Response to STI571 in Chronic Myelomonocytic Leukemia with Platelet Derived Growth Factor Beta Receptor Involvement: A new case report

Based on its ability to inhibit the tyrosine kinase activity of ABL, as well as the c-kit and the Platelet Derived Growth Factor Receptor tyrosine kinases, the spectrum of diseases that may respond to STI571 is increasing. A recently recognized subgroup of myeloproliferative disorders/myelodysplastic syndromes (MPD/MDS) has a t(5;12)(q33;p13) with the activation of the gene for PDGFBR which encodes a receptor tyrosine kinase. Here, we present the case of a patient, with MPD/MDS, and eosinophilia, carrying a translocation t(5;12)(q33;p13) who achieved a complete remission following treatment with STI571, 400 mg daily. At the time of writing he still remains in complete remission with an excellent performance status. There is clearly a need for further studies of STI 571in MPD/MDS with chromosomal translocations involving PDGFBR to confirm this promising initial result.

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Recent cytogenetic and molecular studies suggest the existence of some new single subset of patients with Myeloproliferative Disorders with defined cytogenetic abnormality. The most common abnormality is the t(5;12)(q33;p13),[1] which fuses the ETV6/TEL gene to the Platelet Derived Growth Factor Beta Receptor (PDGFBR), that maps to 5q33.[2] Clinically most patients present a myeloproliferative disorder with eosinophilia, eosinophilic leukemia or chronic myelomonocytic leukemia and thus fall into the newly proposed WHO category of MPD/MDS.[3] STI571 is a small molecule that selectively inhibits the enzymatic activity of several tyrosine kinases, including the ABL and BCR-ABL fusion protein of chronic myeloid leukaemia, the platelet-derived growth factor receptor; and the product of the c-kit gene.[4] Here, we present the case of a patient with MPD/MDS carrying a translocation t(5;12)(q33;p13), who achieved a complete remission maintained at ten months after beginning STI571 therapy. A 68 year-old-man come to our department in March 2002 with moderate upper abdominal pain, fever and widespread skeletal pain. Clinical examination revealed splenomegaly palpable 6 cm below the left costal margin. The blood count in peripheral blood showed 8.4g/dL haemoglobin, 60.7x10^9/L leucocytes with 15% blast cells, 3% promyelocytes, 12% neutrophil myelocytes, 5% eosinophil myelocytes and promyelocytes, 19% polymorphonuclear neutrophils, 16% mature eosinophils, 10% lymphocytes, 20% monocytes, and 60x10^9/L platelets. Bone marrow aspirate and biopsy revealed both dysplastic and proliferative features that were difficult to assign to either refractory anemia with excess blasts type 2 or chronic myelomonocytic leukemia-2 with eosinophilia. Fluorescent *in situ* hybridization and reverse transcriptase chain reaction (RT-PCR) tests for the bcr-abl oncogene were negative. All the G-banded metaphase cells we examined, contained the t(5;12)(q33;p13) translocation (Figure 1.). Southern blot analysis on patient's DNA from bone marrow cells using a genomic PDGFBR probe revealed rearrangement of the PDGFBR gene in all restriction enzyme digests tested (Figure 2.). As STI571 has been shown to be a potent PDGFRB tyrosine kinase inhibitor, in April 2002 the patient began treatment with STI571 at a dose of 400mg a day. The blood count normalized within three weeks with resolution of eosinophilia, after 16 weeks, 30 out of 30 cells in metaphase were cytogenetically normal. During this short report, after 10 months of therapy, the appearance of the bone marrow was normal He has continued to receive STI571 at a dose of 400mg daily without any side effects since the start of therapy. Fusion oncogenes generated as a consequence of reciprocal chromosomal translocations are commonly seen in hematologic malignancies. It has been recognized for several years that the t(5;12) is associated with an unusual MPD/MDS that is difficult to classify within defined French-American-British subtypes. Specifically, patients typically present with eosinophilia plus other clinical features that are suggestive of both CML and CMML.[2] Very similar clinical pictures were seen in other patients who had diseases characterized by primary deregulation of PDGFBR and to date four additional partner genes (H4, HIP1, CEV14 and Rab5) have been reported.[5-6] At the molecular level almost all of these translocations result in a constitutive activation of protein tyrosine kinases. So far, to our knowledge, four cases with t(5;12)(q33;p13) and one patient with CMML with t(5;17)(q33;p13)[7] have been treated with STI571 and reported in the literature.[4,6] All had prompt responses with normalization of the blood count, disappearance of eosinophilia, resolution of cytogenetic abnormalities, decrease or disappearance of fusion transcripts. All these responses were durable at 9 to 12 months of follow-up. Our case demonstrates many

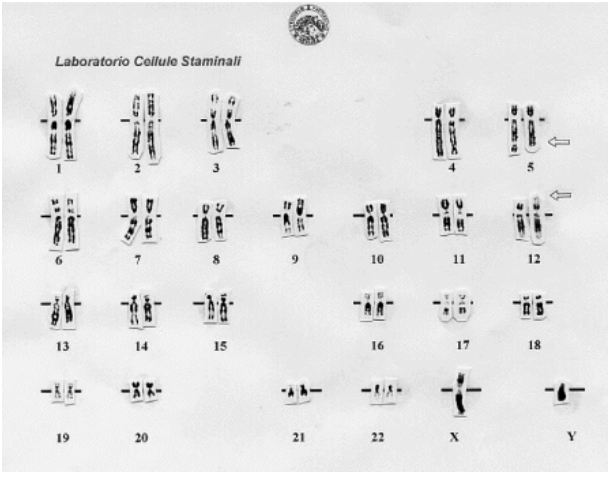

Figure 1. G-banded karyotype of bone marrow cells showing 46, XY, t(5;12)(q33;p13).

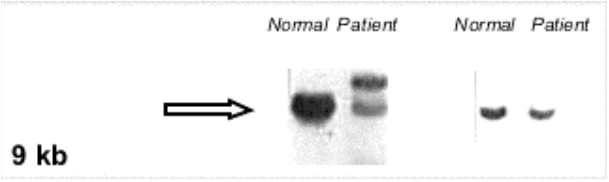

Fig.2. Southern hybridization with a 1.1 kb Hind m-XhoI PDGFBR genomic probe detects rearrangement in Hind III-digested patient DNA sample; a single band 9kb is seen in normal DNA and in patient after treatment.

typical features of myeloproliferative disorders with translocation t(5;12)(q33;p13), involvement of PDGFRB and response to STI571 treatment. Interestingly, all cases are male, hypereosinophilia, monocytosis and splenomegaly appear as characteristic features. In view of the availability of STI571, a potent inhibitor of several tyrosine kinases, there is clearly a need for further studies of STI571 in this setting to confirm these promising initial results.

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References

1. Golub T.R., Barker G.F., Lovett M., and Gilliand D.G. (1994). Fusion of PDGF Receptor _ to a novel ets-like gene, tel, in chronic myelomonocytic leukemia with t(5;12) chromosomal translocation. Cell, 77, 307-316.
2. Steer E.J. & Cross N.C.P. (2002). Myeloproliferative Disorders with translocations of chromosome 5q31-35: role of Platelet-derived growth factor receptor beta. Acta Haematologica, 107, 113-122.
3. Vardiman J.W., Lee Harris N., & Brunning R.D. (2002). The World Healt Organization (WHO) classification of myeloid neoplasm. Blood, 100, 2292-2302.
4. Apperley J.F., Gardembas M., Melo J.V., Russel-Jones R., Bain BJ., Baxter E.J., Chase A., Chessels J.M., Colombat M., Deahden C.E., Dimitrijvic S., Mahon F.X., Marin D., Nikolova Z., Olavarria E., Silberman S., Schultheis B., Cross N.C.P., & Goldman J.M.(2002). Response to Imatinib mesylate in patients with chronic myeloproliferative diseases with rearrangements of the platelet-derived growth factor receptor beta. N Engl J Med, 7: 481-486.
5. Kulkarni S., Healt C., Parker S., Chase A., Iqbal S., Pocock C.F., Kaeda J., Cwynarski K., Goldman J.M., & Cross N.C.P. (2000). Fusion of H4/D10S170 to Platelet-derived Growth Factor Receptor _ in BCR-ABL-negative Myeloproliferative Disorders with a t(5;10)(q33;q21). Cancer Research 60, 3592-3598.
6. Magnusson M.K., Meade K.E., Brown K.E., Arthur D.C., Krueger L.A., Barret J.,& Dunbar C.E. (2001). Rabatin-5 is a novel fusion partner to platelet-derived growth factor _ receptor in chronic myelomonocytic leukemia. Blood, 98,2518-2525.
7. Magnusson M.K., Meade K.E., Nakamura R., Barret J., & Dunbar C.E. (2002). Activity of STI571 in chronic myelomonocytic leukemia with a Platelet-derived growth factor _ receptor fusion oncogene. Blood, 100, 1088-1091.