

LETTER TO THE EDITOR

Successful allogeneic stem cell transplantation in second chronic-phase CML induced by the tyrosine kinase inhibitor nilotinib (AMN107) after blast crisis under imatinib

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Allogeneic stem cell transplantation (allo-SCT) in the pre-imatinib era was the treatment of choice for chronic myelogenous leukemia (CML) in first chronic phase for patients under 45 years of age if an human leukocyte antigen (HLA)-identical donor was available, with 5-year leukemia-free survival rates of up to 60%.¹ In newly diagnosed chronic phase CML, imatinib produced a complete cytogenetic response rate of 84% at 42-month follow-up.² Patients achieving a major molecular response have a high probability of sustained responses.³ Thus, allogeneic transplantation is no longer the treatment of choice in first chronic phase CML.⁴ However, in advanced-phase CML and Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph + ALL), responses to imatinib are usually of short duration.^{5–8} Data for transplantation in blast crisis are discouraging.⁹ Therefore, attempts have been made to convert CML blast crisis into a second chronic phase by conventional chemotherapy. Unfortunately, only about 30% of the patients thereby entered the second chronic phase.¹⁰

Alternative BCR-ABL kinase inhibitors, such as nilotinib (AMN107) or dasatinib (BMS-354825), have been developed. Both agents have already entered clinical trials and both display promising activity in patients with imatinib-resistant chronic- and advanced-phase CML and imatinib-resistant Ph + ALL, respectively.^{11,12} To our knowledge, no data are currently available about allo-SCT after induction of a second chronic phase with either nilotinib or dasatinib.

We report here the case of a 46-year-old male patient who was diagnosed with Philadelphia chromosome-positive CML in first chronic phase. He received imatinib 400 mg daily and gained complete hematologic remission within 4 months of treatment. However, cytogenetic analysis at that time revealed duplication of the Philadelphia chromosome in 4/25 metaphases, indicating amplification of the *BCR-ABL* gene. At that time, the imatinib dose was not increased. Five months later, the patient was presented at our institution with myeloid blast crisis. No point mutation in the *BCR-ABL* kinase domain was detected. Doubling the dose of imatinib to 800 mg daily resulted in clearance of blasts in the peripheral blood. However, thrombocytopenia and anemia persisted and bone marrow analysis demonstrated 70% myeloid blasts with duplication of the Philadelphia chromosome in 11/25 metaphases. A second

chronic phase was achieved after 4 months of treatment with nilotinib (400 mg b.i.d.) in a phase I/II clinical trial. A major cytogenetic response was gained and the clone harboring the Philadelphia chromosome duplication had disappeared. However, *BCR-ABL* transcripts persisted with a *BCR-ABL* to *ABL* ratio of 2.034. An allogeneic peripheral blood SCT from an HLA-identical male sibling was performed after conventional conditioning with fractionated total body irradiation 12 Gy and cyclophosphamide 120 mg/kg BW. ATG was added at a dose of 5 mg/kg BW for 3 days. The patient received standard immunosuppression with cyclosporin-A and a short course of methotrexate. Prociclide was given for veno-occlusive disease prophylaxis. The patient received standard antibiotic, antiviral and antifungal prophylaxis. Post transplant, the patient displayed an increase in serum bilirubin to a maximum of 9.3 mg/dl on day +6. No other unexpected toxicity was noted. The patient had rapid and sustained engraftment with a neutrophil count above $1 \times 10^9/l$ on day +14 and platelet count above $50 \times 10^9/l$ on day +18. Chimerism analysis (STR-PCR) on days +28 and +100 showed complete donor hematopoiesis. Complete molecular remission as evidenced by real-time quantitative PCR negativity for *BCR-ABL* transcripts was reached on day +28. The patient developed acute GVHD of the skin grade 3 on day +18 and responded to steroid treatment. Furthermore, he developed CMV reactivation and received pre-emptive antiviral therapy with oral valganciclovir for 21 days. The patient did not receive AMN107 after the transplant and is still in complete molecular remission with nested PCR negativity >365 days after the transplant. He is off immunosuppression with limited chronic GVHD of the skin.

In the treatment of imatinib-resistant, accelerated and blast-phase CML as well as Ph-positive ALL, even novel ABL kinase inhibitors like nilotinib or dasatinib may not produce long-term disease-free survival in a substantial proportion of cases. Thus, patients achieving a significant remission receiving one of the novel kinase inhibitors who are eligible for allo-SCT should be considered for SCT as consolidation, which may offer the chance of long-term survival. It is currently not clear whether or not treatment with nilotinib or dasatinib should be continued after allo-SCT in these patients.

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