Mutation of FLT3 is not a general phenomenon in CD117-positive T-ALL
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Mutation of FLT3 is not a general phenomenon in CD117-positive T-ALL

Keywords: Acute lymphoblastic leukemia; CD117; FLT3 mutation; Kinase inhibitor therapy

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 anemia. Bone marrow analysis revealed 70% blasts with an L1 ALL morphology according to the French-American-British classification. There was no cytogenetical 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 was 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, CD133 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, del(1)(q21)(p13q21), +mar, -Y, +13(q21), +18, +20(q21q22), der(3)t(3;17)(q21q22), der(5)t(5;17)(q21q22), der(9)t(9;19), t(12;17)(q24;q21). 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, V842C) [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 a 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 and FLT3 mutation status.
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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References


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