ELSEVIER

Cancer Genetics and Cytogenetics 183 (2008) 89–93

Cancer Genetics and Cytogenetics

FLT3 internal tandem duplication during myelodysplastic syndrome follow-up: a marker of transformation to acute myeloid leukemia

Ronald Feitosa Pinheiro[a], Eloisa de Sá Moreira[b], Maria Regina Régis Silva[c], Fernando Lopes Alberto[b], Maria de Lourdes L.F. Chauffaille[a,b,*]

[a]*Section of Hematology and Hemotherapy, Federal University of Sao Paulo–UNIFESP-EPM, Rua Botucatu,740, 3° andar, CEP 04023-900, São Paulo, SP, Brazil*

[c]*Section of Applied Pathology, Federal University of Sao Paulo—UNIFESP-EPM, São Paulo, SP, Brazil*

[b]*Fleury Institute, São Paulo, SP, Brazil*

Received 11 December 2007; received in revised form 15 February 2008; accepted 20 February 2008

Abstract Myelodysplastic syndrome (MDS) is a clonal hematopoietic stem cell disorder characterized by ineffective hematopoiesis and risk for evolving to acute leukemia. Some molecular abnormalities related to acute myeloid leukemia (AML) transformation have been reported, such as *FLT3* (FMS-like tyrosine kinase 3) mutations. *FLT3*, a member of the class 3 receptor tyrosine kinase family, mediates stem cell proliferation and differentiation, and its mutations, internal tandem duplication (ITD) and Asp835, have been reported in rare MDS patients. We studied *FLT3* ITD, prospectively, in 50 MDS patients at diagnosis, at 6 and 12 months follow-up, and at any other time-point if AML transformation was detected. *FLT3* ITD was not observed at diagnosis, but during follow-up the mutation was present in 2 of 50 patients (4%). Of these, one case exhibited *FLT3* ITD at the end of the 6 months of follow-up in ~8% of bone marrow cells; this case evolved into AML at 8 months, at which time *FLT3* ITD was present in ~85% of bone marrow cells. The other case exhibited *FLT3* ITD in 68% of bone marrow cells at 7 months, precisely at the time of AML transformation. Although rare in MDS, *FLT3* ITD is associated with a high probability of evolution to AML.

1. Introduction

Myelodysplastic syndrome (MDS) is a clonal hematopoietic stem cell disorder characterized by ineffective hematopoiesis, peripheral cytopenias, and additional risk of evolving to acute leukemia in ⩽30% of the cases [1]. Disease progression has been associated with decrease in telomere length and inactivation of tumor supressor genes *TP53* (alias *P53*) and *CDKN2B* (alias *P15*) [1]. Recently, *FLT3* mutations have been associated with AML transformation [2].

FMS-like tyrosine kinase 3 (*FLT3*), a member of the class 3 receptor tyrosine kinase family, is more commonly expressed on hematopoietic progenitor cells and mediates stem cell proliferation and differentiation [3,4]. There are two types of activating *FLT3* mutations in hematological neoplasias. The first and most common one is an internal tandem duplication (ITD), which can be detected in ⩽30% of younger adults with acute myeloid leukemia (AML) and with a lower frequency (3–6%) in MDS [5–7].

FLT3 ITD in the JM domain has been reported to result in constitutive activation of FLT3 kinase, with subsequent activation of proliferative pathways [8]. These mutations would interfere with the normal kinase-inhibitory function of the JM domain, leading to kinase activation independent of the ligand.

The aim of this prospective study was to detect *FLT3* ITD in 50 MDS patients during 1 year of follow-up, from the diagnosis of MDS to the follow-up at 12-months, and to determine whether *FLT3* ITD is correlated with AML evolution.

2. Patients, materials, and methods

2.1. Patients

The study population was 50 patients diagnosed with MDS according to WHO criteria [9]. Screening for *FLT3* ITD was performed at diagnosis and at 6 and 12 months of follow-up (or at AML transformation, if sooner). Patients

* Corresponding author. Tel.: +55-1-5576-4240; fax: +55-11-5571-8806.

E-mail address: chauffaill@hemato.epm.br (M.deL.L.F. Chauffaille).

0165-4608/08/$ – see front matter
doi:10.1016/j.cancergencyto.2008.02.006

were classified according to the International Prognosis Scoring System [10] (Table 1). Karyotype analysis was performed by G-banding at diagnosis and at 6 and 12 months of follow-up (or at transformation, if sooner) (Table 2).

2.2. Detection and quantification of FLT3 ITD in bone marrow cells

Genomic DNA was extracted from bone marrow (BM) cells using the QIAamp blood mini kit (Qiagen, Valencia, CA). Two to four microliters (~100 ng) of DNA was subjected to polymerase chain reaction (PCR) in 15-L-reactions containing 6 μL of Eppendorf MasterMix (Eppendorf, Westbury, NY) and 4 pmol of each of the primers FLT 3-14F1 (5′-6FAM-TGCCTATTCCTAACTGACTCATC-3′) and FLT3-15R1 (5′-TCTTTGTTGCTGTCCTTCCAC-3′), designed using Primer 3 [11]. The PCR program consisted of denaturation at 94°C for 20 seconds, annealing at 57°C for 30 seconds, and extension at 72°C for 45 seconds, with an initial preheating at 94°C for 5 minutes and a final extension at 72°C for 20 minutes. After dilution (1:20) in water, 1 μL of each PCR product was mixed with 9 μL of HiDi formamide (Applied Biosystems [ABI], Foster City, CA) and 0.5 μL of GeneScan 500-ROX size marker and was denatured for 5 minutes at 95°C. Samples were analyzed on an ABI PRISM 3100 genetic analyzer, with the aid of GeneScan software version 3.7.1. The percentage of cells harboring the mutation was calculated based on the areas under the curves representing the wild (397 bp) and the ITD (>397) alleles.

2.3. Sequencing of PCR products

Selected samples were amplified according to the protocol just described, using an unlabeled version of primer FLT3-14F1. The PCR products were purified either directly or after agarose gel electrophoresis, followed by band excision using the GFX PCR DNA and gel purification kit (Amersham Biosciences, Piscataway, NJ). Sequencing reactions were performed in both directions with the ABI PRISM BigDye Terminator version 3.0 cycle sequencing kit and either of the internal primers FLT3-14F2 (5′-GCAATTTAGGTATGAAAGCCAGC-3′) and FLT3-15R2 (5′-CTTTCAGCATTTTGACGGCAACC-3′) [12], according to the manufacturer's instructions. After ethanol–sodium acetate precipitation, samples were analyzed on an ABI PRISM 3100 Genetic Analyzer.

3. Results

The incidence of *FLT3* ITD was 2/50 (4%) (Cases 3 and 46), detected only during follow-up, not at diagnosis. At the end of 6 months of follow-up, case 3 exhibited *FLT3* ITD (confirmed by sequencing) in ~8% of bone marrow cells. This patient evolved into AML at 8 month, and at this time *FLT3* ITD was present in ~85% of bone marrow cells

Table 1
Age, sex, and WHO, FAB, and IPSS classification of 50 MDS patients studied for *FLT3* ITD mutation

Case[a]	Age/Sex	WHO	FAB	IPSS
1	93/M	RA	RA	L
2	66/M	RCDM	RA	I-1
3	***87/M***	***RCDM-RS***	***RARS***	***I-1***
4	64/F	RA	RA	I-1
5	77/M	RCDM	RA	L
6	76/M	RCDM	RA	I-1
7	70/M	RARS	RARS	L
8	69/M	RCDM	RA	I-1
9	90/M	RCDM	RA	I-1
10	75/M	RCDM	RA	L
11	90/F	RA	RA	L
12	59/M	RCDM-RS	RARS	I-1
13	22/M	RCDM	RA	I-1
14	70/M	RARS	RA	L
15	79/M	5q−	RA	L[19]
16	56/M	RA	RA	L
17	60/M	RCDM	RA	I-1
18	60/F	Tx-related	RA	—
19	62/M	RCDM	RA	I-1
20	70/F	RCDM	RA	I-1
21	88/F	RAEB-2	RAEB	H
22	81/M	RAEB-2	RAEB	I-2[20]
23	70/F	RARS	RARS	L
24	60/F	RCDM-RS	RARS	I-1
25	71/F	RAEB-1	RAEB	I-2
26	29/F	RCDM	RA	I-1
27	16/F	RCDM	RA	I-1
28	80/M	RAEB-2	RAEB	I-2
29	87/M	RCDM	RA	I-1
30	83/M	RCDM	RA	I-1
31	58/F	RCDM	RA	I-1
32	74/F	RCDM	RA	I-1
33	40/F	Tx-related	RA	—
34	69/F	RCDM	RA	I-1
35	62/F	Unclassified	RA	I-1[21]
36	49/M	RAEB-2	RAEB	H
37	78/M	RCDM	RA	?
38	63/M	RAEB-2	RAEB	?
39	71/F	MDS-U	RA	?
40	63/F	RARS	RARS	L
41	80/M	5q−	RA	L[19]
42	66/M	RARS	RARS	I-1
43	81/M	RCDM	RA	I-1
44	62/F	RCDM	RA	I-1
45	64/F	RCDM	RA	I-1
46	***60/F***	***RCDM-RS***	***RARS***	***I-1***[13]
47	70/F	RCDM-RS	RARS	I-1[22]
48	74/M	RARS	RARS	L
49	47/F	RCDM	RA	I-1
50	68/M	5q−	RA	L[19]

Abbreviations: AML, acute myeloid leukemia transformation; F, female; FAB, French–American–British classification; H, high risk; I-1, intermediate risk 1; I-2, intermediate risk 2; IPSS, International Prognosis Scoring System; ITD, internal tandem duplication; L, low risk; M, male; MDS-U, myelodysplastic syndrome, unclassifiable; RA, refractory anemia; RAEB, refractory anemia with excess of blasts; RARS, refractory anemia with ringed sideroblasts; RCDM, refractory cytopenia multilineage dysplasia; RCDM-RS, refractory cytopenia multilineage dysplasia with ringed sideroblasts; Tx-related, therapy related (i.e., secondary to treatment); 5q−, 5q− syndrome; —, not evaluated, secondary MDS; ?, not possible to evaluate.

[a] Of the 50 cases, only 2 exhibited *FLT3* ITD mutation: cases 3 and 46 (highlighted in bold italic type). Cases 15, 22, 35, 41, 46, 47, and 50 have been previously published.

Table 2
Karyotype of the 50 MDS patients at different time-points

Case[a]	WHO	Karyotype		
		At diagnosis	6 mo, or at transformation	12 mo
1	RA	46,XY[20]	46,XY[20]	46,XY[20]
2	RCDM	46,XY[20]	46,XY[20]	(Dead)
3	***RCDM-RS***	***46,XY[12]***	***46,XY[10] (at 6 mo)*** 46,XY[8] (8 mo: AML)	***(Dead)***
4	RA	46,XX,del(7)(q32)[8]	46,XX,del(7)(q32)[4]	46,XX,del(7)(q32)[4]
5	RCDM	46,XY[20]	46,XY[20]	46,XY[20]
6	RCDM	46,XY[10]	46,XY[8]	46,XY[20]
7	RARS	46,XX[12]	46,XX[15]	46,XX[20]
8	RCDM	46,XX[10]	46,XX[10]	46,XX[20]
9	RCDM	46,XY[19]	46,XY[10]	46,XY[20]
10	RCDM	46,XY[10]	46,XY[10]	46,XY[12]
11	RA	46,XX[20]	46,XX[20]	46,XX[20]
12	RCDM	46,XY[10]	46,XY[15]	46,XY[20]
13	RCDM	46,XY[6]	(BMT)	
14	RARS	46,XY[20]	46,XY[20]	46,XY[20]
15	5q−	(No metaphases)	46,XY,del(5)(q15q33)[18]/46,XY[1]	46,XY,del(5)(q15q33)[20] [reference 19]
16	RA	46,XY[20]	46,XY[20]	46,XY[20]
17	RCDM	46,XY[20]	(No metaphases)	(No metaphases)
18	Tx-related	46,XX[20]	(Dead)	
19	RCDM	46,XY[20]	46,XY[20]	46,XY[20]
20	RCDM	46,XX[20]	46,XX[20]	46,XX[20]
21	RAEB-2	92,XXXX[6]/46,XX[14]	(Dead)	
22	RAEB-2	46,XY,del(7)(q32),i(17)(q10)[4]/46,XY[4]	46,XY,del(7)(q32),i(17)(q10)[8]/46,XY[4]	46,XY,del(7)(q32),i(17)(q10)[10] [reference 20]
2	RARS	46,XX[20]	46,XX[20]	46,XX[20]
24	RCDM-RS	47,XX,+8[10]/46,XX[5]	(No metaphases)	(No metaphases)
25	RAEB-1	47,XX,+8[20]	47,XX,+8[20]	47,XX,+8[20]
26	RCDM	(No metaphases)	(No metaphases at 6 mo) 46,XY,del(11)(q23)[3]/46,XY[5] (8 mo: AML)	(BMT)
27	RCDM	46,XY[20]	(BMT)	
28	RAEB-2	46,XX[4]	46,XY[20] (2nd mo: AML)	(Dead)
29	RCDM	46,XX[20]	46,XY[5]	(Dead)
30	RCDM	46,XX[20]	46,XY[20]	46,XY[20]
31	RCDM	46,XX[20]	46,XX[4]	46,XX[5]
32	RCDM	46,XX[7]	46,XX[20]	(No metaphases)
33	Tx-related	46,XY[10]	(lost to follow-up)	
34	RCDM	(No metaphases)	46,XX[20]	(Dead)
35	Unclassified	(No metaphases)	46,XX,del(9)(q12q22)[4]	(lost to follow-up) [reference 21]
36	RAEB-2	46,XX[20]	46,XY,del(16)(q22)[10]/46,XY[2] (2nd mo: AML)	
37	RCDM	(No metaphases)	(No metaphases)	(Dead)
38	RAEB-2	No metaphases)	(Dead)	
39	MDS-U	46,XX[20]	46,XX[20]	46,XX[20]
40	RARS	46,XX[20]	46,XX[15]	46,XX[20]
41	5q−	46,XY,del(5)(q15q33)[4]/46,XY[12]	46,XY,del(5)(q15q33)[5]/46,XY[10]	46,XY,del(5)(q15q33)[4]/46,XY[6] [reference 19]
42	RARS	46,XY,del(20)(q11q13)[9]	46,XY,del(20)(q11q13)[4]	46,XY,del(20)(q11q13)[4]/46,XY[8]
43	RCDM	46,XY[20]	46,XY[20]	(lost to follow-up)
44	RCDM	46,XX[20]	46,XX[20]	46,XX[20]
45	RCDM	47,XX,+8[3]/46,XX[2]	(No metaphases)	47,XX,+8[17]/46,XX[2]
46	***RCDM-RS***	***46,XX[20]***	***46,XX,t(8;21)(q22;q22),dup(9)(q13)[5]/46,XX[13]***	***(Dead)*** [reference 13]
47	RCDM-RS	46,XX[10]	46,XX[12]	46,XX,der(19)t(1;19)(q21;p13)[14]/46,XX[6] (12 mo: AML) [reference 22]
48	RARS	46,XX[20]	46,XX[15]	46,XX[20]
49	RCDM	46,XX[20]	(BMT)	
50	5q−	46,XY,del(5)(q15q33)[4]/46,XY[16]	46,XY,del(5)(q15q33)[5]	46,XY,del(5)(q15q33)[4]/46,XY[5] [reference 19]

Abbreviations: AML, acute myeloid leukemia transformation; BMT, bone marrow transplantation; MDS-U, myelodysplastic syndrome, unclassifiable; RA, refractory anemia; RAEB, refractory anemia with excess of blasts; RARS, refractory anemia with ringed sideroblasts; RCDM, refractory cytopenia multilineage dysplasia; RCDM-RS, refractory cytopenia multilineage dysplasia with ringed sideroblasts; Tx-related, therapy-related (i.e., secondary to treatment); 5q−, 5q− syndrome.

[a] Of the 50 cases, only 2 exhibited *FLT3* ITD mutation: cases 3 and 46 (highlighted in bold italic type).

(Fig. 1). Case 46 exhibited *FLT3* ITD in 68% of bone marrow cells at 7th month follow-up precisely at the time of AML transformation [13].

4. Discussion

Although we performed a prospective evaluation looking for the mutation at three different follow-up time-points, previously defined, we found *FLT3* ITD in just 2 of 50 of MDS cases (4%), and one of these was found at an additional time-point (any sign of transformation into AML triggered a search, apart from the defined time-points). The incidence of *FLT3* ITD in MDS was reported in 1997 by Horiike et al. [7] as 2 of 58 cases (3%) and by Yokota et al. [7,14] as 1 of 37 cases (2.7%). More recently, Fidler et al. [15] did not find any *FLT3* ITD mutation among 40 MDS patients with deletion 5q, and Shih et al. [2] reported an incidence of 5 of 82 cases (6%) at diagnosis of MDS diagnosis, further confirming the low prevalence of this mutation in MDS.

The two patients who exhibited the mutation had just evolved into AML. Of utmost importance, case 3 exhibited *FLT3* ITD in ~8% of bone marrow cells at the 6-month follow-up, but then at the 8th month (AML transformation) *FLT3* ITD was detected in 85% of bone marrow cells, suggesting that the ITD clone was responsible for AML transformation.

To our knowledge, there are only two previous studies that screening for *FLT3* ITD in adult MDS during disease progression. In the study of Shih et al. [2], among 82 patients who transformed to AML, 70 had samples analyzed both at the diagnosis of MDS and after progression to AML. *FLT3* ITD was detected at both stages in three patients: one case of chronic myelomonocytic leukemia (CMML) and two cases of refractory anemia with excess of blasts in transformation (RAEB-t). Seven more patients acquired the mutation at the time of AML transformation: two case of RA, one RAEB, one CMML, and three RAEB-t [2]. Georgiou et al. [16] evaluated serial determination of *FLT3* mutations (ITD and Asp835) in 97 MDS patients. Three patients had mutations at presentation and three additional patients acquired the *FLT3* mutations and progressed to AML in 1 month. Horiike et al. [7] also presented two cases with *FLT3* ITD who had transformed to overt leukemia by 1 and 3 months after the detection of the mutations. Based on these findings, we believe that *FLT3* ITD is an important step to AML progression.

Case 46 exhibited the t(8;21) besides *FLT3* ITD at the time of AML transformation [13], further corroborates the two hit model of leukemogenesis [17,18]. Schessl

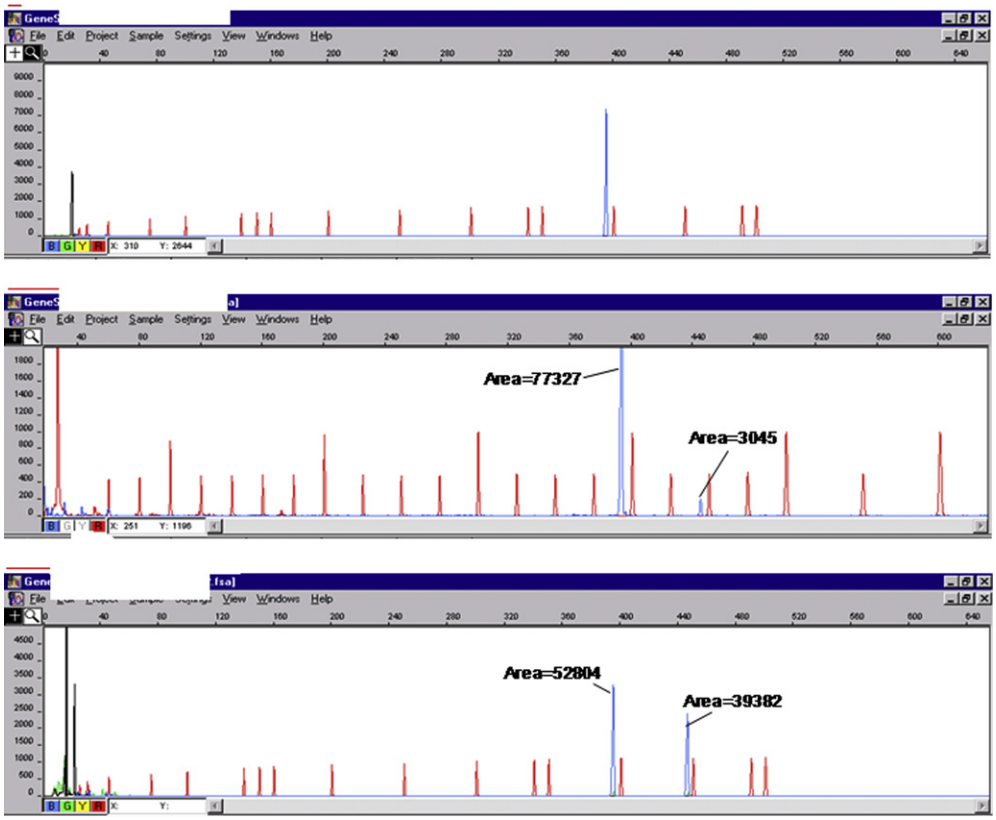

Fig. 1. Development of FLT3 internal tandem duplication (ITD) in case 3, one of two cases with *FLT3* ITD mutation out of 50 myelodysplastic syndrome cases screened. The top panel shows the absence of *FLT3* ITD, the middle panel shows the ITD mutation (>397 alleles) in ~8% of bone marrow cells (confirmed by sequencing) at the 6-month follow-up, and the bottom panel shows *FLT3* ITD present in ~85% of bone marrow cells at 8-months follow-up, when the case had evolved into AML.

et al [18] demonstrated, for the first time, that retrovirally engineered coexpression of *RUNX1–RUNX1T1* (previously *AML1–ETO*) and *FLT3* ITD potently synergized to trigger the development of aggressive leukemia in a murine transplantation model. Mice engrafted with bone marrow cells coexpressing *RUNX1–RUNX1T1* and *FLT3* ITD died of aggressive acute leukemia after a median latency time of 233 days after transplantation. (According to this model, these two abnormalities were demonstrated as being able of inducing acute leukemia.).

Although no cytogenetic abnormality was detected by G-banding in case 3, we believe that additional mutations in the ITD clone would contribute to AML transformation.

In conclusion, *FLT3* ITD is an uncommon mutation in MDS, but its presence is associated with a high probability of evolution to AML within a short time.

References

[1] Mufti GJ. Pathobiology, classification, and diagnosis of myelodysplastic syndrome. Best Pract Res Clin Haematol 2004;17: 543–57.

[2] Shih LY, Huang CF, Wang PN, Wu JH, Lin TL, Dunn P, Kuo MC. Acquisition of *FLT3* or *N-ras* mutations is frequently associated with progression of myelodysplastic syndrome to acute myeloid leukemia. Leukemia 2004;18:466–75.

[3] Abu-Duhier FM, Goodeve AC, Wilson GA, Care RS, Peake IR, Reilly JT. Genomic structure of human FLT3: implications for mutational analysis. Br J Haematol 2001;13:1076–7.

[4] Agnes F, Shamoon B, Dina C, Rosnet O, Birnbaum D, Galibert F. Genomic structure of the downstream part of the human *FLT3* gene: exon/intron structure conservation among genes encoding receptor tyrosine kinases (RTK) of subclass III. Gene 1994;145:283–8.

[5] Kiyoi H, Naoe T. *FLT3* in human hematologic malignancies. Leuk Lymphoma 2002;43:1541–7.

[6] Nakao M, Yokota S, Iwai T, Kaneko H, Horiike S, Kashima K, Sonoda Y, Fujimoto T, Misawa S. Internal tandem duplication of the flt3 gene found in acute myeloid leukemia. Leukemia 1996;10: 1911–8.

[7] Horiike S, Yokota S, Nakao M, Iwai T, Sasai Y, Kaneko H, Taniwaki M, Kashima K, Fujii H, Abe T, Misawa S. Tandem duplications of the FLT3 receptor gene are associated with leukemic transformation of myelodysplasia. Leukemia 1997;11:1442–6.

[8] Gilliland DG, Griffin JD. The roles of FLT3 in hematopoiesis and leukemia. Blood 2002;100:1532–42.

[9] Harris NL, Jaffe ES, Diebold J, Flandrin G, Muller-Hermelink HK, Vardiman J, Lister TA, Bloomfield CD. World Health Organization classification of neoplastic diseases of the hematopoietic and lymphoid tissues: report of the Clinical Advisory Committee meeting–Airlie House, Virginia, November 1997. J Clin Oncol 1999;17: 3835–49.

[10] Greenberg P, Cox C, LeBeau MM, Fenaux P, Morel P, Sanz G, Sanz M, Vallespi T, Hamblin T, Oscier D, Ohyashiki K, Toyama K, Aul C, Mufti G, Bennett J. International scoring system for evaluating prognosis in myelodysplastic syndromes [Erratum in: Blood 1998;91:1100]. Blood 1997;89:2079–88.

[11] Rozen S, Skaletsky HJ. Primer3 on the WWW for general users and for biologist programmers. In: Misener S, Krawetz SA, editors. Bioinformatics methods and protocols. Methods in Molecular Biology 132. Totowa, NJ: Humana Press, 2000. pp. 365–86.

[12] Reilly JT. FLT3 and its role in the pathogenesis of acute myeloid leukaemia. Leuk Lymphoma 2003;44:1–7.

[13] Pinheiro RF, Moreira Ede S, Silva MR, Greggio B, Alberto FL, Chauffaille M de L. *FLT3* mutation and *AML/ETO* in a case of myelodysplastic syndrome in transformation corroborates the two hit model of leukemogenesis. Leuk Res 2007;31:1015–8.

[14] Yokota S, Kiyoi H, Nakao M, Iwai T, Misawa S, Okuda T, Sonoda Y, Abe T, Kahsima K, Matsuo Y, Naoe T. Internal tandem duplication of the *FLT3* gene is preferentially seen in acute myeloid leukemia and myelodysplastic syndrome among various hematological malignancies: a study on a large series of patients and cell lines. Leukemia 1997;11:1605–9.

[15] Fidler C, Watkins F, Bowen DT, Littlewood TJ, Wainscoat JS, Boultwood J. *NRAS, FLT3* and *TP53* mutations in patients with myelodysplastic syndrome and a del(5q). Haematologica 2004;89:865–6.

[16] Georgiou G, Karali V, Zouvelou C, Kyriakou E, Dimou M, Chrisochoou S, Greka P, Dufexis D, Vervesou E, Dimitriadou E, Efthymiou A, Petrikkos L, Dima K, Lilakos K, Panayiotidis P. Serial determination of FLT3 mutations in myelodysplastic syndrome patients at diagnosis, follow up or acute myeloid leukaemia transformation: incidence and their prognostic significance. Br J Haematol 2006;134:302–6.

[17] Gilliland DG. Hematologic malignancies. Curr Opin Hematol 2001;8:189–91.

[18] Schessl C, Rawat VP, Cusan M, Deshpande A, Kohl TM, Rosten PM, Spiekermann K, Humphries RK, Schnittger S, Kern W, Hiddemann W, Quintanilla-Martinez L, Bohlander SK, Feuring-Buske M, Buske C. The *AML1-ETO* fusion gene and the *FLT3* length mutation collaborate in inducing acute leukemia in mice. J Clin Invest 2005;115:2159–68.

[19] Pinheiro RF, Silva MR, Chauffaille Mde L. The 5q- syndrome and autoimmune phenomena: report of three cases. Leuk Res 2006;30: 507–10.

[20] Pinheiro RF, Chauffaille Mde L, Silva MR. Isochromosome 17q in MDS: a marker of a distinct entity. Cancer Genet Cytogenet 2006; 166:189–90.

[21] Feitosa Pinheiro R, Maranhão Bahia D, Artur Flores Pelloso L, Guimaraes Vaz De Campos M, De Lourdes Chauffaille M. Isolated interstitial 9q deletion in a case of unclassifiable myelodysplastic syndrome. Cancer Genet Cytogenet 2004;153:183–4.

[22] Pinheiro RF, Chauffaille Mde L, Silva MR. A rare case of acute myeloid leukemia evolving from a myelodysplastic syndrome with der(19)t (1;19). Cancer Genet Cytogenet 2006;169:181–3.