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## **Response to lenalidomide in patients with myelodysplastic syndrome with deletion 5q: clinical and cytogenetic analysis of a single centre series**

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Abstract: Introduction

Interstitial deletions of 5q31 are the most common abnormalities in myelodysplastic syndromes (MDS). Lenalidomide induces cytogenetic remissions and abolishes transfusion needs in patients with low-risk MDS and del(5q).

Material and methods

This prospective study reports clinical and cytogenetic responses to lenalidomide in 9 patients with MDS and del(5q), half of whom had one additional cytogenetic abnormality, and compares conventional cytogenetics and FISH in the assessment of del(5q).

Results

All patients achieved complete erythroid response and transfusion independence at a median of 8 weeks of treatment and maintain the response at the last follow up. Two patients interrupted treatment for more than 17 months without losing hematologic response. Two other patients lost the complete cytogenetic response after more than 24 months of treatment, although no changes in the hemoglobin level were observed.

Conclusions

FISH may have higher sensitivity to detect cells harbouring del(5q) at diagnosis and over treatment.

Response to Reviewers: Dear editors,

We completely agreed with your critics, but we felt limited by the number of words admitted for a letter, as well as by the number of tables. We were prepared to publish this paper as a short communication, but by revising your recent publications we decided that our data would be more adequate for a letter. As you surely confirmed our text file had around the limit 500 words, so we did not change the text much. Finally, we tried to reunite all our data in only one table (although we believe that it would result better in two).

We continue to consider our data raises very important points for the management of patients with MDS treated with lenalidomide. We are at your complete disposal for any other question or change that you believe important before publication.

**\*Conflict of interest**

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**Letter to the editor**

1  
2 **Title:** Response to lenalidomide in patients with myelodysplastic syndrome with deletion 5q: clinical and  
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4 cytogenetic analysis of a single centre series  
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30 **KEYWORDS:** Myelodysplastic syndrome, chromosome 5q deletion, lenalidomide, cytogenetics  
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**GLOSSARY OF ABBREVIATIONS:**

34  
35  
36 RAEB-1: refractory anemia with excess of blasts type 1  
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38 RCMD: refractory citopenia with multilineage dysplasia  
39

40 IPSS: international prognostic scoring system  
41

42 BM: bone marrow  
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44 CC: conventional karyotype  
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46 FISH: fluorescence in situ hybridization  
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48 Hb: Hemoglobine  
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50 MRD: minimal residual disease  
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Dear editor,

1 We assessed clinical and cytogenetic responses to lenalidomide in nine transfusion dependent patients  
2 with myelodysplastic syndrome (MDS) with deletion 5q (del5q) (Table 1). One patient was classified as  
3 RAEB-1, seven as RCMD and one as unclassified MDS. Six patients had low risk and three intermediate-  
4 1 risk according to the IPSS. BM samples were analysed by CC and by FISH every six months. All  
5 patients received Lenalidomide 10 mg daily during 21 days each cycle, with adjustments according to  
6 tolerance.

7  
8 Five of the patients had del5q with one additional chromosomal abnormality.

9  
10 Reciprocal translocations are rare in MDS [1, 2]. Patient #2 had a primary t(6;11)(q21;q23) and acquired  
11 the del(5q), which supports a higher genetic instability. Deletion of MLL gene was excluded by FISH.

12  
13 Individual studies suggested that a constitutional trisomy 8 mosaicism may be a first mutation in a  
14 multistep carcinogenic process [3]. Patient #4 had a constitutional trisomy 8, but after 91 months of  
15 follow up without treatment no leukemic evolution has been observed.

16  
17 Patient #8 had an isolated trisomy 9 detected by CC, but due to high clinical and morphological suspicion  
18 of 5q minus syndrome FISH was performed, with 5q31 deletion being detected in 9% of the nuclei. We  
19 question as to whether treatment response depended of abolishing such a low 5q deleted cell burden.

20  
21 Patients #3 and #4 interrupted treatment and have been followed for 17 and 19 months, respectively. All  
22 patients had persistent complete erythroid response and transfusion independence after a median of 17  
23 months (6-26) of follow-up, including the ones who stopped treatment. Five patients achieved complete  
24 cytogenetic response, but two of them lost it after more than 24 months of treatment, without changes in  
25 Hb level. In these two cases, FISH studies performed 6 months before reappearance of del5q metaphases  
26 revealed  $\geq 5\%$  of 5q- cells.

27  
28 Most published data of lenalidomide in MDS comes from multicentric trials. In our single centre series  
29 we confirm that patients with del5q are those who better respond to lenalidomide [4]. Since molecular  
30 methods to detect MRD are lacking, FISH has been studied as a more sensitive technique to predict  
31 response to lenalidomide [5]. Taking the cut-off of  $\geq 5\%$  of cells with del5q to consider FISH as positive,  
32 the results between CC and FISH were concordant in 88% of the studies. It is likely that a higher number  
33 of FISH 5q deleted cells can be found before reappearance of an abnormal karyotype during treatment  
34 with lenalidomide, but more cases are needed to establish whether FISH can or not predict the loss of  
35 cytogenetic complete response in treated patients.

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With lenalidomide the quality of life of a mainly old population has been improved by avoiding transfusional side effects in del5q patients. Published data suggest that lenalidomide should be maintained until loss of erythroid or cytogenetic response or until intolerance [6]. However, authors showed that complete suppression of the del5q clone was not required for transfusion independence [7]. We have shown that patients that interrupt lenalidomide can sustain hematologic response even with the malignant clone in bone marrow, and that complete cytogenetic response can be lost during treatment without compromising the erythroid response.

## BIBLIOGRAPHY

1. Haase D, Germing U, Schanz J, Pfeilstocker M, Nosslinger T, Hildebrandt B, Kundgen A, Lubbert M, Kunzmann R, Giagounidis AA, Aul C, Trumper L, Krieger O, Stauder R, Muller TH, Wimazal F, Valent P, Fonatsch C, Steidl C (2007) New insights into the prognostic impact of the karyotype in MDS and correlation with subtypes: evidence from a core dataset of 2124 patients. *Blood* 110:4385–4395.
2. Haase D (2008) Cytogenetic features in myelodysplastic syndromes. *Ann Hematol* 87:515–526.
3. Steensma DP, List A (2005) Genetic Testing in the Myelodysplastic Syndromes: Molecular Insights Into Hematologic Diversity. *Mayo Clin Proc* 80(5):681-698.
4. List A, Dewald G, Bennett J, Giagounidis A, Raza A, Feldman E, Powell B, Greenberg P, Thomas D, Stone R, Reeder C, Wride K, Patin J, Schmidt M, Zeldis J, Knight R (2006) Lenalidomide in the myelodysplastic syndrome with chromosome 5q deletion. *N Engl J Med* 355:1456-1465.
5. Haferlach C, Bacher U, Tiu R, Maciejewski JP, List A (2008) Myelodysplastic syndromes with del(5q): indications and strategies for cytogenetic testing. *Cancer Genetics and Cytogenetics* 187:101-111.
6. Giagounidis A, Fenaux P, Mufti GJ, Muus P, Platzbecker U, Sanz G, Cripe L, Lilienfeld-Toal MV,

1 Wells RA (2008) Practical recommendations on the use of lenalidomide in the management of  
2 myelodysplastic syndromes. *Ann Hematol* 87:345–352.  
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6 7. Giagounidis AA, Haase S, Heinsch M, Gohring G, Schlegelberger B, Aul C (2007) Lenalidomide in  
7 the context of complex karyotype or interrupted treatment: case reviews of del(5q) MDS patients with  
8 unexpected responses. *Ann Hematol* 86:133–137.  
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**Table 1. Patients characteristics**

	Age (years)	Sex	Hb (mg/dl)	Neut (x10 <sup>9</sup> /L)	Plat (x10 <sup>9</sup> /L)	Karyotype	Initial FISH <sup>1</sup>	Transfusional support <sup>2</sup>	Treatment with Lenalidomide <sup>3</sup>	Cytogenetic f.u. (during treatment)		Hb at last f.u.(mg/dl)
										CC <sup>4</sup>	FISH <sup>1</sup>	
1	77	F	8,8	0,6	298	46,XX,del(5)(q13q31)[11] /46,XX[7]	44	48	25	0/20 0/20 1/20	1 6,3 6	12,1
2	78	M	8,4	1,0	450	46,XY,t(6;11)(q21;q23)[8] /46,idem,del(5)(q13q31)[12]	63	90	27	2/20 3/20 4/20 2/20	7 1,4 12 27	12,8
3	73	F	9,5	2,7	349	46,XX,del(5q)(q21q33)[10] /45,idem,-12[3]/46,XX[6]	68	30	30	9/20	21	13,2
4	45	F	8,5	1,5	713	47,XX,+8[3] /46,XX,del(5)(q13q33)[22]	48	14	11	2/20 12/20	6,2 56	13,0
5	73	F	10,2	1,3	452	46,XX,del(5)(q22q33)[29]	84	22	5	0/20 0/30 0/30 1/20	0 1,8 5 2,5	13,1
6	76	F	10,0	2,2	236	46,XX,del(5)(q13q33)[17] /46,XX[3]	37	26	8	0/20	0	11,8
7	64	M	10,8	2,4	361	46,XY,del(5)(q14q34)[5] /46,XY[15]	25	4	10	0/20	0	12,6
8	79	F	8,7	0,8	490	47,XX,+9[2]/46,XX[18]	9	6	8	0/20	0	12,3
9	92	F	9,8	2,6	165	46,X,t(X;20)(q13;p11.2), del(5)q13q31[20]	73	8	6	17/20	92	11,1

Hb: hemoglobine; Neut: neutrophils; Plat: platelets; RBC: red blood cell; F.U.: follow-up

<sup>1</sup> percentage of del(5)(q31) cells observed; <sup>2</sup> number of red blood cell units transfused prior to initiating lenalidomide; <sup>3</sup> number of treatment cycles until last follow-up;

<sup>4</sup> number of pathological metaphases over total observed