short report
Haematologica 1995; 80:338-340

DONOR BUFFY-COAT INFUSION AND CHEMOTHERAPY FOR LEUKEMIA IN RELAPSE AFTER MARROW TRANSPLANTATION

Vinko BogdaniÊ*, Igor Aurer*, Vlasta Hitrec°, Dubravka Boban#, Damir Nemet*, Silva ZupanËiÊ-©alek*, Boris Labar*

**Division of Hematology, Department of Internal Medicine; °Cytogenetic Laboratory, Department of Pediatrics; #Department of Clinical Laboratory Diagnostics, Medical School and University Hospital Rebro, Zagreb, Croatia*

ABSTRACT

A patient relapsing with blastic lymphoid transformation of chronic myeloid leukemia after bone marrow transplantation received donor buffy-coat infusion. Low-dose chemotherapy was added because of a rapid WBC increase. Complete hematologic and cytogenetic remission was obtained. The patient remained in complete hematologic and cytogenetic remission for four months until he died in an accident. Two patients with acute leukemia failed to respond to a similar treatment.

Key words: bone marrow transplantation, acute leukemia, chronic leukemia

Treatment of patients with leukemia who relapse after allogenic bone marrow transplantation (BMT) is generally futile. However, remissions can be achieved in many patients relapsing post BMT with chronic myeloid leukemia (CML) in chronic phase through the use of donor leukocyte (buffy-coat) infusions.[1-3] This treatment seems to be unsuccessful in CML in blastic transformation or acute leukemia in relapse after BMT.[3-5]

We report a patient with CML who relapsed after BMT. He was transplanted in chronic phase but relapsed in lymphoid acute phase. He responded to a combination of donor buffy-coat infusion and low-dose chemotherapy; two other patients with acute leukemia failed to respond to this treatment.

Case report

Patient #1

A 30-year-old man received an allogeneic bone marrow transplant from his HLA-identical brother a year after diagnosis of Philadelphia chromosome positive CML while in first chronic phase. Prior to BMT he was treated with hydroxyurea. Conditioning was performed with busulfan and cyclophosphamide.[6] Cyclosporine and methotrexate were given for GvHD prophylaxis.[7] He developed acute gut GvHD, grade 1, that resolved after steroid therapy. Cytogenetic analyses were not performed during hematologic remission.

Eighteen months after BMT, while off all immunosuppression, he relapsed with CML in acute lymphoblastic phase (Table 1). Blasts were HLA/DR and CD34 positive, PAS positive, POX and Sudan black negative. Karyotype was 45,XY,t(9;22)(q34;q11),del9p, –3/–,der(11) t(11q21;?). He received buffy-coat cells from his original donor divided in four doses over two days. Eleven days after infusion because of a rapid increase in WBC, the patient was given methylprednisolone 1 mg/kg/day for 22 days and a single dose of vincristine 2 mg. WBC fell promptly. Thirty-five days after buffy coat infusion and 23 days after chemotherapy, WBC rose to 1.0×10^9/L and the patient became platelet transfusion independent. On day 50 the blood

Correspondence: Dr. Igor Aurer, Division of Hematology, Department of Internal Medicine, University Hospital Rebro, Ki patiÊeva 12, 41000 Zagreb, Croatia. Tel. & Fax international +385.1.233368.
Acknowledgments: this work was supported in part by grants 3-01-074 and 3-01-075 from the Croatian Ministry of Science.
Received November 10, 1994; accepted April 10, 1995.

count returned to normal. Bone marrow examination showed that leukemia was in remission. Cytogenetic analysis was performed on days 40 and 54. Twelve and 25 metaphases were analyzed, respectively, and all were normal. There were no signs of GvHD.

The patient remained well with normal blood counts until he died in an accident four months after treatment.

Patient #2

A 38-year-old woman received an allogeneic bone marrow transplant from her HLA-identical brother eight months after diagnosis of acute lymphoblastic leukemia (ALL) (FAB L2, immunophenotype 0) while in first complete remission. Conditioning was performed with cyclophosphamide and total body irradiation. Cyclosporine and methotrexate were given for GvHD prophylaxis.[7] There were no signs of acute GvHD.

Six months after BMT she relapsed (Table 1). Karyotype was 46,XX,t(4;11)(q21;q23). She received two doses of vincristine, 2 mg each and methylprednisolone 1 mg/kg/day for three weeks without improvement. One week after the last dose of vincristine, buffy-coat from her original donor was administered in four doses over two days. Leukemia persisted. Vincristine was reintroduced but the patient died of fungal pneumonia in aplasia 38 days after the start of chemotherapy and 17 days after buffy-coat administration.

Patient #3

A 32-year-old woman received an allogeneic bone marrow transplant from her HLA-identical brother six months after diagnosis of acute myeloid leukemia (AML) while in first relapse. Conditioning was performed with cyclophosphamide and total body irradiation. Cyclosporine and methotrexate were given for GvHD prophylaxis.[7] There were no signs of acute GvHD. One month post-transplant she suffered leukemia relapse (Table 1). Buffy coat from the same donor was administered in four doses over two days starting 49 days after transplantation. A week later she received a single dose of vincristine 2 mg and daunorubicin 45 mg/m^2 and cytarabine 200 mg/m^2 for two days. Leukemia persisted and she died of progressive AML 77 days after BMT and 28 days after buffy-coat administration.

Table 1. Hematologic data from the three treated patients.

Patient	*1*		*2*		*3*	
Data at administration of	buffy coat	chemo	buffy coat	chemo	buffy coat	chemo
WBC ($\times 10^9$/L)	20.7	78.0	1.0	3.3	20.8	64.3
Blasts in blood (%)	78	91	17	36	80	80
Blasts in marrow (%)	95	ND	82	98	41	60
Buffy-coat (cells $\times 10^8$/kg)	2.15		8.5		4.4	
Days between buffy-coat and chemo	11		18		7	

ND = not done

Discussion

All fully reported patients relapsing with acute phase CML after BMT failed to respond to donor buffy-coat infusions with or without interferon-α.[3-5] Our patient received only low-dose chemotherapy directed primarily at preventing hyperleukocytosis. Even so, cytopenia was profound and prolonged, as seen after donor buffy-coat infusions in transplanted patients relapsing with chronic phase CML.[2] Although the interpretation of this case is marred by its short follow-up, it seems that adding low-dose chemotherapy to donor buffy-coat infusion might have additive effects in patients relapsing with blastic transformation of CML after BMT. In fact, this may favor the recruitment of residual donor stem cells: it should be noted that benign stem cells frequently coexist with leukemic cells in CML patients, irrespective of BMT, and that treatment may positively select the normal ones.[8,9]

A similar combination of donor leukocyte infusions and low-dose chemotherapy was described in four patients with acute leukemia in relapse post BMT:[10] only one responded. We tried this combination in one patient with acute myeloid leukemia and one with acute lymphoid leukemia relapsing after BMT. Although they received more chemotherapy,

they failed to respond, indicating a much lower sensitivity of acute leukemias to this therapeutic approach.

References

1. Kolb HJ, Mittermuller J, Clemm C, et al. Donor leukocyte transfusions for treatment of recurrent chronic myelogenous leukemia in marrow transplant patients. Blood 1990; 76:2462-5.
2. Antin JH. Graft-versus-leukemia: no longer an epiphenomenon. Blood 1993; 82:2273-7.
3. Porter DL, Roth MS, McGarigle C, Ferrara JLM, Antin JH. Induction of graft-versus-host disease as immunotherapy for relapsed chronic myeloid leukemia. N Engl J Med 1994; 330:100-6.
4. Drobyski WR, Keever CA, Roth MS, et al. Salvage immunotherapy using donor leukocyte infusions as treatment for relapsed chronic myelogenous leukemia after allogeneic bone marrow transplantation: efficacy and toxicity of a defined T-cell dose. Blood 1993; 82:2310-8.
5. Hertenstein B, Bunjes D, Novotny J, et al. Donor buffy coat transfusions (BC) for treatment of relapsed chronic myeloic leukemia (CML) after allogeneic bone marrow transplantation (BMT)(Abstr). Exp Hematol 1993; 21:1107.
6. Tutschka PJ, Copelan EA, Klein JP, et al. Bone marrow transplantation for leukemia following a new busulfan and cyclophosphamide regimen. Blood 1987; 70:1382-8.
7. MrsiÊ M, Labar B, BogdaniÊ V, et al. Combination of cyclosporin and methotrexate for prophylaxis of acute graft-versus-host disease after allogeneic bone marrow transplantaion for leukemia. Bone Marrow Transpl 1990; 6:137-41.
8. Lemoli RM. Characterization and selection of benign stem cells in chronic myeloid leukemia. Haematologica 1993; 78: 393-400.
9. Martinelli G, Lemoli RM, Farabegoli P, et al. Persistence of non-clonal hematopoietic progenitor cells in blastic phase chronic myelogenous leukemia (CML). Haematologica 1994; 79:445-7.
10. Szer J, Grigg AP, Phillips GL, Sheridan WP. Donor leucocyte infusions after chemotherapy for patients relapsing with acute leukaemia following allogeneic BMT. Bone Marrow Transpl 1993; 11:109-11.