

CASE REPORT

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A novel five-way translocation $t(7;11;9;22;9)(q22;q13;q34;q11.2;q34)$ involving Ph chromosome in a patient of chronic myeloid leukemia: a case report

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Abstract

About 5-10 % of chronic myelogenous leukemia (CML) patients show variant Philadelphia (Ph) translocations. The formation mechanisms and clinical significance of variant Ph translocations remain unclear. We report a CML case with a novel five-way complex translocation. Although the result of initial G-banding was $46,XY,t(7;11;9)(q22;q13;q34),t(9;22)(q34;q11.2)$, fluorescence *in situ* hybridization (FISH) demonstrated $t(7;11;9;22;9)(q22;q13;q34;q11.2;q34)$ consisting of sequential rearrangements involving five chromosomes. The patient was successfully treated by imatinib and obtained a major molecular response. To our knowledge, this is the tenth CML case with a complicated Ph translocation involving five chromosomes and the third one treated by imatinib. Good response with imatinib therapy suggested that a single-event rearrangement was involved in the chromosomal changes.

Keywords: CML, Variant Ph translocation, Five-way translocation

Background

Chronic myelogenous leukemia (CML) is a clonal myeloproliferative disorder of primitive hematopoietic stem cells. Most CML patients show a Philadelphia (Ph) chromosome with the characteristic $t(9;22)(q34;q11.2)$ translocation. However, about 5-10 % of Ph positive patients with CML show variant translocations. The formation mechanisms and clinical significance of variant Ph translocations remain unclear.

We describe a CML case with a novel five-way chromosomal translocation $t(7;11;9;22;9)(q22;q13;q34;q11.2;q34)$, who has been successfully treated by imatinib. To our knowledge, this is the tenth CML case with a complicated Ph translocation involving five chromosomes, and the third one treated by imatinib.

Case presentation

The patient was 58-year-old Japanese male with no significant medical history. He was found to have increased white blood cell count (WBC) at a medical checkup at his workplace and referred to our hospital. The laboratory

data on admission showed that his WBC was $19.1 \times 10^9/L$, with a differential of 67.5 % neutrophils, 5.5 % myelocytes, 3.0 % metamyelocytes, 6.0 % basophils, 1.5 % eosinophils, 3.0 % monocytes, 13.5 % lymphocytes. Hemoglobin concentration of 13.0 g/dL was within a normal range and platelet count of $390 \times 10^9/L$ was slightly elevated. Neutrophil alkaline phosphatase (NAP) score was decreased to 79 (control score, 170–285). Bone marrow aspirate showed marked hypercellularity. Reverse-transcription polymerase chain reaction (RT-PCR) of RNA from his bone marrow cells amplified major *BCR/ABL* chimeric transcript (b3a2 type). He was diagnosed as having CML in the chronic phase, then received treatment with orally imatinib at daily of 400 mg. He obtained a complete cytogenetic response as well as a major molecular response (MMR), as *BCR/ABL* transcripts have not been detected by quantitative RT-PCR analysis after thirteen months treatment. The MMR status has been maintained for 44 months.

G-banding chromosomal analysis of the bone marrow cells presented $46,XY,t(7;11;9)(q22;q13;q34),t(9;22)(q34;q11.2)$ [20/20] (Figure 1A). After imatinib treatment, karyotype of the patient's bone marrow cells showed $46,XY$ [20/20].

To confirm these cytogenetic aberrations, we performed Spectral karyotyping (SKY) analysis with a SkyPaint kit

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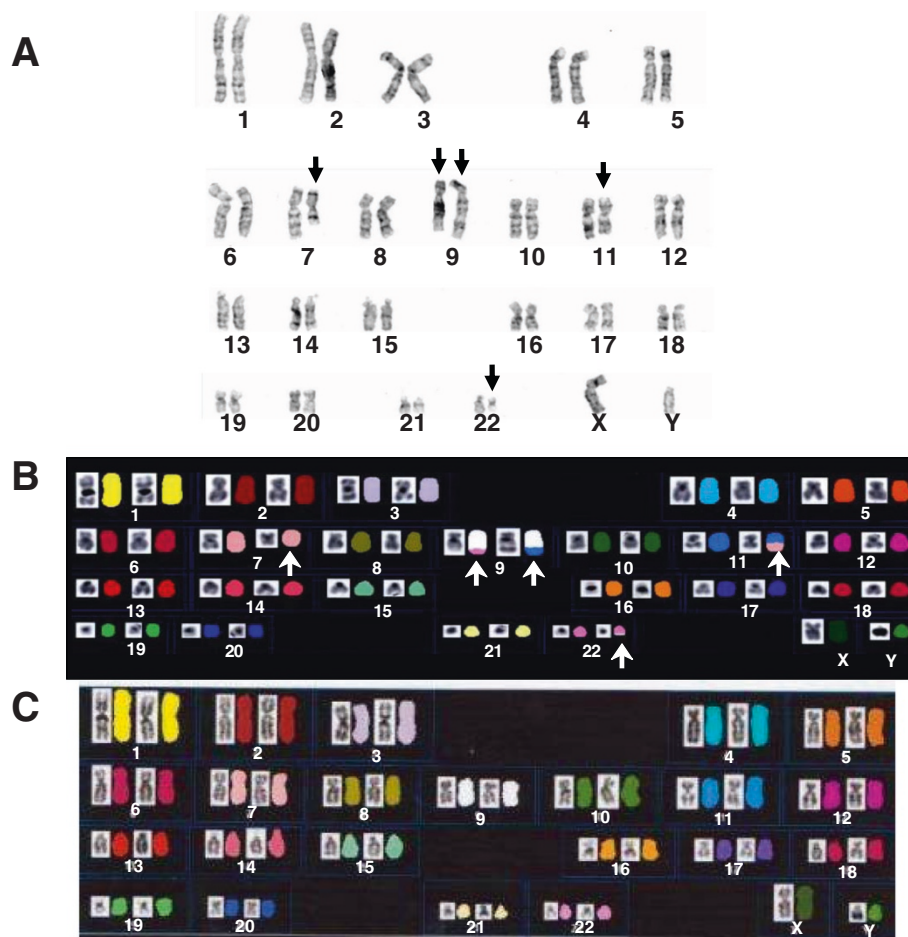


Figure 1 (A) G-banded karyotype of the bone marrow cells. The karyotype was initially decided as 46,XY,t(7;11;9)(q22;q13;q34),t(9;22)(q34;q11.2). Arrows indicate rearranged chromosomes. **(B) Spectral karyotyping of the metaphase of the patient's leukemic cells spread after spectrum-based classification.** Chromosomes were assigned a pseudocolor according to the measured spectrum. Four derivative chromosomes, der(9)t(9;11)(q34;q13), der(9)t(9;22)(q34;q11), der(11)t(7;11)(q22;q13) and der(22)t(9;22)(q34;q11) and the truncated chromosome 7 were indicated by arrows. The grayscale images are reverse DAPI; the colored images, SKY. **(C) Normal SKY image.**

(Applied Spectral Imaging, Migdal Ha'Emek, Israel). As shown in Figure 1B, SKY confirmed four derivative chromosomes, der(9)t(9;11)(q34;q13), der(9)t(9;22)(q34;q11), der(11)t(7;11)(q22;q13), and der(22)t(9;22)(q34;q11). SKY could not visualize the small segment 9q34-9qter on the der(7)t(7;9)(q22;q34). The size of this segment was supposed to be smaller than a minimum genomic alteration that SKY could detect.

For further characterization of these translocations, we next performed fluorescence *in situ* hybridization (FISH) analyses. In order to detect the *BCR/ABL* rearrangement and determine the 9q34 breakpoints, the LSI *BCR/ABL* ES Dual Color Translocation Probe Set (Vysis, Inc.) was used (assay 1). This probe set is a mixture of an *ABL* probe, which covers not only the *ABL* but also the centromeric located *ASS* gene (Spectrum Orange) and a

BCR probe (Spectrum Green). In assay 1, one yellow (red-green) signal, showing the *BCR/ABL* fusion, one *BCR* (green), one *ASS-ABL* (larger red), and one *ASS* (smaller red) signal were detected (Figure 2A). This finding indicated that the two der(9) chromosomes had different 9q34 breakpoints, one within the *ABL*, generating the *BCR/ABL* fusion gene, the other within or centromeric to the *ASS*.

Additionally, we used two types of probe. One is the CEP7 (Vysis, Inc.) (Spectrum Green) that hybridizes to the centromere of chromosome 7 (assay 2). The other is the mixture consisted of 11p (Spectrum Green), 11q (Spectrum Orange), 18p (Spectrum Green and Spectrum Orange) and 18 centromeric (Spectrum Aqua) probes (Vysis, Inc.) (assay 3). Assay 2 indicate that the *ASS-ABL* segment (larger red signal) from the chromosome 9 was on der(7) with CEP7 signal. The fusion *BCR/ABL*

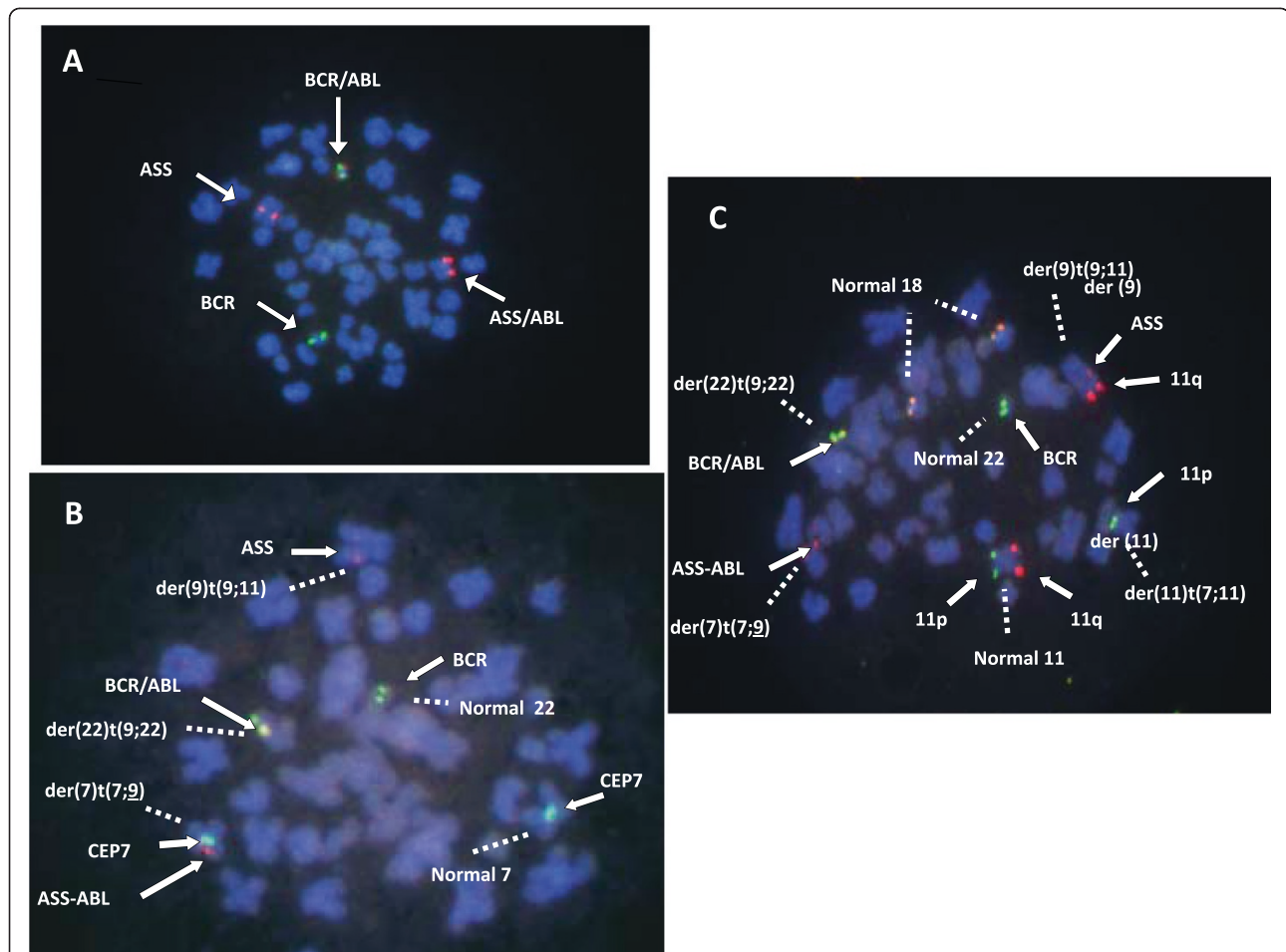


Figure 2 FISH analyses with (A) *ABL* and *BCR* probes, (B) additional *CEP7* probe and (C) additional 11p, 11q and chromosome 18 probes. FISH probes and chromosomes of attention were indicated by arrows and dashed lines, respectively. (A) One yellow (red-green) signal, showing the *BCR/ABL* fusion, one *BCR* (green), one *ASS-ABL* (larger red), and one *ASS* (smaller red) signal were detected. (B) The segment (*ASS-ABL*, larger red signal) from the chromosome 9 was on *der(7)*. The fusion *BCR/ABL* signal was on *der(22)*, and the smaller red signal (*ASS*) was retained on the other chromosome 9. (C) The larger red signal, 11q, was on *der(9)* which retained the smaller red signal *ASS*.

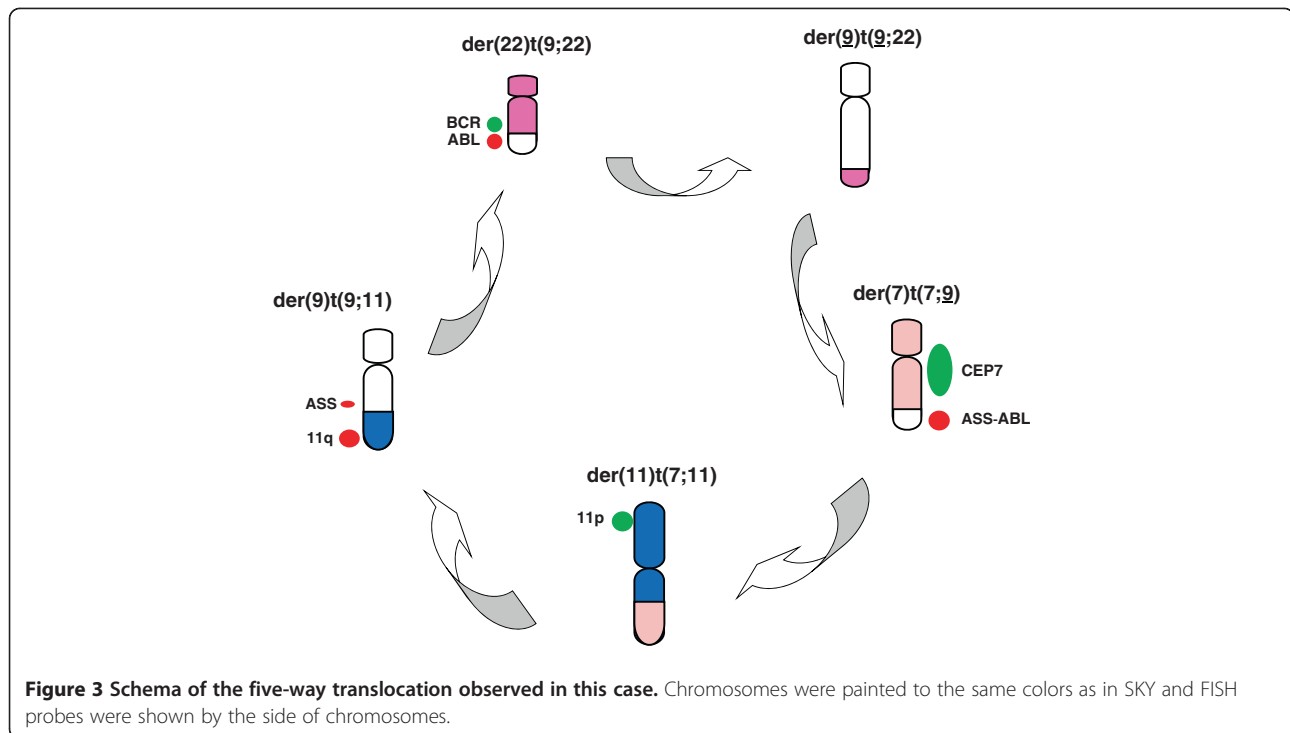
signal was on *der(22)*, and the smaller red signal, *ASS*, was retained on the other chromosome 9 (Figure 2B). In assay 3, the larger red signal, 11q, was on one of *der(9)* which retained the smaller red signal *ASS* (Figure 2C), indicating that the 11q segment was translocated to a chromosome 9 with rearrangement within the *ABL*, but not to the other from which *ASS-ABL* was translocated to *der(7)*.

The results from G-banding, SKY and FISH analyses finally revised the karyotype as 46,XY,t(7;11;9;22;9)(q22;q13;q34;q11.2;q34) (Figure 3). We found nine other CML cases with five-way translocation, two of which were treated by imatinib [1-9] (Table 1). However, to our knowledge, this combination has not reported so far [10].

Two possible mechanisms have been postulated for formation of variant translocations. One is a single-event

rearrangement via simultaneous breakage of several chromosomes followed by mismatched joining [11]. The other is a multi-step mechanism in which a classical Ph translocation is followed by further translocation events involving chromosomes 9 and 22 and other chromosomes [12]. These mechanisms may have prognostic importance in that a single genomic rearrangement may confer a similar prognosis to the classical Ph translocation, whereas a multi-step mechanism represents clonal evolutions associated with a worse prognosis [13].

Conflicting data were reported on clinical relevance of variant Ph translocation to tyrosine kinase inhibitor treatment [14-16] and its clinical significance has not been determined yet. Our case had achieved a MMR by imatinib therapy, suggesting that a single-event rearrangement was involved in the chromosomal change. However, careful follow-up will be needed, as complex translocations



might be associated with a higher degree of genomic instability.

Conclusions

We report a patient with CML presenting a complex five-way translocation, $t(7;11;9;22;9)(q22;q13;q34;q11.2;q34)$. In our case, the initial finding on G-banding analysis suggested that an additional chromosomal aberration would occur independently from the Ph translocation. Chromosomal breaks occurred on both alleles of band 9q34 in the translocation, but only one of

them was involved for the formation of *BCR/ABL* fusion. FISH method identified sequential rearrangements involving five chromosomes. Good response with imatinib therapy suggested that a single-event rearrangement was involved in the chromosomal changes.

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this Journal.

Table 1 Previously reported CML cases with five-way translocations and the present case

Case no.	Age/Sex	Karyotype of five-way translocation	Reference no.	Treatment	Outcome
1	10/Male	$t(4;18;13;9;22)(q12;q11.2;q14;q34;q11.2)$	[1]	BSF	Died 81months
2	23/Male	$t(9;22;15;19;10)$	[2]	Not reported	Not reported
3	68/Not reported	$t(3;4;9;11;22)$	[3]	Not reported	Died in benign phase
4	64/Female	$t(9;22;21;11;inv\ ins(12)(q15p12p13)(q34;q11;q22;q13;q15)$	[4]	BSF/VCR and PSL/ADM, CPA and MTX	Died 33 months
5	63/Male	$t(9;22;10;12;1)(q34;q11.2;q22;p12;p36.1)$	[5]	DNR,VCR,AND and PSL	Died 34 months
6	68/Female	$t(9;22;15;13;17)(q34;q11;q26;q14;q11)$	[6]	Chemotherapy	Not reported
7	Not reported/ Male	$t(2;9;16;22;22)(q32;q34;q21;q11;q11)$	[7]	Not reported	Not reported
8	32/Male	$t(4;12;7;9;22)(q33;q24;p13;q34;q11)$	[8]	GLI	41 months
9	45/Female	$t(1;4;5;9;22)(q42;p14;q31;q34;q11.2)$	[9]	HU/GLI	62 months
10	58/Male	$t(7;11;9;22;9)(q22;q13;q34;q11.2;q34)$	The present case	GLI	44 months

BSF:Busulphan, VCR:Vincristine, PSL: Prednisolone, ADM:Adriamycin, CPA:Cyclophosphamide, MTX:Methotrexate, DNR:Daunorubicin, GLI:Imatinib, HU:Hydroxyurea.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

SY performed the cytogenetic studies in the present case and collected the data relative to this case report. SY, YN and MB did the molecular cytogenetic analysis and interpretation. SY and YN drafted the paper and all authors contributed to the finalizing of the manuscript. All authors read and approved the final manuscript.

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References

1. Nakajima F, Takagi M, Tsuchiya K, Imashuku S, Arakawa S, Misawa S, Abe T: A five-way complex translocation in a patient with chronic myelocytic leukemia: t(4;18;13;9;22)(q12;q11.2;q14;q34;q11.2). *Cancer Genet Cytogenet* 1988, **30**:163–164.
2. Hayata I, Sasaki M: A case of Ph¹-positive chronic myelocytic leukemia associated with complex translocations. *Proc Japan Acad* 1976, **52**:29–32.
3. Potter AM, Watmore AE, Cooke P, Lilleyman JS, Sokol RJ: Significance of non-standard Philadelphia chromosomes in chronic granulocytic leukaemia. *Br J Cancer* 1981, **44**:51–54.
4. Abe R, Shiga Y, Ookoshi T, Tanaka T, Maruyama Y: A complicated translocation involving five chromosomes (Nos. 9, 11, 12, 21 and 22) in a patient with chronic myelocytic leukemia (CML). *Int J Hematol* 1991, **54**:479–482.
5. Lau LC, Knight L, Tien SL, Lim P, Yong MH, Chong YY: Highly complex chromosomal rearrangement of chromosome 9 in a case of chronic myeloid leukemia. *Cancer Genet Cytogenet* 1998, **104**:153–156.
6. Young C, Di Benedetto Jr J, Glasser L, Mark HFL: A Philadelphia chromosome positive CML patient with a unique translocation studied via GTG-banding and fluorescence in situ hybridization. *Cancer Genet Cytogenet* 1996, **89**:157–162.
7. Morel F, Herry A, Le Bris MJ, Morice P, Bouquard P, Abgrall JF, Berthou C, De Braekeleer M: Contribution of fluorescence in situ hybridization analyses to the characterization of masked and complex Philadelphia chromosome translocations in chronic myelocytic leukemia. *Cancer Genet Cytogenet* 2003, **147**:115–120.
8. Ikuta K, Torimoto Y, Jimbo J, Inamura J, Hosoki T, Shindo M, Sato K, Takahashi H, Kohgo Y: A novel five-way chromosomal translocation observed in chronic myelogenous leukemia. *Cancer Genet Cytogenet* 2008, **183**:69–71.
9. Al Achkar W, Wafa A, Mkrtychyan H, Moassass F, Liehr T: Novel complex translocation involving 5 different chromosomes in a chronic myeloid leukemia with Philadelphia chromosome: a case report. *Mol Cytogenet* 2009, **2**:21–24.
10. Mitelman F, Johansson B, Mertens F: *Mitelman Database of Chromosome Aberrations and Gene Fusions in Cancer* (2010). [http://cgap.nci.nih.gov/Chromosomes/Mitelman].
11. Fitzgerald PH, Morris CM: Complex chromosomal translocations in the Philadelphia chromosome leukemia. Serial translocations or a concerted genomic rearrangement? *Cancer Genet Cytogenet* 1991, **57**:143–157.
12. Nacheva E, Holloway T, Brown K, Bloxham D, Green AR: Philadelphia-negative chronic myeloid leukaemia: detection by FISH of BCR-ABL fusion gene localized either to chromosome 9 or chromosome 22. *Br J Haematol* 1994, **87**:409–412.
13. Reid AG, Huntly BJP, Grace C, Green AR, Nacheva EP: Survival implication of molecular heterogeneity in variant Philadelphia-positive chronic myeloid leukaemia. *Br J Haematol* 2003, **121**:419–427.

14. El-Zimaity MM, Kantarjian H, Talpaz M, O'Brien S, Giles F, Garcia-Manero G, Verstovsek S, Thomas D, Ferrajoli A, Hayes K, Bekele N, Zhou X, Rios MB, Glassman AB, Cortes JE: Results of imatinib mesylate therapy in chronic myelogenous leukaemia with variant Philadelphia chromosome. *Br J Haematol* 2004, **125**:187–195.
15. Stagno F, Vigneri P, Del Fabro V, Stella S, Cupri A, Massimino M, Consoli C, Tambe L, Consoli ML, Antolino A, Di Raimondo F: Influence of complex variant chromosomal translocations in chronic myeloid leukemia patients treated with tyrosine kinase inhibitors. *Acta Oncol* 2010, **49**:506–508.
16. Marin D, Milojkovic D, Olavarria E, Khorashad JS, de Lavallade H, Reid AG, Foroni L, Rezvani K, Bua M, Dazzi F, Pavlu J, Klammer M, Kaeda JS, Goldman JM, Apperley JF: European LeukemiaNet criteria for failure or suboptimal response reliably identify patients with CML in early chronic phase treated with imatinib whose eventual outcome is poor. *Blood* 2008, **112**:4437–4444.

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