Favourable outcome in an APL patient with PLZF/RARalpha fusion gene: quantitative real-time RT-PCR confirms molecular response

Rare cases of acute promyelocytic leukemia (APL) are associated with a t(11;17) translocation and a PLZF-RARalpha fusion transcript. Because of molecular specificities of the fusion protein, ATRA efficiency is often reduced in these cases. We present herein the case of an 83 year old patient which has been successfully treated by ATRA and Daunorubicin. The described quantitative RT-PCR method allowed successful monitoring and confirmation of the molecular response.

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Acute Promyelocytic Leukemia (APL) or AML-M3 according to the FAB classification is usually defined by morphological and clinical criteria. Though the majority of APL blasts are defined by heavy azurophilic granules, bundles of Auer rods, and a reniform or bilobed nucleus, 20% of patients display features consistent with a hypogranular or potential agranular variant of APL (FAB-M3V). APL is associated at the molecular level with the presence of reciprocal translocations involving chromosome 17. The first identified and most frequent translocation is the t(15;17)(q22;q21) translocation generating the chimeric gene PML-RARalpha. This fusion gene is involved in the APL leukemogenesis and the blockage at the promyelocytic stage of the myeloid stem cell, where RARalpha and Retinoic Acid (RA) play a key role. It is also the target of the all-trans retinoic acid (ATRA) and arsenic trioxide (AS2O3) sensitivity of APL blasts (see ref 1 for a review). Other cytogenetic variants have been reported: t(11;17)(q23;q21), t(5;17)(q35;q21), t(11;17)(q13;q21) and der (17) (see ref 2 for a review). The RARalpha gene, located on chromosome 17q21 is always involved, supporting the central role of the x-RARalpha fusion genes in the pathogenesis of this leukaemia which animal models have confirmed.2 However, several cellular or clinical characteristics differ according to the fusion partner.3 The first and most frequently reported translocation is the t(11;17)(q23;q21) generating the PLZF-RARalpha fusion gene.4 The presence of PLZF-RARalpha fusion gene has been reported to be associated to cytological and molecular features of APL and arsenic trioxide (As2O3) APL patients harbouring this unusual fusion gene have a poor outcome.5 Thus, these rare PLZF-RARalpha APL cases require molecular diagnosis for accurate diagnosis and quantitative RT-PCR to monitor efficacy of potential therapeutic approaches.

We report herein the case of an 83 year old patient in whom an AML-M3 variant was diagnosed and cytogenetic analysis evidenced the presence of a t(11;17) translocation. A specific RT-PCR, identified a PLZF-RARalpha transcript (Figure 1a-b). No sign of disseminated intravascular coagulation or abnormal fibrinolysis was observed. Due to age, the patient was treated with ATRA alone (90 mg/day) resulting in a bone marrow blast decrease from 85% to 25% by day 17. At day 20, the patient received a first course of Daunorubicin (60 mg/m2 on 3 consecutive days) while ATRA was main-
Table 1. Primer and probe sequences for RT-PCR amplification of the PLZF-RARα gene

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<th>Primer and probe sequences for RT-PCR amplification of the PLZF-RARα gene</th>
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<tbody>
<tr>
<td>Standard RT-PCR</td>
<td>Forward primer: 5'-CCGTGACCTCTGGCCTCCAC-3'</td>
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<td></td>
<td>Reverse primer: 5'-GCTGGGCACTATCTCTTCAG -3'</td>
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<tr>
<td>Quantitative RT-PCR</td>
<td>Forward primer: 5'-GAAGACGTACGGGTGCGAGCTC-3'</td>
</tr>
<tr>
<td></td>
<td>Reverse primer: 5'-CTCACAGGCGCTGACCCCATAGT-3'</td>
</tr>
<tr>
<td></td>
<td>Probe: 5'-CCAGCCCTCCCTCGCCACCCCCTA -3'</td>
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Key words: quantitative, RT-PCR, APL, PLZF/RAR, t(11;17)

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References


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