Unusual clonal evolution involving 5q in a case of myelodysplastic syndrome with deletion 5q 31 treated with lenalidomide

Lenalidomide is a very active drug in myelodysplastic syndrome with del (5q). We report such a patient treated with this drug who developed unusual complex cytogenetic abnormalities, which were elucidated by multi-FISH and FISH analysis as jumping translocations involving the long arm of chromosome 5, that resulted in an increase of 5q copies. This unusual findings is discussed in the context of resistance to lenalidomide observed in this patient.

Haematologica. 2008 Feb; 93:(2)315-316. DOI: 10.3324/haematol.11917

The *5q- syndrome*,[1] is characterized by female predominance, refractory anemia with macrocytosis, normal or elevated platelet counts, frequent erythoblastopenia, abnormal monolobulated megakaryocytes, no excess of marrow blasts count, isolated del(5)(q13q33), rare progression to overt leukemia and prolonged survival.[2] Lenalidomide (Revlimid; Celgene Corporation) is a thalidomide analogue with particular activity in MDS with del(5q), especially in the *5q- syndrome*, leading to transfusion independence and cytogenetic response in over two-thirds of cases.[3] We report a patient with the *5q- syndrome*, who had resistance to lenalidomide treatment, associated to emergence of clonal evolution involving chromosome.[5]

A 50-year-old woman presented at our institution in December 2005 with anemia (hemoglobin 7.1 g/dL), low WBC count (1.6×10^9/L) neutropenia (0.46×10^9/L) and normal platelet count (256×10^9/L). Anemia had required transfusion of 8 red blood cell (RBC) units in the previous 4 months. The bone marrow examination showed abnormal megakaryocytes typical of the*5q- syndrome*, erythroblasts with dysplastic features and 4% blasts. Cytogenetic analysis revealed: 46, XX, del(5)(q31q35) in 19 out of 28 examined mitoses. Hybridization with EGRF1 specific probe (Abbott diagnostic, Rungis, France) located on 5q31, showed deletion in 75% of the cells. The patient received lenalidomide 5 mg/day orally from February 2006. During the following 4 months, anemia persisted and the patient required transfusion of 8 RBC units. After these 4 months, WBC count was in the normal range, platelet count was 130×10^9/L, bone marrow examination showed 4% blasts and no further dysmegakaryopoeisis but persistent dyserythropoiesis. Karyotype showed 46, XX, del(5)(q31q35) in 22 out of 26 examined metaphases. The dose of lenalidomide was increased to 10 mg once daily, 3 weeks every month. After another four months, the red blood cell transfusion requirement remained unchanged and lenalidomide was stopped. Bone marrow examination revealed erythroid hyperplasia with megaloblastoid features, decrease in granulocytes, recurrence of typical dysmegakaryopoiesis, without excess of blasts.

Cytogenetic examination showed a complex karyotype with del(5)(q31q35) associated with 2-4 derivative chromosomes consisting of the long arm of chromosome 5 and variable partners as short arm: 45-46,XX, del(4)(q21q35)[7],add(5)(p10)[5],+add(5)(p10)del(5)(q31q35)[3], del(5)(q31q35),dic(5;19)(q11, ?),+dic(5;6)(q11;p11)[8], der(10)t(10;12)(q24;q?)[8],der(12)t(12;?)(q11;q?)[12], add(12)(q14)[4],der(14)t(14;20),dic(19;22)[5],+1-2mar[cp25]. Multi-FISH analysis (MetaSystem, Altlusheim, Germany) clarified those findings, showing 4q; 6p ; 10q, 12q ;19 or 21q as chromosome 5 partners in different sub clones (Figure 1). Hybridization with EGRF1 probe, showed 3 spots in 45% of cells and 4 spots in 5%. Hybridization with centromeric probes (pGA-16 and pEDZ6, a gift from S. Romana, Hopital Necker Paris) confirmed the dicentric dic(5;6) in 30% of the cells. The patient died in December 2006 from lung infection.

Our patient showed no erythroid response to lenalidomide and clonal cytogenetic evolution that was unusual in the *5q- syndrome*. The cytogenetic evolution with numerous 5q derivatives resulting from unbalanced translocations between different partners had not, to our knowledge, been previously described, with chromosome 5. It suggests jumping translocations (JT) rarely described in different hematologic malignancies including lymphoma, myeloma, and AML or ALL.[4,5] JT are characterized by relocalization of the same part of a donor chromosome to several recipient chromosomes, usually arising during disease progression or in complex karyotypes, and associated with poor prognosis.[6,7] In our case JT are associated with other abnormalities of chromosome 5.

In fact, in MDS with del(5q) treated with lenalidomide, emergence of cytogenetic abnormalities in different clones, not associated with overt disease progression, have often been observed in patients responding to the drug.[3] They mainly consisted of trisomy 8 or 7q abnormalities and were often transient. To our knowledge, this is the first report of clonal evolution involving chromosome 5 occurring during the evolution of MDS with isolated del(5q).

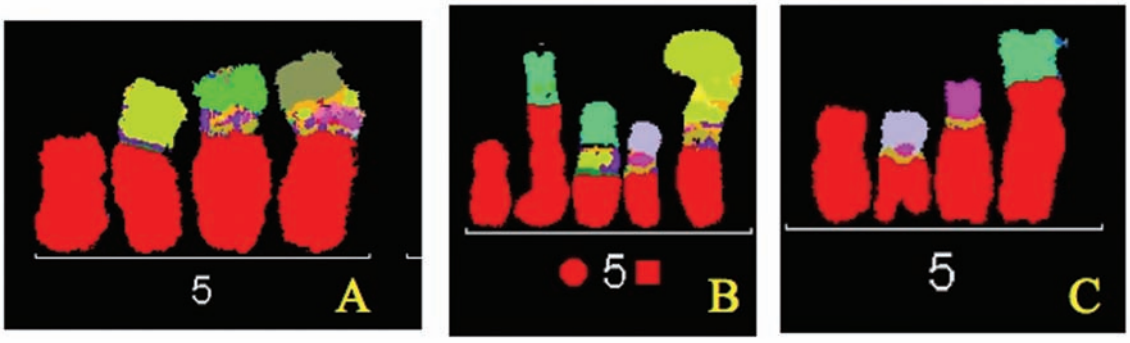

Figure 1. Representative M-FISH partial karyotype of the patient: from left to right 3 mitoses are shown respectively mitose A: one del(5)(q31q35), derivative chromosomes 5 dic(5;6)(p11;q11), dic(4;5)(q11;p11), dic (5;10)(p11;q11). Mitoses B del(5q), derivatives 5 fused with respectively chromosomes 12q, 6 and 12q; 21q and 6q. Mitose C: del 5q, derivatives 5 fused with respectively chromosomes 21; 19 and 12.

Although its exact mechanism remains unknown, lenalidomide has multiple biologic activities, including anti-angiogenesis, immunomodulation, anti-cytokine, and direct toxic effects on marrow cells carrying del(5q)4. Up regulation of the tumor suppressor gene SPARC located in 5q31 was recently implicated in the effect of the drug.[9] Whether or not treatment with lenalidomide was a triggering factor for this chromosomal evolution is uncertain. However, it resulted in an increase in the number of 5q copies (as confirmed by FISH analysis using a EGR1 probe). Because lenalidomide appears to exert a direct cytotoxic effect on hematopoietic cells with 5q deletion, genetic events leading to an increase in copies of 5q could represent a mechanism of resistance to the drug, as seen for example in CML treated with imatinib, where amplification of the BCR/ABL fusion gene may occur.[10]

Virginie Eclache, Anna Da Rocha, Génevieve Le Roux, and Pierre Fenaux

Services d'Hematologie Clinique et Biologique, Hôpital Avicenne, Université Paris-XIII, APHP, Bobigny, France

Key words: lenalidomide, myelodysplastic syndromes, del(5q) MDS, transfusion-dependent, case study.

Correspondence: Virginie Eclache, Services d'hematologie clinique & biologique, Hôpital Avicenne, Universite Paris-XIII, APHP, 125, rue de Stalingrad, 93000 Bobigny, France
E-mail: virginie.eclache@avc.ap-hop-paris.fr

References

1. Van den Berghe H, Cassiman JJ, David G, Fryns JP, Michaux JL, Sokal G. Distinct haematological disorder with deletion of long arm of no. 5 chromosome. Nature 1974;251:437-8 .
2. Giagounidis AA, Germing U, Haase S, Hildebrandt B, Schlegelberger B, Schoch C, et al. Clinical, morphological, cytogenetic, and prognostic features of patients with myelodysplastic syndromes and del(5q) including band q31. Leukemia 2004; 18:113-9.
3. List A, Dewald G, Bennett J, Giagounidis A, Raza A, Feldman E, et al. Lenalidomide in the myelodysplastic syndrome with chromosome 5q deletion. N Engl J Med 2006; 355:1456-65.
4. Bernard M, Lemee F, Picard F, Ghandour C, Drenou B, Le Prise PY, Lamy T. Jumping translocation in acute leukemia of myelomonocytic lineage: a case report and review of the literature. Leukemia 2000;14:119-22.
5. Najfeld V, Hauschildt B, Scalise A, Gattani A, Patel R, Ambinder EP, et al. Jumping translocation in leukemia. Leukemia 1995;9:634-9.
6. Busson le Coniat M, Brizard F, Smadja NV, Maarek O, Der Sarkissian H, Berger R. Intertitial telomere repeats in translocation of hematopoietic disorders. Leukemia 2000; 14:1630-3.
7. Wan TS, Ma SK, Chow EY, Li YH, Lin SY, Chan LC. Pathogenesis of jumping translocations: a molecular cytogenetic study. Leuk Res 2004;28:1075-9.
8. Dredge K, Horsfall R, Robinson SP, Zhang LH, Lu L, Tang Y, et al. Orally administered lenalidomide (CC-5013) is anti-angiogenic in vivo and inhibits endothelial cell migration and Akt phosphorylation in vitro. Microvasc Res 2005;69: 56-63.
9. Pellagatti A, Jädersten M, Forblom AM, Cattan H, Christenson B, Emanuelsson E, et al. Lenalidomide inhibits the malignant clone and up-regulates the SPARC gene mapping to the commonly deleted region in 5q- syndrome patients. Proc Natl Acad Sci USA 2007;104:11406-11.
10. Hochhaus A, Kreil S, Corbin AS, La Rosee P, Muller MC, Lahaye T, et al. Molecular and chromosomal mechanisms of resistance to imatinib (STI571) therapy. Leukemia 2002; 16: 2190-6.