

LETTER TO THE EDITOR

IMATINIB MESYLATE TREATMENT IN A PATIENT WITH CHEMORESISTANT Ph+ ACUTE MYELOID LEUKEMIA: POSSIBLE ROLE OF WILMS' TUMOR GENE 1

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Dear Sir,

Acute myeloid leukemia (AML) is frequently associated with chromosomal alterations. However, the presence of the Philadelphia chromosome (Ph) is rare in *de novo* AML, as it is found in only 1% to 2% of cases. In 60% to 80% of these patients, conventional therapy is followed by a short-term response, lasting no longer than 8 months¹.

Imatinib mesylate, an effective and selective inhibitor of BCR-ABL tyrosine kinase activity, is commonly used in the treatment of Ph-positive chronic myeloid leukemia (CML), also in the blastic phase, whereas its role in the treatment of Ph+ AML is not yet well understood. To our knowledge, few cases of Ph + AML have been treated with imatinib mesylate^{2,3}.

In January 2005 a 17-year-old woman presented to our division with a diagnosis of AML (FAB M1). At conventional cytogenetic analysis, the Philadelphia chromosome was found in all metaphases (100%). The polymerase chain reaction with reverse transcriptase (RT-PCR) was already positive for the p190 product of the fusion gene BCR-ABL at the first step of RT-PCR. Quantitative molecular analysis of the Wilms' tumor gene (WT1) with the real-time method using ABI PRISM 7700 SDS revealed a significant increase in the number of copies of WT1/10⁴ copies of ABL (417; range, 3-70).

The patient was treated with daunorubicin, etoposide and cytosine arabinoside, but bone marrow aspirate examination on day +30 still revealed persistent AML, with 60% blasts. A second course of chemotherapy (FLANG regimen) was therefore administered and granulocyte-colony stimulating factor (G-CSF from day 0 to neutrophil recovery) was started.

Bone marrow recovery, which occurred on day +24, was compatible with a complete hematological response. Qualitative molecular analysis for the BCR-ABL fusion transcript showed positivity for the p190 gene (e1 a2), which was weaker than that found at diagnosis.

In view of the presence of the Philadelphia chromosome, the tyrosine kinase inhibitor imatinib mesylate was administered after the patient's written informed consent had been obtained. Oral treatment with imatinib mesylate was started on day +30 after FLANG therapy. The onset of side effects such as neutropenia required a dose reduction to 400 mg daily. After 6 weeks the patient showed a complete cytogenetic response with persistence of BCR-ABL transcript by nested PCR. Another FLANG cycle was therefore administered on day +67 after the last cycle, with subsequent collection of stem cells.

Allogeneic bone marrow transplantation was not feasible because no HLA-identical donor was available; the patient therefore underwent autologous bone marrow transplantation. At the time of writing she was alive and well and in complete cytogenetic remission, while qualitative molecular analysis for the BCR-ABL fusion transcript was positive.

FLANG therapy, given in association with imatinib mesylate, resulted in a complete hematological and cytogenetic response. However, no molecular response was achieved, as the patient had persistent BCR-ABL transcript.

Several hypotheses can be put forward to explain the different responses reported in the literature following imatinib administration to patients with Ph+ AML. Our patient had marked WT1 expression, a finding that may explain the persistence of the BCR-ABL transcript after imatinib treatment.

The Wilms' gene is considered a panleukemic marker, a prognostic factor, and a useful index for identifying minimal residual disease in patients with acute leukemia⁴. In a study conducted on CML patients, higher levels of WT1 expression were associated with shorter overall survival and event-free survival⁵. However, evaluation of WT1 in patients with leukemia may be more relevant than generally believed, because it is more than a simple prognostic factor: it may play an important role in leukemogenesis⁶.

The effects of WT1 on cell proliferation have previously been attributed to direct transcriptional regulation of certain genes such as p21 and the insulin-like growth factor receptor⁷, but cdk inhibitor p21^{waf1/Cip1} expression alone is probably not sufficient to explain the effects of WT1 on proliferation and differentiation⁸. WT1 is likely to affect hematopoiesis by means of distinct mechanisms, and mutation affecting the zing-finger domain of WT1 could interfere with normal differentiation, thus playing a role in the pathogenesis of leukemia⁹. Moreover, recent studies have shown correlations between WT1 and imatinib mesylate, and the presence or absence of the WT1 transcript appears

to determine the degree of therapeutic response to imatinib.

Inhibition of WT1 transcript levels after a short period of *in vitro* exposure of pre-therapy bone marrow samples to imatinib appears to predict the sensitivity of patients to future treatment with imatinib¹⁰. Quantification of WT1 might therefore be useful for a prospective and proper use of imatinib in patients with BCR-ABL rearrangement.

Although on the basis of our case no definitive conclusion can be drawn regarding the relationship between WT1 and therapy with imatinib mesylate in patients with AML, we believe that further studies should be conducted to clarify this issue.

References

1. Jentsch-Ulrich K, Pelz AF, Braun H, Koenigsmann M, Mohren M, Wieacker P, Franke A: Complete molecular remission in a patient with Philadelphia-chromosome positive acute myeloid leukemia after conventional therapy and imatinib. *Haematologica*, 89: 15, 2004.
2. Viniou NA, Vassilakopoulos TP, Giakoumi X, Mantzouranis M, Pamgalis GA: Ida-FLAG plus imatinib mesylate-induced molecular remission in a patient with chemoresistant PH1(+) acute myeloid leukaemia. *Eur J Haematol*, 72: 58-60, 2004.
3. Ito K, Tominaga K, Suzuki T, Jimai I, Bessho M: Successful treatment with imatinib mesylate in a case of minor bcr/abl-positive acute myelogenous leukaemia. *Int J Hematol*, 81: 242-245, 2005.
4. Kusumoto S, Murohashi I, Bessho M, Matsumoto H, Shimazu M: The importance of WT1 gene expression in the detection of minimal residual disease. A comparison of WT1 AML/MTG8 transcripts. *Rinsho Ketsueki*, 40: 511-514, 1999.
5. Weisser M, Kern W, Rauhut S, Schoch C, Hiddemann W, Haferlach T, Schnittger S: Prognostic impact of RT-PCR-based quantification of WT1 gene expression during MRD monitoring of acute myeloid leukemia. *Leukemia*, 19: 1416-1423, 2005.
6. Hu S, Chen Z, Gu W, Chen J, Zhao Y: High expression of RbAp46 gene in patients with acute leukemia or chronic myelogenous leukemia in blast crisis. *Chin Med J*, 118: 1295-1298, 2005.
7. Englert C, Maheswaran S, Garvin AJ, Kredberg J, Heber DA: Induction of p21 by the Wilms' tumor suppressor gene WT1. *Cancer Res*, 57: 1429-1434, 1997.
8. Ellisen LW, Carless N, Cheng T, Scadden DT, Heber DA: The Wilms' tumor suppressor WT1 directs stage specific quiescence and differentiation of human hematopoietic progenitor cells. *EMBO J*, 20: 1897-1909, 2001.
9. Svensson E, Eriksson H, Gekas C, Olofsson T, Richter J, Gullberg U: DANN-binding dependent and independent functions of WT1 protein during human hematopoiesis. *Exp Cell Res*, 308: 211-221, 2005.
10. Cilloni D, Messa F, Gottardi E, Fava M, Arroga F, Defilippi I, Carturan S, Messa E, Morotti A, Giugliano E, Rege-Cambrin G, Alberti D, Baccarani M, Saglio G: Sensitivity to imatinib therapy may be predicted by testing Wilms tumor gene expression and colony growth after short *in vitro* incubation. *Cancer*, 101: 979-988, 2004.