Persisting molecular remission ten years after donor lymphocyte infusion for hematologic relapse in chronic myeloid leukemia

We report of the case of a persisting cytogenetic and molecular remission 10 years (yrs) after donor lymphocyte infusion (DLI) for hematologic relapse of chronic myeloid leukemia (CML) following HLA-identical allografting, achieved without acute or chronic-graft-versus host disease (GVHD) or pancytopenia.

A female patient, aged 36, was diagnosed in March 1986 as having Ph' positive CML. At diagnosis her platelet count was $3,300\times10^9$/L. It dropped after hydroxyurea (HU) and plateletpheresis, but after a few months again reached $1,800\times10^9$/L with refractoriness to HU and peptichemiotherapy. In January 1987 she was grafted with bone marrow (BM) from her ABO incompatible, HLA identical brother, after conditioning with total body and splenic irradiation (10 Gy) and cyclophosphamide (120 g/kg).

HLA typing was as follows: A2; B7, 35; Cw6. Cyclosporin A (CsA) and methotrexate were given as GVHD prophylaxis.

Hematologic remission was achieved without GVHD, and on day +41 a bone marrow specimen revealed a normal male karyotype. Cytogenetic relapse with 10% Ph' positive metaphases occurred on day+361. CsA was discontinued and the karyotype again became 100% 46,XY on day +590. Ph' positive metaphases reappeared later : there were 20% on day +905 and increased up to 60% on day +1122 with an additional inv(3)(p23;q29) in some metaphases. Blood counts were in the normal range until day +1122; thereafter the patient had an hematologic relapse with a platelet count of $2,000\times10^9$/L and was given 1 month of oral melphalan.

Assessment of bcr-abl chimeric transplant by means of qualitative polymerase chain reaction (PCR) turned out to be positive; the type of transcript was b2a2.

On day +1275 - with white blood cells 0.6×10^9/L, hemoglobin 10.2 g/dL, platelets 625×10^9/L - she received a single dose of 1×10^8/kg DLI.

She achieved hematologic and cytogenetic remission without acute or chronic GVHD or pancytopenia. The time to complete cytogenetic remission was 54 days. No BM Ph'positive metaphases have since been detected during the following 10 yrs.

Monitoring of BM and blood bcr-abl transcripts by means of qualitative PRC on days +3232 and + 4739 and by means of quantitative PRC on day +4739 turned out to be negative.

Figure 1 depicts the course of platelets and Ph' positive metaphases.

There are various approachs to relapse following allografting in CML aiming to restore complete remission (CR).

The first is to reduce or terminate immunosuppression. Another is DLI, a particularly effective therapeutic option in CML, which induces CR in up to 100% of patients in molecular/cytogenetic relapse.[1-4]

Patients with hematologic relapse fare worst, although those in chronic phase do slightly better than those with accelerated or blastic phase.[5,6]

DLI appears to be able to eradicate clonogenic leukemia cells or to control their regrowth inducing durable remission.[2,7]

The assessment of bcr-abl transcripts by means of qualitative and quantitative PCR appears to have a significant clinical value. In such settings quantitative PCR provides pratical indications capable of directing the subsequent therapeutic options such as suspension of CsA and DLI.[1,8]

Our patient had many adverse prognostic factors: absence of acute or chronic GVHD post-BM transplantation, early relapse, hematologic relapse in accelerated phase, a long interval between transplant and DLI, a long interval between relapse and DLI, absence of acute or chronic GVHD post-DLI.[6,7,9]

An EBMT retrospective analysis reported that survival after the first relapse in allografted CML patients was related to: time from diagnosis, disease phase at transplant, disease stage at relapse, time from transplant to relapse and donor type. The probability of patients with 2 risk factors surviving for 10 years appeared to be only 14%.[10] Nevertheless our patient achieved CR, confirmed by a follow up of 10 years, with absence of BM Ph'-positive metaphases, and no bcr-abl transcripts as detectable by means of qualitative and quantitative PCR.

This case points out the durability of molecular remission in CML after DLI, proves that this effect can be achieved and that may lead to a cure of CML even in poor risk patients.

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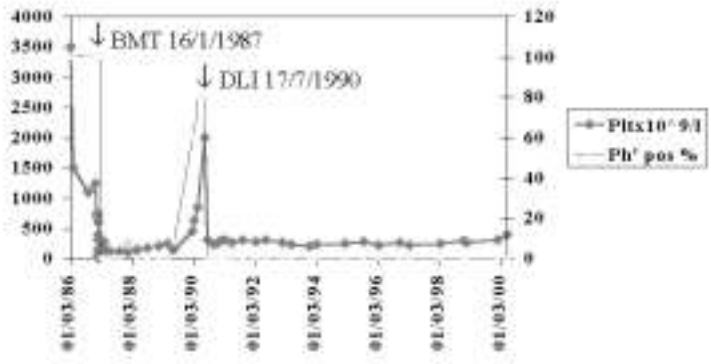

Figure 1.

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