with 5q– since the diagnosis (65 vs. 45%). The patient refused transfusion and lenalidomide was initiated at a dose of 10 mg/day for 21 days every 4 weeks, together with aspirin as thromboprophylaxis (ANC was 1.6×10^9 /l and platelet count 301×10^9 /l). Weekly blood controls showed grade 3 neutropenia and growth factor (G-CSF) support was initiated biweekly from the second cycle of treatment to the fifth.

After 5 cycles of standard treatment, the patient obtained complete hematological and cytogenetic remission: Hb was 12.6 g/dl, MCV 98 fl, vitamin B₁₂ 600 pg/ml, WBC 4.4×10^9 /l, ANC 3.3×10^9 /l, and platelet count was 135×10^9 /l. We suspended the growth factor support and tapered off the dose of lenalidomide (initially 5 mg for 21 days every 4 weeks for 3 cycles and subsequently 5 mg every other day for 21 days every 4 weeks for 6 cycles). Then we treated him with 5 mg biweekly for 3 weeks of every 28-day cycle for 12 cycles, remaining transfusion independent and in complete hematological and cytogenetic remission (fig. 1; table 1), with a range of platelet count between 149 and 128×10^9 /l. After 1 year of this schedule, the patient had a cytogenetic relapse with 2/10 metaphases and 18% interphase nuclei showing a 5q– (fig. 1), but he remained transfusion independent (Hb 13.9 g/dl, MCV 100 fl, platelet count 128×10^9 /l, WBC 3.5×10^9 /l, ANC 1.09×10^9 /l and vitamin B₁₂ 831 pg/ml). However, we decided to stop lenalidomide treatment and observed him for 14 months; at this time, 5q– was detected in 8/10 metaphases and in 60% of the interphase nuclei (Hb 12.1 g/dl, MCV 108 fl, vitamin B₁₂ 792 pg/ml, platelet count 182×10^9 /l); the patient was rechallenged with lenalidomide 10 mg for 21 days every 4 weeks (fig. 1). No G-CSF was used but the patient restarted thromboprophylaxis with aspirin. He responded to the reintroduction of lenalidomide, achieving complete cytogenetic remission after 3 cycles and continuing lenalidomide at a standard dose of 10 mg until the sixth course [Hb was 14 g/dl (fig. 2), MCV decreased to 99 fl and vitamin B₁₂ decreased to 442 pg/ml, platelet count 122×10^9 /l, WBC 3.03×10^9 /l, and ANC 2.2×10^9 /l]. Cytogenetic and FISH analysis were negative and no blasts were detected in bone marrow aspirate. We reduced the dose at 10 mg biweekly for 3 weeks every 28 days for 4 months; then 5q– was detected in 44% interphase nuclei (fig. 1), karyotype was not available, Hb was 13.5 g/dl, MCV 100 fl and vitamin B₁₂ 280 pg/ml. Then we changed the schedule with the dose of 5 mg for 21 days every 4 weeks for 6 courses, when 4/10 metaphases and 22% of interphase nuclei showed 5q–; Hb was 13.9 g/dl, MCV 96 fl, vitamin B₁₂ 1,344 pg/ml, bone marrow blasts 3%, and a partial cytogenetic remission was obtained (fig. 1). Here we increased lenalidomide to 10 mg for 21 days every 4 weeks (6 cycles). In this period, we observed grade 3 neutropenia, and we started G-CSF once a week for 5 months. After these 6 cycles, 1/10 metaphases and 4% of interphase nuclei showed 5q–, no bone marrow blasts were observed, but the development of a new independent clone was detected by cytogenetic and FISH analyses, containing loss of the Y chromosome in 2/10 metaphases and in 28% of interphase nuclei (fig. 1). Other parameters were: Hb 14 g/dl, MCV 97 fl, vitamin B₁₂ 448 pg/ml, platelet count 105×10^9 /l, WBC 3.3×10^9 /l, and ANC 1.2×10^9 /l.

Pisani et al.: Long-Term Response in a Patient with del(5q) Myelodysplastic Syndrome Who Discontinued Lenalidomide and Obtained a Good Response and Tolerance to Rechallenge

We continued lenalidomide treatment for another 3 cycles at 10 mg dose, when 1/10 metaphases and 3% of interphase nuclei showed 5q- and 3/10 metaphases and 31% of interphase nuclei were positive for loss of the Y chromosome with Hb 14.3 g/dl, MCV 98 fl, vitamin B₁₂ 411 pg/ml, platelet count 117 × 10⁹/l, WBC 2.9 × 10⁹/l, and ANC 1.3 × 10⁹/l. At this point, we decided to reduce lenalidomide at 10 mg every other day for 21 days of every 28-day cycle, and this schedule was administered for 6 cycles; after that, 8/12 metaphases and 24% of interphase nuclei showed 5q- and 3/12 metaphases and 28% of interphase nuclei were positive for loss of the Y chromosome with bone marrow blasts 3%, Hb 12.2 g/dl, MCV 102 fl, vitamin B₁₂ 744 pg/ml, platelet count 132 × 10⁹/l, WBC 2.5 × 10⁹/l, and ANC 1.08 × 10⁹/l. Then we increased lenalidomide dosage at 10 mg for 21 days of every 4-week cycle; after 6 cycles, 7% of interphase nuclei showed 5q- and 38% loss of Y chromosome, bone marrow blasts 2%, Hb was 13.6 g/dl, MCV 97 fl, vitamin B₁₂ 682 pg/ml, platelet count 91 × 10⁹/l, WBC 2.42 × 10⁹/l, and ANC 1.17 × 10⁹/l; at present, this schedule is still administered. The patient has never taken a supplement of vitamin B₁₂, he continues thromboprophylaxis with aspirin (100 mg/day), no thrombotic events have so far been observed, he has a good quality of life, assessed with the Functional Assessment of Cancer Therapy-Anemia (FACT-An) questionnaire [10], and he continues to perform daily sport activity by jogging for 2 h a day since the first achievement of complete hematological and cytogenetic remission.

Discussion

Consequences of the long-term effects of continuous immunomodulation with lenalidomide are unknown. Furthermore, there is limited evidence that discontinuation of lenalidomide may lead to long-term transfusion freedom.

Our patient with IPSS-defined low-risk MDS with isolated 5q- within 12 weeks of initiating lenalidomide 10 mg achieved TI and complete hematological and cytogenetic remission. He maintained TI from February 2008 until March 2014 (6 years) also stopping lenalidomide for 13 months (December 2010 to December 2011); in many cases reported in the literature, the median duration of TI is 2 years. We observed a correlation between cytogenetic response and normalization of MCV and vitamin B₁₂ levels, with a decrease of the amount of abnormal interphase nuclei, showing 5q-, detected by FISH.

Long-term outcome data indicate that a cytogenetic response to lenalidomide therapy might offer a survival advantage, compared with cytogenetic nonresponders, and lenalidomide treatment does not increase AML progression risk, among lower-risk, transfusion-dependent MDS patients, but instead confers a possible benefit in red blood cell transfusion-dependent patients with del(5q) low- or intermediate-1-risk MDS [9, 11]. In our patient, after 5 cycles of standard treatment, we obtained complete hematological and cytogenetic remission; we then tapered off the dose of lenalidomide, and the patient remained transfusion independent and in complete hematological and cytogenetic remission for further 9 months (fig. 1, fig. 2). In November 2009, the patient had a cytogenetic relapse remaining transfusion independent; we, however, stopped lenalidomide and observed him. Subsequently the patient was rechallenged with lenalidomide and he responded to the reintroduction of lenalidomide intervention as other cases described by Giagounidis et al. [9], achieving complete cytogenetic remission after 3 cycles and continuing this dosage until the sixth course (July 2011). We continued to modulate the dose of lenalidomide on the basis of FISH analysis (table 1); in our patient, the reappearance of 5q- was not equivalent to transfusion dependence and as in other patient series he remained transfusion-free, without being

Pisani et al.: Long-Term Response in a Patient with del(5q) Myelodysplastic Syndrome Who Discontinued Lenalidomide and Obtained a Good Response and Tolerance to Rechallenge

exposed for many months to any medication [9]. MCV and vitamin B₁₂ levels, in our case, have always correlated with the hematologic and cytogenetic response, normalizing when the patient achieved complete remission and rising again to more than the normal reference value when the patient relapsed, indicating in our patient a variation in the promotion of effective erythropoiesis. Therefore, MCV and vitamin B₁₂ values may be very simple parameters to monitor regularly. To our knowledge, this observation has never been stressed in previous publications and monitoring those easily available parameters could help, together with cytogenetic and hematological analyses, to follow the response and eventually to modulate the lenalidomide schedule, in a manner as to reduce drug toxicity; specially if the patients maintain a good hematological response with TI, at least in low-risk MDS patients. Previously Sekeres et al. [12] analyzed the relationship between the development of treatment-induced cytopenias and the response to therapy in MDS. They specifically found that among lower-risk MDS patients with del(5q) whose platelet count decreased by ≥50%, packed red blood cell TI was likely to be achieved, as compared with patients not experiencing the same magnitude of thrombocytopenia; however, they did not analyze MCV and vitamin B₁₂ as parameters that predict the response. Also in our case we registered a platelet count of less than 150 × 10⁹/l (range 91–149 × 10⁹/l), except after 14 months of stopping treatment, when the platelet count was 182 × 10⁹/l and 5q– was detected in 60% of interphase nuclei; however, we still observed TI but Hb decreased to 12.1 g/dl. A platelet count decline was again evident after the restart of lenalidomide treatment; a platelet drop was also present when we used the schedule 5 mg for 21 days or every other day or biweekly. With the dose of 5 mg biweekly that, compared to the schedule of 5 mg every other day [13], was never published, we still had TI and a progressive normalization of the platelet count but eventually an increase in 5q– and interphase nuclei.

Six and a half years after the diagnosis and 5 years after the onset of lenalidomide treatment, we registered in our patient the development of a new independent clone with the loss of the Y chromosome, detected in both conventional cytogenetics and FISH. The deletion of the Y chromosome in men was not considered abnormal in a previous study [5]; the clinical association between the loss of the Y chromosome and AML/MDS is still debated because both phenomena are related to aging. It has been demonstrated that normal males start to lose the Y chromosome in bone marrow cells at the age of 60 years, and in a series of 142 patients with loss of Y chromosome the cases with karyotype, demonstrating less than 100% loss of the Y chromosome, were not statistically associated with AML/MDS [14].

Our patient was 60 years old at diagnosis and developed loss of Y chromosome in about 30% of cells at the age of 65, 5 years after the start of lenalidomide treatment, with periods of discontinuation of treatment and dose tapering. Clearly, the loss of Y chromosome is still a gray zone and we will thus continue to monitor our patient.

Treatment with lenalidomide improved health-related quality of life (FACT-An); improvements were apparent at week 12 and were significantly demonstrated through 6 years, with absolute change from baseline FACT-An scores exceeding 7 points.

Neutropenia grade 3 was the most common treatment-associated adverse event, no venous thromboembolism was registered, but aspirin as thromboprophylaxis was administered. Current recommendations state that treatment with lenalidomide in del(5q) MDS should be continued until disease progression [8]. The question whether interruption of lenalidomide treatment is beneficial in patients in remission has never been formally addressed. This concept is appealing for several reasons: first, it would reduce costs and side effects; second, the progression to AML in 5q– disease is not entirely understood. Reducing lenalidomide exposure would prevent a notional selective pressure of the compound on 5q– stem cells, facilitating disease progression. It has been speculated that continuous admin-

Pisani et al.: Long-Term Response in a Patient with del(5q) Myelodysplastic Syndrome Who Discontinued Lenalidomide and Obtained a Good Response and Tolerance to Rechallenge

istration of lenalidomide may lead to selective pressure on stem cells that induces genomic instability, resulting in acute leukemia transformation. Our patient, as other cases in the literature, remained in long-term complete cytogenetic remission without lenalidomide treatment, before showing reappearance of 5q- [15]. The reappearance of 5q- is not equivalent to transfusion dependence and many patients remain transfusion free for years without being exposed to lenalidomide; in our case, the restart of lenalidomide treatment did not result in a very profound cytogenetic response compared to using lenalidomide as a first-line treatment.

Conclusion

In our case, lenalidomide interruption was safe and feasible as also reported in other MDS patients with 5q- of low and intermediate-1 risk according to the IPSS. MCV and vitamin B₁₂ levels could help together with platelet count decline to predict the response.

References

- 1 Greenberg P, Cox C, LeBeau MM, Fenaux P, Morel P, Sanz G, et al: International scoring system for evaluating prognosis in myelodysplastic syndromes. *Blood* 1997;89:2079–2088.
- 2 Haase D, Germing U, Schanz J, Pfeilstocker M, Nosslinger T, Hildebrandt B, et al: New insights into the prognostic impact of the karyotype in MDS and correlation with subtypes: evidence from a core dataset of 2,124 patients. *Blood* 2007;110:4385–4395.
- 3 Solè F, Luño E, Sanzo C, et al: Identification of novel cytogenetic markers with prognostic significance in a series of 968 patients with primary myelodysplastic syndromes. *Haematologica* 2005;90:1168–1178.
- 4 Giagounidis A, Germing U, Strupp C, Hildebrandt B, Heinsch M, Aul C: Prognosis of patients with del(5q) MDS and complex karyotype and the possible role of lenalidomide in this patients subgroup. *Ann Hematol* 2005;84:569–571.
- 5 List A, Dewald G, Bennet J, Giagounidis A, Raza A, Feldman D, Powell B, Greenberg P, Thomas D, Stone R, Reeder C, Wride K, Patin J, Schmidt M, Zeldis J, Knight R: Lenalidomide in the myelodysplastic syndrome with chromosome 5q deletion. *N Engl J Med* 2006;355:1456–1465.
- 6 Komrokji RS, Lancet J, Swern A, Chen N, Paleveda J, Lush R, Saba H, List A: Combined treatment with lenalidomide and epoetin alfa in lower-risk patients with myelodysplastic syndrome. *Blood* 2012;120:3419–3424.
- 7 Wei S, Chen X, McGraw K, Zhang L, Komrokji R, Clark J, Caceres G, Billingsley D, Sokol L, Lancet J, Fortenberry N, Zhou J, Eksioglu EA, Sallman D, Wang H, Epling-Burnette PK, Djeu J, Sekeres M, Maciejewski JP, List A: Lenalidomide promotes p53 degradation by inhibiting MDM2 auto-ubiquitination in myelodysplastic syndrome with chromosome 5q deletion. *Oncogene* 2013;32:1110–1120.
- 8 Giagounidis A, Fenaux P, Mufti GJ, Muus P, Platzbecker U, Sanz G, et al: Practical recommendations on the use of lenalidomide in the management of myelodysplastic syndromes. *Ann Hematol* 2008;87:345–352.
- 9 Giagounidis A, Kulasekararaj A, Germing U, Radkowski R, Haase S, Petersen P, Göhring G, Busche G, Aul C, Mufti GJ, Platzbecker U: Long-term transfusion independence in del(5q) MDS patients who discontinue lenalidomide. *Leukemia* 2012;26:855–858.
- 10 Cella D: The functional assessment of cancer therapy-anemia (FACT-An) scale: a new tool for the assessment of outcomes in cancer anemia and fatigue. *Semin Hematol* 1997;34(suppl 2):13–19.
- 11 Kuendgen A, Lauseker M, List AF, Fenaux P, Giagounidis A, Brandeburg NA, Backstrom J, Glasmacker A, Hasford J, Germing U: Lenalidomide does not increase AML progression risk in RBC transformation-dependent patients with low- or intermediate-1-risk MDS with del(5q): a comparative analysis. *Leukemia* 2013;27:1072–1079.
- 12 Sekeres M, Maciejewski JP, Giagounidis A, Wride K, Knight R, Raza A, List A: Relationship of treatment-related cytopenias and response to lenalidomide in patients with lower-risk myelodysplastic syndromes. *J Clin Oncol* 2008;26:5943–5949.
- 13 Defina M, Rondoni M, Gozzetti A, Aprile L, Chitarrelli I, Fabbri A, Lauria F, Bocchia M: Lenalidomide on alternative days is effective in myelodysplastic syndrome with 5q-deletion. *Br J Haematol* 2009;148:483–484.
- 14 Zhang LJ, Shin ES, Yu X, Li B: Molecular genetic of Y chromosome loss in male patients with hematological disorder. *Chin Med J* 2007;120:2002–2005.

Pisani et al.: Long-Term Response in a Patient with del(5q) Myelodysplastic Syndrome Who Discontinued Lenalidomide and Obtained a Good Response and Tolerance to Rechallenge

- 15 Tehranchi R, Woll PS, Anderson K, Buza-Vidas N, Mizukami T, Mead AJ, et al: Persistent malignant stem-cells in del(5q) myelodysplasia in remission. *N Engl J Med* 2010;363:1025–1037.

Table 1. Time and lenalidomide treatment schedules

October 2007	Lenalidomide 10 mg, 1–21 days
January 2008	After 5 cycles, lenalidomide 10 mg, 1–21 days
February 2008	Lenalidomide 5 mg, 1–21 days
April 2008	After 3 cycles, lenalidomide 5 mg, 1–21 days
October 2008	After 6 cycles, lenalidomide 5 mg every other day, 1–21 days
November 2009	After 12 cycles, lenalidomide 5 mg biweekly, 1–21 days
February 2011	After 14 months, without lenalidomide
May 2011	After 3 cycles, lenalidomide 10 mg, 1–21 days
August 2011	After 6 cycles, lenalidomide 10 mg, 1–21 days
November 2011	After 3 cycles, lenalidomide 10 mg biweekly, 1–21 days
April 2012	After 6 cycles, lenalidomide 5 mg, 1–21 days
November 2012	After 6 cycles, lenalidomide 10 mg, 1–21 days
March 2013	After 9 cycles, lenalidomide 10 mg, 1–21 days
September 2013	After 6 cycles, lenalidomide 10 mg every other day, 1–21 days
March 2014	After 6 cycles, lenalidomide 10 mg, 1–21 days

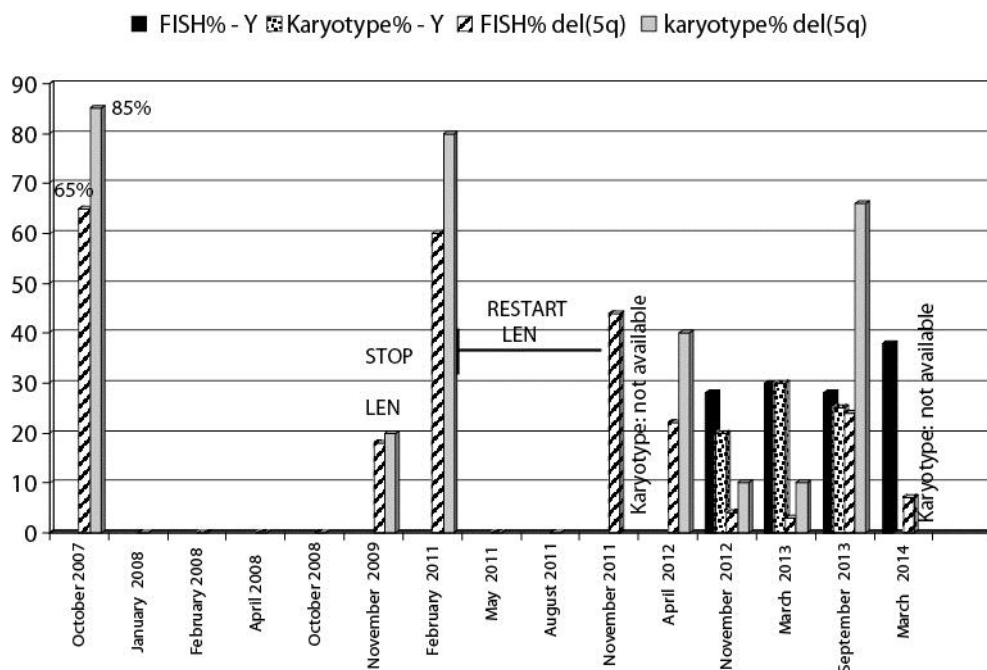


Fig. 1. Sequential bone marrow karyotype and FISH studies: percentage of del(5q) and Y chromosome loss from October 2007 to March 2014 during the various phases of lenalidomide treatment.

Pisani et al.: Long-Term Response in a Patient with del(5q) Myelodysplastic Syndrome Who Discontinued Lenalidomide and Obtained a Good Response and Tolerance to Rechallenge

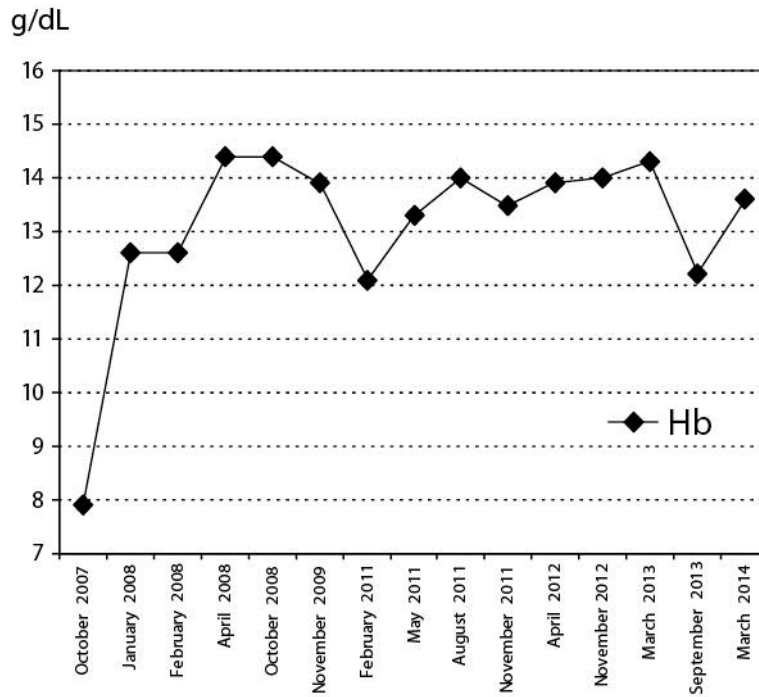


Fig. 2. Changes in Hb levels from October 2007 to March 2014 under various phases of lenalidomide treatment.