Reduced-intensity allografting for chronic myeloid leukemia in the first chronic phase

Haematologica 2004; 89:(2)e24-e25

To the editor:

We have read with great interest the recent comment by O´Dwyer,[1] which discusses the treatment of chronic myeloid leukemia (CML) using imatinib. The results of imatinib in CML in the first chronic phase (CP) are impressive.[2] However, several major questions remain.1 We would like to mention another treatment option for CML without detracting from the importance of imatinib in the treatment of CML. The present report summarizes our experience with the treatment of CML in the first CP using reduced-intensity allogeneic stem cell transplantation (reduced-intensity conditioning regimen, RIC). The rationale behind RIC is to induce the optimum graft-versus-leukemia effect to eliminate all malignant cells by donor alloreactive immunocompetent cells.[3,4] RIC consisted of intensive immunosupression with intravenously administered fludarabine (30 mg/m^2/d on days – 10 to – 5), oral busulfan (4 mg/kg/d administered in 4 daily doses of 1 mg/kg on days – 6 and – 5), and anti-human T-lymphocyte globulin (ATG) at a dose of 10 mg/kg/d on days – 4 to – 1.3,4. Between July 1998 and January 2003, we carried out transplants on 16 patients with CML in the first CP at two transplant centres in the Czech Republic (The University Hospital Brno and The Institute of Hematology and Blood Transfusion Prague) using this NST regimen. Graft-versus-host disease (GVHD) prophylaxis consisted of cyclosporine A in 12 patients. The remaining 4 patients received additional methotrexate (MTX). There was no distinctive reason for MTX in GVHD prophylaxis. MTX was administered at the Prague centre according to its use at this centre. Early discontinuation of cyclosporine A was tried in the cases of mixed chimerism in an attempt to amplify the graft-versus-leukemia effect. Peripheral blood stem cells (n=14) and bone marrow (n=2) from 1 human leukocyte antigen (HLA) fully matched unrelated donor and 15 HLA-identical siblings were used. The median age of our patients was 52 years (44-59). The median number of transplanted CD34$^+$ cells and CFU-GM was 8.6*10^6/kg (3.1-16.0), and 85.6*10^4/kg (16.0-114.7), respectively. All patients engrafted. The time to recovery of the absolute neutrophil count above 0.5*10^9/L ranged between 0 and 20 (median 16) days. The period of thrombocytopenia with platelet transfusion requirements ranged between 0 to 14 days (median 1 day). Only two patients experienced oral mucositis. Hepatic veno-occlusive disease was not observed. Mortality at day 100 was zero. Febrile neutropenia was noted in 6 patients. Acute GVHD occurred in 6 patients. Acute GVHD developed in 1 patient receiving additional MTX. Chronic GVHD occurred in 7 patients. Chronic GVHD developed in 2 patients receiving additional MTX. MTX did not significantly affect the results of the patients. On day +60, complete chimerism was achieved in 50% of the patients. After a follow up in 58 months, 4 patients had relapsed (2 hematologic relapses, 2 molecular relapses), and 1 patient had died of severe GVHD after donor lymphocyte infusion for a relapse of CML (day +669 after transplantation). Nine patients are free of leukemia by quantitative reverse transcriptase polymerase chain reaction. The overall survival and relapse-free survival curves are shown in Figure 1. A high proportion of CML patients treated using RIC appear to be cured as defined by the absence of molecular evidence of disease.5 Our pilot study confirms the previous results from Or *et al.*[3] (Jerusalem group) in CML patients. The results of the Or et al study are remarkable. The Kaplan-Meier probability of survival and disease-free survival at 5 years was 85%. From our reports and those of Or *et al.*[3] it could be concluded that although the results with imatinib look promising, given the continuous improvement in the results of patients undergoing allogeneic transplantation, it is critical in the decision-making process to have extensive information on the patients even in the imatinib era (as suggested by Silver *et al.*[6] prior to imatinib). It could also be concluded, regarding conventional allogeneic transplantation, that our report would support the development of a prospective randomised trial comparing RIC and conventional allogeneic transplantation. RIC provide a safe and well-tolerated therapeutic option for patients with CML in the first CP with a matched donor.

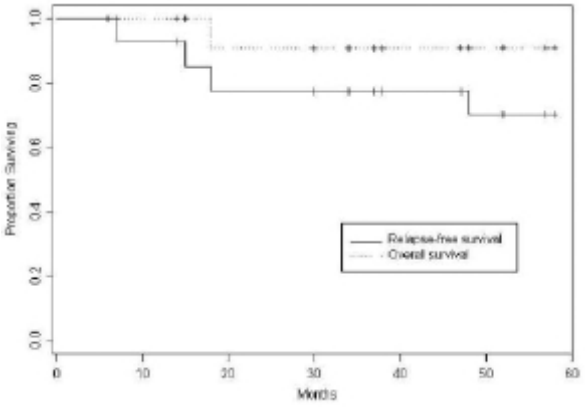

Figure 1. The overall survival and relapse-free survival of patients with chronic myeloid leukemia in the first chronic phase treated with nonmyeloablative stem cell transplantation in the Czech Republic.

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