Key words: low affinity hemoglobin, unstable hemoglobin, codon 108 mutation, β-globin gene.

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Two more inv(16) acute myeloid leukemia cases with infrequent CBFβ-MYH11 fusion transcript: clinical and molecular findings

Ten different CBFβ-MYH11 fusion transcripts are reported. Two female patients with inv(16) acute myeloblastic leukemia were positive for type D and E CBFβ-MYH11 transcripts. We investigated the relationship of these rare transcripts with the clinical presentation and therapeutic outcome.

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The pericentric inversion of chromosome 16, inv(16), and the related translocation t(16;16), associated with acute myeloid leukemia (AML)-M4 with abnormal eosinophils (M4Eo), fuse the CBFβ (core binding factor β subunit) (16q22) to the MYH11 gene (16p13). Ten different CBFβ-MYH11 fusion transcripts have been reported. More than 85% of the positive patients have type A, and transcripts D and E account for many of the rest.[1]

Two female patients with inv(16) AML were positive for type D and E transcripts; at diagnosis, both our patients showed typical AML-M4 with eosinophilic abnormalities, and no atypical clinical or laboratory features were recognizable. We investigated the relationship of these type D and E transcripts with clinical presentation and therapeutic outcome (Table 1). CBFβ and MHY11 primers, specific amplifications and specific enzyme restriction digestions were used, as we have previously reported.[2,3]

In patient #1, after amplification, a 1157 base pairs (bp) product was obtained. Following digestion with two restriction enzymes, *Pst*I and *Acc*I, two fragments of 630 bp and 527 bp (PstI) and of 769 bp and 388 bp (AccI) were obtained, respectively. Both these analyses were compatible with a type D CBFβ (exon 5)-MYH11 (exon 8).[4] Similarly, in patient #2, a 1364 bp product was found, and after restriction digestions with PstI and AccI two bands of 769 bp and 595 bp and four bands of 630, 386, 285 and 63 bp, respectively were obtained: in this case a type E CBFβ (exon5)-MYH11 (exon7) was identified. Sequence analysis confirmed the breakpoints (GenBank accession numbers *AF249898, AF249897*).

The breakpoints of CBFβ gene in intron 5 (nucleotide 495) occur in nearly 99% of cases, comprising our two variant ones; in rare cases the breakpoints are located in intron 4 (nucleotide 399). Within the MYH11 gene, the breakpoint occurs in at least eight different points; seven different exons (from exons 7 to 13) are variably included in CBFβ-MYH11 fusion transcripts. Fusion breakpoints mostly occur at exon boundaries but rare case of intra-exonic breaks have also been recently reported.[5] Inv(16) positive AML is associated with a good prognosis, particularly after induction and consolidation chemotherapy including intermediate/high dosage aracytin.[3,6,7,9] In both our patients the response to chemotherapy was excellent with complete clinical and cytogenetic remission (overall survival: 29 and 40 months).

A firm conclusion can be drawn concerning the clinical value of molecular remission of type A CBFβ-MYH11 since patients with long-lasting clinical remission usually display negative qualitative[8] and quantitative polymerase chain reaction (PCR) results in their molecular follow up.[9,10] In contrast, given the limited number of patients with rare CBFβ-MYH11 fusion transcripts analyzed, to our knowledge, no information about the value of detection of such transcripts during follow-up can be obtained from literature. In this context, the present study is the first report of PCR negativity at remission in inv(16) AML patients without type A transcript. This finding, coupled with the typical clinical and morphologic features found at presentation, suggest that the clinical outcome of patients with type

Table 1. Characteristics of the patients.

Pt.	Sex/age	Hb g/L	WBC×10⁶/L	%BC	PLT×10⁶/L	FAB	Karyotype	CBFβ/MYH11 transcript	Therapy	DFS (months)	OS (months)
1	F/25	9.6	35.9	85	57	M4+E	46,XX,inv(16)(p12q22)(30)	E	ICE FLAN FLAN ABMT	28	29
2	F/62	7.3	22.4	42	11	M4+E	46,XX,inv(16)(p12q22)(12) 48,XX,+8,inv(16)(p12q22), +21(8)	D	ICE FLAN FLAN	39	40

D and E transcripts may be rather similar to that of patients with type A.

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Intensified induction followed by high-dose therapy with autologous peripheral blood stem cell support in poor-prognosis aggressive non-Hodgkin's lymphoma: results of a pilot study

We conducted intensified induction followed by high-dose therapy (HDT) in patients with previously untreated poor prognosis non-Hodgkin's lymphoma (n= 28). The 3-year overall survival and disease-free survival (DFS) rates were 56% and 66%, respectively. The 3-year DFS rate of patients who actually received HDT was 83%.

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It is still unclear whether high-dose chemotherapy (HDT) is beneficial to patients with poor-prognosis non-Hodgkin's lymphoma (NHL). Several randomized trials regarding this topic have yielded conflicting results.[1-6] It is notable that the trials which suggested a possible benefit of HDT included full-course conventional-dose induction[1,2] or intensified induction,[3,4] whereas the other trials which did not find a superiority of HDT contained abbreviated-course conventional-dose induction.[5,6] These results would suggest that, to be beneficial, HDT should be done as consolidation when the tumor burden after induction is minimal. On this hypothesis, intensified induction might be more reasonable than full-course conventional-dose induction because an intensified induction could induce more patients to