

Treatment of leukemia relapse after allogeneic hematopoietic stem cell transplantation by donor lymphocyte infusion and STI-571

Donor lymphocyte infusion (DLI) has become standard therapy for relapse after allogeneic hematopoietic stem cell transplantation (allo-HSCT).¹⁻³ However, results in acute leukemia are disappointing, probably because of the high proliferative capacity of blast cells and the delayed anti-leukemic effect of DLI. STI-571 is a tyrosine kinase inhibitor that has substantial activity in Ph-chromosome-positive acute leukemia. We present a patient illustrating that the association of STI-571 (early reduction of the proportion of blasts) and DLI (delayed anti-leukemic activity) may be useful.

Donor lymphocyte infusion (DLI) has become standard therapy for relapse after allogeneic hematopoietic stem cell transplantation (HSCT).¹⁻⁵ However, although DLI permits achievement of complete remissions in the majority of cytogenetic or hematologic relapses of CML, results in more advanced disease or in acute leukemia are disappointing, probably because of the high proliferative capacity of blast cells¹ and the delayed anti-leukemic effect of DLI.⁶

STI-571 is a tyrosine kinase inhibitor that has substantial activity in blast crises of CML and in Ph-chromosome-positive acute leukemia.⁷ Since the outcome of DLI is better in early phase CML than in more advanced relapse, a reduction in the proportion of blasts in the marrow of patients with CML in blast crisis or with Ph-chromosome-positive acute leukemia may be a useful step before DLI. This observation reports the first successful use of STI-571 and DLI in a patient relapsing with Ph-chromosome-positive acute leukemia after HSCT.

A 33-year old woman with biphenotypic Ph-chromosome-positive acute leukemia in first relapse underwent an allogeneic

CD34-selected (6.1×10^6 CD34⁺ cells) peripheral blood stem cell transplant from an unrelated male donor after a conditioning regimen consisting in 12 Gy total body irradiation, Ara-C (18 g/m²) and melphalan (140 mg/m²). She also received pre-emptive DLI on day 0, 60 and 100 (with 1, 1 and 2×10^7 CD3⁺ cells recovered from the CD34-negative fraction, respectively). Graft-versus-host disease (GVHD) prophylaxis was carried out with cyclosporine (CyA) plus short-course methotrexate. The post-transplant course was unremarkable except for the occurrence of grade III cutaneous acute GVHD that responded well to steroids.

Evaluation of response was carried out by cytology, standard cytogenetics and fluorescent *in situ* hybridization (FISH) analysis and evaluation of bone marrow (BM) chimerism by FISH. BM analysis on days 40 and 100 evidenced complete cytogenetic remission (Figure 1) (although reverse transcription polymerase chain reaction (RT-PCR) was still strongly positive) and a BM chimerism of 98% and 99%, respectively. Unfortunately, the patient relapsed on day 152 (0.2×10^9 blasts/L in blood and 75% blasts in BM). Cytogenetics showed 100% Ph-chromosome-positive cells as well as a complex karyotype. Cyclosporine was discontinued and the patient received a large dose of donor lymphocytes (20×10^7 CD3⁺ cells). STI-571 therapy (600 mg/day) was started on day 160 in the presence of 15.7×10^9 blasts/L in the blood. Nine days later, blasts had disappeared from her blood. Subsequently, the patient developed grade IV cutaneous acute GVHD on day 172 that responded well to steroids and tacrolimus. BM analysis on day 193 showed a complete response with a BM chimerism of 99.8% and no BCR-ABL rearrangement on FISH analysis (although RT-PCR remained slightly positive). A new BM analysis on day 240 evidenced a complete molecular response and the patient remains in CR for more than 150 days after the onset of STI-571 therapy. STI-571 is being continued without any side effects, except possibly the persistence of pre-existing thrombocytopenia.

Whereas responses to DLI are often delayed,¹⁻⁴ the kinetics of

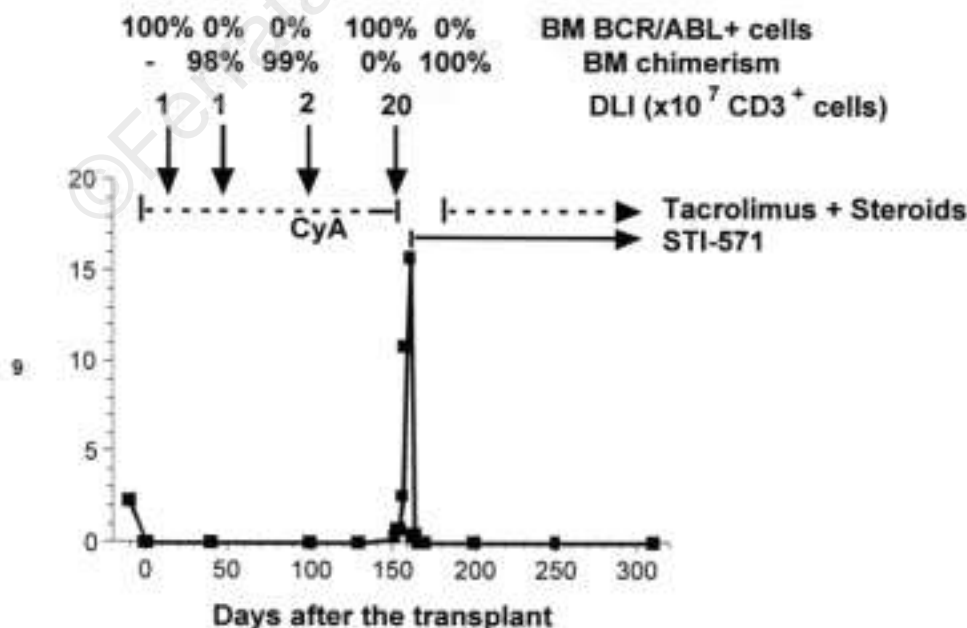


Figure 1. Evolution of blasts in peripheral blood as well as marrow leukemia and chimerism.

response in our patient was similar to that reported by Druker⁷ in a patient with chronic myeloid leukemia in blast crisis receiving STI-571 alone, suggesting that the mechanism of blast clearance in our patient was related to STI-571. However, less than 10% of patients with Ph-chromosome-positive acute leukemia achieved complete cytogenetic response (and molecular responses were not even reported) with STI-571 alone.⁷ In addition, less than 15% of such patients treated with STI-571 remained in hematologic remission after a follow-up of 58 to 349 days.⁷ Therefore, DLI with cyclosporine withdrawal most probably also played an important role in the elimination of blast cells in our patient who previously failed to benefit from much lower doses of donor lymphocytes given under cyclosporine prophylaxis. On the other hand, waiting for the probable relapse to occur before administering donor lymphocytes would have substantially jeopardized the potential benefit of DLI.

We conclude that the combination of STI-571 and DLI may be highly effective as treatment for Ph-chromosome-positive acute leukemia relapsing after HSCT.⁸ Although we hope that reduction of tumor burden by STI-571 would enhance the efficacy of DLI, longer follow-up is needed to see whether this strategy can result in durable remission.

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