Mutation of FLT3 is not a general phenomenon in CD117-positive T-ALL
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CD117 is considered to be a marker of leukemic cells committed to the myeloid lineage, however up to 11% of T-ALLs have been found to express CD117 [1]. Activating mutations in the FLT3 gene are common in acute myeloid leukemia (AML) but are rarely found in acute lymphoblastic leukemia (ALL) [2]. Recently, a subset (3 out of 55) of adult T-ALLs characterized by expression of CD117 (in >90% of T-lymphoblasts) and FLT3 mutations (either internal tandem duplications (ITD) in the juxtamembrane region or mutations in the activation-loop coding region) was described [3]. These data suggested that CD117 expression in T-ALL lymphoblasts might identify a subset of T-ALLs in which activating FLT3 mutations are essential in oncogenesis. If FLT3 mutations would be present in all CD117-positive T-ALLs, up to 11% of all T-ALL patients could potentially benefit from therapy with FLT3 inhibitors, which are currently under investigation for AML treatment [2,4].

We report here on the FLT3 mutation status of a 75-year-old man diagnosed with CD117-positive T-ALL. The patient presented with pancytopenia and anaemia. Bone marrow analysis revealed 70% blasts with an L1 ALL morphology according to the French-American-British classification. There was no cytochemical evidence of myeloid differentiation, i.e. Sudan black B, specific and non-specific esterase stains were negative. Flowcytometry demonstrated 85% blasts, 9% T-lymphocytes, 1% B-lymphocytes, 2% granulocytes, and <1% monocytes. The blasts were classified as T-lymphoblasts based on intracytoplasmic CD3 expression (Fig. 1). Furthermore, >90% of the blast cells were positive for CD117, CD2, CD7, CD13, CD45, and CD56, whereas CD34, CD33, CD5, and CD19 were expressed on a subset of blast cells only (about 75, 30, 30 and 40% of blasts, respectively). Blast cells did not significantly express TdT, MPO, CD1a, CD4, CD8, CD10, CD14, CD15, CD22, CD65, CD135 and SmCD3 (all <10% positive). Of importance, CD135 (FLT3) expression was weak/negative on the T-lymphoblasts (Fig. 1).

Cytogenetics revealed a complex karyotype in 73% of metaphases: 46, XY, der(1)t(1;9)(p34;q34), der(3)t(1;3), del(5)(q21q34), der(9)t(1;9)(q22;q22), der(12)t(1;12), del(5q)q21, del(12)(q21q22). The balanced translocation between chromosomes 1 and 9 might involve the ABL gene on 9q34. The other translocations have been observed in MDS/AML, like the del(5), or in rare cases of CML, like the t(1;13), t(1;9) and t(12;17), but have never been described in combination so far.

RT-PCR analysis showed no ITD in the FLT3 juxtamembrane region (Exon 14 and 15) [5]. Furthermore, sequence analysis of the FLT3 activation-loop coding region (exon 20) showed the absence of currently known activating mutations (D835, I836, N841 and Y842C) [6]. Immunophenotypically the case presented here is an immature T-ALL expressing CD117 and CD13, comparable to the three cases described earlier [3]. However, the remaining immunophenotype of our patient showed some differences, with (partial) positivity for CD56, CD33 and CD5, and negativity for TdT. More important, our patient lacked significant CD135 expression and showed no activating FLT3 mutations. Although we cannot exclude the presence of mutations outside exon 14, 15 and 20, our data strongly suggest that CD117-positive T-ALLs do not necessarily carry FLT3 mutations. Apparently, CD117-positive T-ALL are more heterogeneous than previously reported [3]. Further research into the frequency of FLT3 mutations in CD117-positive T-ALL is necessary to establish the correlation between the immunophenotype of T-lymphoblasts.
Fig. 1. Immunophenotype of the T-lymphoblasts. Immunophenotyping was performed using four-color labelings and data were acquired on a FACS Calibur (BD Biosciences, San Diego, CA). (A) The T-lymphoblasts (85% of the leukocytes) showed a low side scatter and intermediate expression of CD45, which clearly distinguished them from the remaining normal lymphocytes (10%), monocytes (<1%), and granulocytes (2%). By gating on the SSC-CD45 characteristics, the immunophenotype of the T-lymphoblasts was further evaluated, showing intracytoplasmic CD3 expression in the absence of surface membrane CD3 expression (B); positivity for CD117 and CD13/CD33 (C); and no/weak expression of CD135 (D).

and FLT3 mutations. Such analysis will finally show which percentage of patients with CD117-positive T-ALLs might benefit from therapy with FLT3 inhibitors.

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