Successful treatment with low-dose imatinib mesylate of therapy-related myeloid neoplasm harboring *TEL-PDGFRB* in a patient with acute promyelocytic leukemia

The introduction of all-*trans* retinoic acid (ATRA) has been a major breakthrough in the treatment of acute promyelocytic leukemia (APL) with t(15;17)(q22;q21). However, chemotherapeutic drugs in the induction and post-remission therapies seem to increase the risk of therapy-related myeloid neoplasms (t-MNs), which has an extremely poor clinical outcome.[1-3] Therefore, the occurrence of t-MN after successful therapy for acute promyelocytic leukemia is an important problem. We describe a patient with t-MN who was successfully treated with low-dose imatinib at seven years after treatment for acute promyelocytic leukemia. The study was approved by the Institutional Review Boards and written informed consent was obtained from the patient according to the revised Declaration of Helsinki.

In August 1999, a 58 year-old Japanese man was referred to our hospital because of purpura on his thigh and gum bleeding. His leukocyte count was $1.4x10^9$/L with 59% abnormal promyelocytes. Bone marrow aspiration showed hyperplastic and 87% abnormal promyelocytes including faggot cells. A diagnosis of acute promyelocytic leukemia with t(15;17) was made. The patient was treated with ATRA in combination with idarubicin and cytarabine. He achieved a complete remission (CR), but developed APL differentiation syndrome. The patient received consolidation and intensive maintenance chemotherapies according to the Japan Adult Leukemia Study Group (JALSG) APL97 protocol.[4] No *PML-RARA* was detected in the bone marrow at the end of consolidation and maintenance therapies. Cumulative doses of 60 mg/m^2 idarubicn, 31 mg/m^2 mitoxantrone, 270 mg/m^2 daunorubicin, 56 mg/m^2 aclarubicin and 980 mg/m^2 etoposide were administered until October 2001. Although he had been in continuous complete remission of acute promyelocytic leukemia for 6.5 years, his leukocyte count gradually increased from April 2006 (Figure 1). In May 2007, his hemoglobin was 14.6 g/dL, platelet count $182x10^9$/L and leukocyte count $15.9x10^9$/L, with 4% promyelocytes, 3% metamyelocytes, 62% neutrophils, 9% eosinophils, and 8% monocytes. Bone marrow aspiration showed 1.2% blasts, 3.2% eosinophilis and myeloid cell hyperplasia (76.8%). Karyotypic analysis of the bone marrow revealed 46,XY,t(5;12)(q33;p13)[17]/46,XY[3]. *TEL(ETV6)-PDGFRB* fusion gene was detected in the marrow and peripheral blood cells by RT-PCR analysis (Figure 2),[5] whereas no *PML-RARA* was found in the marrow. A diagnosis of therapy-related chronic myelomonocytic leukemia (t-CMML) with t(5;12) was made.

The patient received no medication until his hemoglobin and platelet count decreased. In October 2008, his hemoglobin was 13.6 g/dL, platelet count $138x10^9$/L, and leukocyte count $16.5x10^9$/L. A diagnosis of t-MN associated with *PDGFRB* rearrangement was made according to the new WHO classification in 2008.[1] The patient received oral imatinib 100 mg daily. His leukocyte count rapidly decreased to the normal range within two weeks (Figure 1). In January 2009, his hemoglobin was 15.3 g/dL, platelet count $176x10^9$/L and leukocyte count $5.9x10^9$/L. Bone marrow aspiration showed normal differentiation and normal karyotype. No *TEL-PDGFRB* fusion gene was detected in marrow and peripheral blood mononuclear cells after imatinib therapy (Figure 2). At the time of writing, the patient has continued in remission after 18 months of therapy with 100 mg imatinib with no adverse effects.

t-MNs are increasingly recognized entities after treatment of various hematologic and non-hematologic diseases.[1] Although most chronic myelomonocytic leukemia (CMML) cases occur *de novo,* a few cases of t-CMML have been reported in literature.[6] In a patient with t-CMML carrying monosomy 7 and t(12;17)(p13;q11.2), FISH analysis showed deletion of the *TEL* gene on chromosome 12, indicating an involvement of the *TEL* gene in t-CMML.[7] To the best of our knowledge, this letter describes the first case of t-MN with t(5;12).

Molecular diagnosis of *TEL-PDGFRB* in myeloid neoplasm has therapeutic implications because a prompt and durable response is obtained in most affected patients after treatment with imatinib.[8,9] Good responses to imatinib have also been described for chronic eosionophilic leukemia with *FIP1L1-PDGFRA*, and this may be a general feature of diseases associated with *PDGFR* fusions.

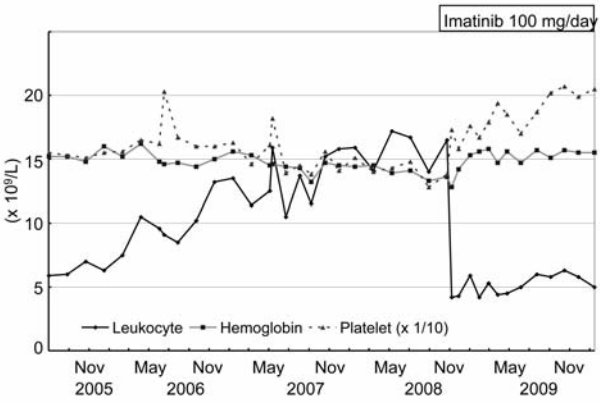

Figure 1. Patient's clinical course. His leukocyte count gradually increased from April 2006. In October 2008, he started to receive oral imatinib 100 mg daily. His leukocyte count rapidly decreased to the normal range within two weeks and his hemoglobin levels and platelet counts gradually increased to the normal range. Solid line shows leukocyte counts, gray line represents hemoglobin levels, and broken line indicates platelet counts.

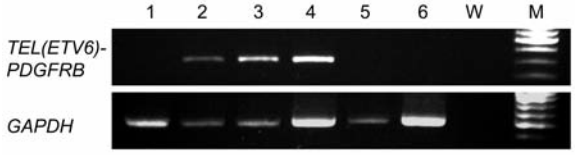

Figure 2. *TEL(ETV6)-PDGFRB* fusion gene detected by RT-PCR. *TEL-PDGFRB* fusion transcripts were size-fractionated in a 2.0% agarose gel. The lower panel shows GAPDH transcripts for examination of RNA. Lane 1: peripheral blood (PB) cells from the patient in July 2000 during maintenance therapy for acute promyelocytic leukemia; lane 2: bone marrow (BM) cells in May 2007; lane 3: PB cells in October 2007; lane 4: PB cells in March 2008; lane 5: PB cells in January 2009; lane 6: BM cells in March 2009. Lane W shows water as a negative control. Lane M shows a 100 bp DNA ladder.

Low-dose imatinib induces rapid hematologic and cytogenetic remission in most patients with *FIP1L1-PDGFRA*.[10] These observations are consistent with *in vitro* studies showing inhibitory effects of lower imatinib concentrations on targeted cells carrying *PDGFR* rearrangement compared to BCR-ABL.[11] Only one reported case of *de novo* chronic myelomonocytic leukemia and eosinophilia harboring *TEL-PDGFRB* showed a sustained response to low-dose imatinib of 100 mg/day.[12] Low-dose imatinib also induced a prompt hematologic, cytogenetic and molecular response in our patient. In conclusion, this is the first report of t-MN with *TEL-PDGFRB* after treatment of acute promyelocytic leukemia which was successfully treated with low-dose imatinib.

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