

## Case Report

# Successful Treatment of Chronic Myelogenous Leukemia (CML) with Imatinib after Renal Transplantation

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## Abstract

Chronic Myelogenous Leukemia (CML) is a rare malignant disorder after solid organ transplantation, especially in renal transplant recipients. Imatinib Mesylate is currently approved as first line treatment of CML. Most reports on CML are from kidney recipients who received azathioprine in combination with cyclosporine and prednisolone as immunosuppressive therapy. We report a case with CML who was treated with Mycophenolate Mofetil.

**Keywords:** Chronic myelogenous leukemia, imatinib, renal transplant

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## Introduction

Malignancies are late complications of organ transplantation. The overall incidence of cancer in patients who undergo transplantation ranges between 4% and 18%. After cancer of the skin, lymphoproliferative disorders are amongst the most common of these malignancies following renal transplantation. Hodgkin's lymphoma, myeloma and acute leukemia of lymphoid and myeloid cells occur at a much lower frequency. Occurrence of CML is rare after organ transplantation.<sup>1,2</sup> The known mechanism of occurrence of malignancy after transplantation is immunosurveillance due to chronic immunosuppression and direct tumorigenic effect of immunosuppressive drugs. Little is known about risk factors of myeloproliferative disorders secondary to renal transplantation.<sup>3</sup> Imatinib mesylate, a potent inhibitor of BCR-ABL protein tyrosine kinase, is effective as the first line treatment of CML.<sup>4</sup>

## Case Report

A 61 year old man with ESRD due to essential hypertension received kidney transplant after 9 months of hemodialysis from an unrelated living donor 3 years ago. The induction regimen consisted of cyclosporine 6 mg/Kg body weight and mycophenolate mofetil 2000 mg daily in addition to three courses of methylprednisolone 1000 mg daily that was followed by prednisolone 1 mg/Kg body weight daily. He did not receive any blood preparation during hemodialysis and after transplantation. The patient was discharged on day 17 after transplantation without any complications and a creatinine level of 1.6 mg/dL. In the first 2 years after transplantation, the immunosuppressive drugs were tapered gradually. The first increase in white blood cell count to 40,000/

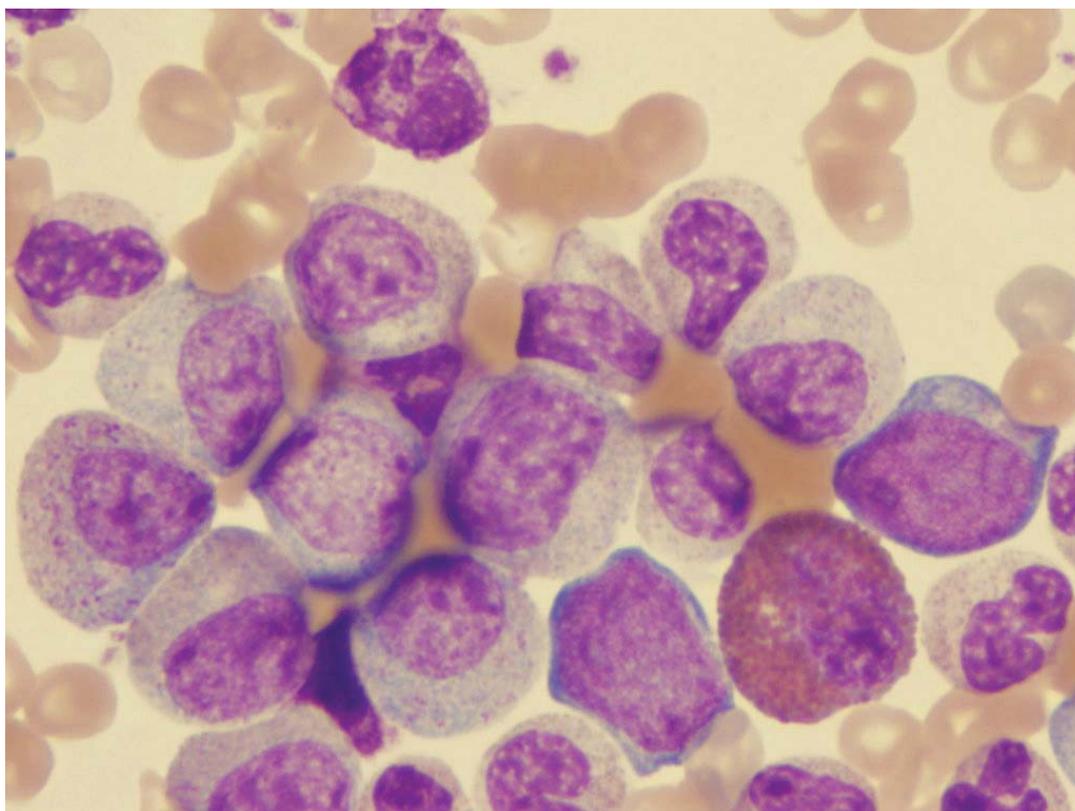
mm<sup>3</sup> emerged 26 months after transplantation when the patient was on cyclosporine 200 mg daily (2.2 mg/Kg body weight), mycophenolate mofetil (MMF) 2 g daily, and prednisolone 5 mg daily. The white blood cell count increased to 59,000/mm<sup>3</sup> on a subsequent laboratory test. Differentiation of white blood cells was normal. The patient did not have organomegaly or peripheral lymphadenopathy. Bone marrow aspiration was done by an oncologist and the diagnosis of CML was confirmed. Philadelphia chromosome was positive on cytogenetic study performed by a specialist in genetics. Treatment was initiated with Imatinib mesylate (200 mg daily). Creatinine was elevated to 3.4 mg/dL with initiation of therapy, as a result of drug interaction between cyclosporine and imatinib, both affecting P450 enzyme, CYP3A4. CSA level was 244 µg/mL at this time. After reducing the dose of cyclosporine to 75 mg twice daily (with CSA serum level of 232 µg/ml), creatinine fell to 2.8 mg/dL. Further lowering the dose of cyclosporine to 50 mg twice daily (with CSA serum level of 95 µg/ml), creatinine fell lower to 1.1 mg/dL. During two months after initiation of Imatinib, the white blood count declined to 5,750/mm<sup>3</sup>, the platelet count was normal and hemoglobin fell from 12 to 9.8 g/dL. After prescription of fer-folic three times daily, hemoglobin was corrected to 11.1 g/dL. The other laboratory tests, including blood sugar, thyroid function tests and liver function tests, were in normal range. EBV and CMV IgM levels measured by ELISA method were negative. At the time of this report, after 24 months of therapy with Imatinib Mesylate (Glevec Novartis) 200 mg daily with maintained use of immunosuppressive drugs including cyclosporine 50 mg twice daily, mycophenolate mofetil 1.5 gr daily and prednisolone 5 mg daily, the patient has good level of transplanted kidney function and his creatinine level is 1.03 mg/dL.

## Discussion

CML is a clonal disorder of hematopoietic stem cell manifesting with increased number of myeloid cell count. Reciprocal translocation between chromosomes 9 and 22 plays a central role in the pathogenesis of CML. Abelson (ABL) oncogene of chromosome 9, which encodes tyrosine kinase, is translocated in a specific re-

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**Figure 1.** Peripheral blood smear with hyperleukocytosis, absolute basophilia, eosiniphillia and less than 5% blast

**Table 1.** Evaluation of hematological and chemical laboratory data after renal transplantation

Time after transplantation (months)	12	24	26	27	28	30	40	50
Time after Imatinib Initiation (months)			0	1	2	4	14	24
WBC (per mm <sup>3</sup> )	4500	5350	40000	59000	5750	8700	6300	7500
PMN (%)	65	63	58	60	59	57	61	60
Hb (g/dL)	11.8	12.1	12	9.8	10	11.1	12.3	12.5
Platelets ( $\times 10^3$ per mm <sup>3</sup> )	193	185	162	198	176	205	218	188
Creatinine (mg/dL)	1.3	1.12	1.4	3.4	2.2	1.1	1.09	1.03
FBS (mg/dL)	98	103	87	100	102	88	93	95
CsA dose (mg/Kg/day)	2.6	2.2	2.2	2.2	1.7	1.14	1.1	1.1
T <sub>0</sub> CsA level ( $\mu$ g/mL)	---	---	---	244	232	95	---	---
ABL- BCR	---	---	+	---	---	---	---	---

gion of chromosome 22 named Break pan Cluster Region (BCR). The product of this 9:22 translocation [t(9;22)] is known as the Philadelphia chromosome. A fusion gene ABL-BCR is produced that encodes a deregulated tyrosine kinase resulting in manifestations of CML.<sup>5,6,7</sup>

Understanding the molecular pathogenesis of CML has improved therapy options for this disorder. Treatment of CML is based on inhibition of BCR-ABL oncogene expression, inhibition of other genes important to pathogenesis of CML, inhibition of BCR- ABL protein function and finally, immunomodulation.<sup>8</sup>

Imatinib mesylate is a potent inhibitor of ABL-BCR protein tyrosine kinase encoded by the Philadelphia chromosome that has been proved to be effective as first line treatment of CML. The goal of treatment with Imatinib is to achieve not only the cytogenetic but also complete molecular remission. Complete molecular remission is defined as the state when the level of ABL-BCR is undetectable by quantitative polymerase chain reaction (PCR).<sup>9,10</sup>

According to reports in the past 35 years, 25 cases of CML have occurred after organ transplantation. Of these, 13 have developed

in renal transplant recipients who were under treatment with cyclosporine, azathioprine and prednisolone.<sup>11</sup> To our knowledge, this is one of the rare reports of occurrence of CML in a renal transplant recipient under treatment with mycophenolate mofetil. Most patients with CML after transplantation have been over 55 years of age, similar to our patient. We evaluated remission in our patient by clinical improvement and blood cell counts only and a second cytogenetic study was not performed.

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