NON-MYELOABLATIVE ALLOGENEIC STEM CELL TRANSPLANTATION
FOR THE TREATMENT OF CHRONIC MYELOID LEUKEMIA IN FIRST CHRONIC PHASE

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Running head: Non-myeloblatative stem cell transplantation in CML

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Trust; the Fig Tree Foundation and the Cancer Treatment Research Foundation. This
work was carried out in the Danny Cunniff Leukemia Research Laboratory.
ABSTRACT

Reduced intensity, or non-myeloblative stem cell transplantation (NST) is designed to induce host-versus-graft tolerance by engraftment of donor stem cells. The rationale behind NST is to induce optimal graft-versus-leukemia (GVL) effects for elimination of all malignant cells by donor alloreactive immunocompetent cells as an alternative to standard high-dose myeloablative chemoradiotherapy. NST based on the use of fludarabine, low-dose busulfan and anti-T-lymphocyte globulin (ATG), was employed in 24 patients with chronic myeloid leukemia (CML) in first chronic phase (CP) aged 3-63 years. Graft-versus-host disease (GVHD) prophylaxis consisted of low-dose cyclosporine (CSP), some with low-dose methotrexate. Early discontinuation of CSP was attempted in cases of mixed chimerism in an attempt to amplify GVL effects. All 24 patients showed rapid 3-lineage engraftment, mostly without complete aplasia; 6 patients did not require transfusion of any blood products. NST was associated with minimal procedure-related toxicity. The incidence of acute GVHD ≥ grade I was 54%, however, this increased following CSP withdrawal. After a follow-up of up to 70 (median 42) months 21/24 patients remain alive and free of disease. The GVL effects induced by donor immunocompetent lymphocytes eradicated all host hematopoietic cells, as evidenced by molecular testing. The Kaplan-Meier probability of survival and disease-free survival at 5 years is 85±8% (confidence interval 70-100%). NST may successfully replace myeloablative stem cell transplantation, thus providing a safer, well tolerated therapeutic option for all patients with CML in first CP with a matched donor, however, this conclusion must be tested in a prospective randomized clinical trial.

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Introduction

The use of bone marrow transplantation (BMT) for chronic myeloid leukemia (CML) from a fully matched donor is considered a most effective curative modality (1,2). Until recently, myeloablative conditioning was considered mandatory for the elimination of malignant hematopoietic cells and for prevention of allograft rejection. However, animal experiments in the 1960’s (3,4), and clinical observations in the 1970’s confirmed that immune-mediated graft-versus-leukemia (GVL) effects play the most important role in the course of BMT (5,7). Furthermore, since 1987 we have documented that donor lymphocyte infusion (DLI) post-grafting, with no additional chemotherapy, can eliminate leukemia cells even in patients fully resistant to maximally tolerated doses of chemoradiotherapy (8,9). Since then, DLI has been confirmed as the most effective therapeutic modality, especially for patients with CML with residual or recurrent disease following BMT (10-12). The rate of complete remission in response to DLI has been impressive, with 70-80% of relapsed CML patients accomplishing durable remissions following DLI (8-12), with lower success rates in other diseases treated by BMT (13-21). Given the unequivocal therapeutic role of donor lymphocytes in patients with CML (22) and considering the documented therapeutic potential of alloreactive donor lymphocytes administered post-BMT in CML patients relapsing following maximally tolerated doses of chemoradiotherapy (8-12), it seemed reasonable to exploit the therapeutic use of alloreactive donor lymphocytes following establishment of host-to-graft transplantation tolerance induced by engraftment of donor stem cells following reduced intensity, lymphoablative yet non-myeloablative, conditioning (23).
The present report summarizes our cumulative experience in a cohort of (24) consecutive patients with CML in first chronic phase and confirms that durable remission, with eradication of molecular evidence of disease, can be accomplished without myeloablative conditioning, thus avoiding or minimizing procedure-related toxicity and mortality.

**Patients and Methods**

Twenty-four consecutive patients with Philadelphia positive CML, in first chronic phase were enrolled in this study, according to previously published criteria (24). Patients were included if they were proved to be in stable first chronic phase and consented to participate in the clinical trial, approved by the Review Board of the Hadassah Hospital in Jerusalem and the Souraski Hospital in Tel Aviv. Fifteen males and 9 females, ranging in age from 3-53 (median 35) years (Table 1). All the patients were referred to BMT between May 1996 and January 2001. Each adult participant in the study signed an approved informed consent form. Parental approval endorsed by the court was obtained for 3 minors. Nineteen patients were transplanted from fully matched HLA class I and II family members (16 sibling and one father); 5 patients received marrow grafts from fully matched unrelated donors (MUD) mildly or non-reactive in mixed lymphocyte culture.

NST consisted of intensive immunosuppression with intravenous (i.v.) fludarabine 30mg/m^2/day (on days -10 to -5); oral busulfan 4mg/kg/day in 4 divided daily doses of 1mg/kg (on days –6 and –5) as previously described (18). All MUD recipients also received rabbit anti-human T lymphocyte globulin (ATG Fresenius) at a dose of 10 mg/kg/day (on days –4 to –1). The dosage of ATG was lowered to 5 mg/kg/day in the
last 10 patients transplanted from first degree relatives. Donors were injected subcutaneously with granulocyte-colony stimulating factor (Neupogen, 5 µg/kg twice daily for 5 days) and mobilized peripheral blood stem cells were collected on days 5 and 6.

The details of the mobilized inoculum are presented in Table 2. Prior to NST, all patients received trimethoprim/sulfamethoxazole (10 mg/kg/day trimethoprin) on days -10 to -2, acyclovir (500 mg/m² x 3/day) from days –6 until day +100, and allopurinol (300 mg/day) on days -10 to -1. Administration of trimethoprim/sulfamethoxazole (twice weekly) was reinstituted after recovery from neutropenia as a preventive measure against pneumocystis carinii infection. CMV infections (diagnosed by 2 successive positive PCR’s) were treated with ganciclovir 10 mg/kg/day.

Graft-vs-host disease prophylaxis consisted of single-drug low-dose, short-term CSP 3 mg/kg i.v. daily in two divided doses starting on day –1 in the first 19 patients. The remaining 5 patients received methotrexate in addition: 15 mg/m² on day +1 and 10 mg/m² on days +3 and +6. Once the patients were dehospitalized, CSP was administered orally. CSP dosage was tapered during the second or third month post transplant, according to chimeric status and evidence of GVHD.

Neutropenic patients with culture-negative fever received a combination of gentamicin, cefazolin and mezlocillin, as a first line antibiotic protocol. Persisting fever was treated with amikacin and tazocin as a second line protocol, while imipenem was used as the third line protocol. In cases of persistent fever not responding to antibiotic therapy within 5 days, amphotericin B (1 mg/kg every other day) was added until the neutropenia resolved.
Starting on day -10, a DNA-PCR test was done weekly to detect cytomegalovirus (CMV). Two consecutive positive PCR results served as an indication for replacing acyclovir with ganciclovir until a minimum of two negative tests was obtained. Patients were treated in reverse isolation rooms equipped with HEPA filters, and received a regular diet. Additional supportive measures, such as parenteral nutrition and blood component transfusion were administered as necessary.

Acute and chronic GVHD were graded according to the Glucksberg’s criteria (25). Immediately upon the appearance of signs and symptoms of GVHD, i.v. methyprednisolone (2 mg/kg) and CSP were administered.

In order to assess engraftment, degree of chimerism, minimal residual disease and early relapse, patients were monitored at regular interval by cytogenetic analysis, and by donor and host-specific DNA markers, including male and female amelogenine gene PCR bands (26), and by VNTR-PCR assay (27). Cytogenetic analysis for Philadelphia chromosome and the BCR/ABL RT-PCR test were applied at the time of diagnosis and for detection of relapse during follow-up (28).

**Results**

The protocol used for conditioning was well tolerated by all 24 patients. Patients were free to leave the hospital in between treatment schedules and 9 were treated partially on an outpatient basis. The large majority of patients did not experience oral mucositis, thus being maintained on normal oral intake; 34% of the entire group required supplemental parenteral nutrition. Moderate to severe hepatic veno-occlusive disease (VOD) occurred in 3 patients, but resolved completely within 3 months. Fever
(> 38°C) was noted in 16 patients and positive blood cultures were documented in 4 patients.

All patients displayed evidence of engraftment shortly after NST and none exhibited immune-mediated rejection. Mixed chimerism was detected in 6 patients and lasted from 4 to 57 (median 11 weeks), all 6 converted to full donor chimerism. Degree of chimerism was evaluated weekly in patients with documented mixed chimerism and monthly in patients with documented full donor engraftment. In the other 18 patients rapid full engraftment of donor cells was confirmed, without evidence of transient mixed chimerism. In 20/24 patients the white blood cell count (WBC) remained above 0.1 x 10^9/L, and neutrophils were observed in the blood smear throughout the post transplant course, while in 4 patients WBC never dropped below 0.5 x 10^9/L. In one patient the WBC dropped to a level of 0.1 x 10^9/L for three days. The period of leukopenia (WBC < 0.5 x 10^9/L) ranged between 0 and 12 (median 4) days. Time to recovery of absolute neutrophil count (ANC) above 0.5 x 10^9/L ranged between 0 and 26 (median 16) days. In 4 patients ANC never dropped below 0.5 x 10^9/L. The period of neutropenia (ANC < 0.5 x 10^9/L) ranged from 0 to 12 (median 4) days. The time interval to platelet recovery (≥20 x 10^9/L) ranged from 0 to 26 (median 10) days. In 6 patients platelet support was not required. The period of thrombocytopenia, with platelet transfusion requirements (platelet < 20 x 10^9/L) ranged between 0 to 16 (median 3) days.

Mortality at day +100 was zero, indicating that NST was well tolerated by all patients in all age groups. Within an observation period of 7 – 63 (median 37) months following NST, both the overall survival and disease-free survival (Fig. 1) were
85±8% (95% confidence interval 70-100%), with no patients relapsing during this period.

Acute GVHD (≥grade I) occurred in 13/24 patients (probability 54% with 95% confidence interval of 34-74%) while on CSP (1 grade I, 7 grade II, 2 grade III and 3 grade IV). Early withdrawal of CSP, in 7 patients, in order to facilitate engraftment and eliminate residual host cells, resulted in 6 additional cases of acute GVHD (1 grade I, 3 grade II and 2 grade IV; thus accounting for an overall cumulative probability of acute GVHD of 75% (95%, confidence interval of 58-92%) (Fig. 2). The overall incidence of severe acute GVHD (grade III-IV), including 2 patients that developed grade IV GVHD only when CSP was discontinued was 29% (95% confidence interval of 2-47%) (Fig. 2). In 11 patients acute GVHD progressed to chronic GVHD. Four of these, developed acute GVHD while on CSP, and one, developed acute GVHD following early discontinuation of CSP. Only one patient developed de novo mild chronic GVHD (Table 1). The overall probability of chronic GVHD was 55% (95% confidence interval of 44-75%) (Fig. 3). Three patients died as a consequence of GVHD, one on day +116 due to acute GVHD, another on day +499 due to chronic GVHD and invasive fungal infection and the third patient on day +726 due to chronic GVHD and recurrent infections (Table 3). These were the only fatalities recorded in this series.

Mixed chimerism was observed in 6 patients, on CSP therapy, hence post-transplant immunosuppression was withdrawn abruptly. Three of these patients responded with total elimination of molecular evidence of disease (negative BCR/ABL RT-PCR), and host-type DNA by VNTR-PCR or amelogenine gene PCR. Of the remaining 3 patients, whose chimeric studies showed a majority of host cells, 3
received DLI. One patient (UPN 1119) received DLI in the form of blood stem cells obtained from the original donor on day +38, after which he converted to 100% donor cells with no residual circulating host DNA in the blood or in the marrow. The second patient (UPN 1137) underwent a course of incremental doses of DLI, starting on day +111, with T cell doses of $10^5$ /kg initially, $10^6$ and $10^7$ T cells/kg during the first 2 months, and $3 \times 10^8$ T cells when last given on day +308. The patient responded with a shift to 100% donor type cells by day +399 with no residual circulating host DNA in the blood or in the marrow. The third patient (UPN 1486) received DLI ($10^5$ T cells/kg) on day +210, again resulting in complete elimination of all detectable host cells. All the patients remain with 100% donor cells, with negative RT-PCT for BCR/ABL. At an observation period ranging from 14 to 70 (median 42) months, none of the patients featured any evidence of molecular relapse. Consequently, the Kaplan-Meier probability of disease-free survival in this cohort remains $85 \pm 8\%$ (95% confidence interval 70-100%) (Fig. 1).

Discussion

Our data based on a cohort of 24 patients with CML in first chronic phase suggest that durable engraftment of fully matched HLA allografts from related or unrelated donors and durable elimination of molecular evidence of disease may be accomplished with minimal procedure-related toxicity and no early mortality following non-myeloablative conditioning. The absence of graft rejection in this, admittedly small, group of patients, is in keeping with our recent publications summarizing larger cohorts of patients conditioned with NST for other indications (17,20), as well as with the cumulative international experience comprising larger numbers of patients.
treated with different NST regimen based on the same principles (18,19,29-31). The common denominator of most recent NST protocols is the use of fludarabine for prevention of graft rejection. This drug induces effective apoptosis of malignant as well as normal lymphocytes. Furthermore, fludarabine has synergistic effects in combination with other alkylating agents like busulfan (17,20), cytoxan (30,32), melphalan (18,29,33) or total body irradiation (TBI) (19,31,34,35), thus explaining proven efficacy for consistent engraftment of matched related and unrelated stem cell allografts. In fact, fully matched related or unrelated donor stem cells engraftment can be accomplished, while avoiding or minimizing early marrow aplasia and pancytopenia. Using the same NST regimen, engraftment was observed in all 16 consecutive recipients of allografts from unrelated donors, with 15 of 16 achieving 100% donor type chimerism (36), while the incidence of procedure-related toxicity, such as severe mucositis, VOD and multi-organ failure, and mortality were reduced. Clinical application of NST, is based on the concept that the transplant procedure is an improved immunotherapy protocol rather than an attempt to eliminate all host tumor cells by aggressive chemoradiotherapy upfront, prior to rescue with donor stem cells. This explains the markedly reduced early mortality rate among our patients as compared to the figures generally encountered in relation to the conventional myeloablative approach (37-39). These observations, if confirmed, may justify the use of NST for elderly patients in need and patients with poor performance status who would not normally qualify for standard myeloablative BMT.

Allogeneic stem cell transplantation is the only proven cure for CML, however, the standard myeloablative procedure is associated with early toxicity and mortality and late complications (1,2,37-39). Therefore, there is a dilemma in using BMT for
patients with asymptomatic CML that can be well controlled, though not necessarily
cured, with conventional cytoreductive agents like hydroxyurea, interferon or the
tyrosine kinase inhibitor STI571 (Glivec) (40). Delaying transplantation in CML
involves a complex decision, as best results are achieved if patients are transplanted
while still in chronic phase, and preferably within the first year of diagnosis.
Whereas postponement of BMT may be justified in patients responding to alpha
interferon or Glivec, other patients showing resistance to these agents, or in patients
with advanced stages of disease, BMT should be offered immediately. Due to
anticipated procedure-related toxicity, BMT is seldom offered to elderly patients,
even when the indication is unequivocal, due to increased procedure-related
mortality (24). Results from younger patients who underwent BMT following a
conventional myeloablative preparatory regimen, with high dose cytoxan and
busulfan or TBI, which were considered mandatory until recently, are unsatisfactory
in many centers due to acceptable procedure related toxicity and mortality in young
patients (37-39). However, using more intensive cytoreductive regimens, including
higher dose TBI or additional splenic irradiation as part of the conditioning, confers
no significant benefit over conventional protocols (38,39,41,42). The efficacy of
well-tolerated NST in CML as suggested by our data could be predicted by the
efficacy of elimination of molecular evidence of disease in the large majority of CML
patients who relapse following myeloablative BMT following treatment with DLI
alone (8-12). Occasionally, as shown herewith and as reported earlier in recipients of
conventional BMT, discontinuation of CSP alone can result in regression or relapse
(43). Likewise, there seems to be an increased risk of leukemia relapse in patients
receiving high-dose CSP after allogeneic BMT (44), thus again indicating the important role of alloreactive T cells in controlling CML.

Our data may also suggest that the use of NST may offer an advantage to recipients with CML in first chronic phase, receiving an allograft from phenotypically matched unrelated donor however, the number of patients in this series is small and a prospective randomized clinical trial with a larger number of patients is required to confirm these clinical impressions.

In spite of the possible advantage of lymphoablative over myeloablative conditioning prior to BMT in the treatment of CML, the problem of severe acute and chronic GVHD remains. Considering the therapeutic role of donor T cells, there is uncertainty as to whether CML patients should receive stem cell allografts derived from the blood which contain higher proportions of immunocompetent T cells as well as committed stem cells, or bone marrow cells. In general, engraftment is more rapid with blood-derived stem cells, probably with the likelihood of an increased incidence of chronic GVHD (45). The feasibility of controlling CML by immunotherapy mediated by in vitro activated alloreactive T cells (46) and/or NK cells or NKT cells that may mediate more potent anti-tumor effects, occasionally with no GVHD (47), or using hematopoietic specific (48,49) or disease-specific cytotoxic donor lymphocytes (50), may provide an option to amplify anti-tumor effects while controlling or eliminating GVHD.

Elimination of all measurable evidence of disease and documentation of durable remission in our small cohort of patients, despite the use of a reduced intensity conditioning, is most encouraging. Based on the data presented and considering the
cumulative international experience, it appears that reduced intensity conditioning may be safely applied for all patients with CML in need, while still in the chronic phase of the disease, especially those with recognized risk factors prohibitive for standard BMT. Confirmation of the benefits of NST as a possible replacement of conventional BMT will require a large prospective multi-center clinical trial currently in progress. However, considering the documented efficacy of NST in a small cohort of patients with CML in first chronic phase, it is not impossible that this approach may ultimately develop into an optimal treatment of choice for patients in need of BMT, especially elderly and patients with poor performance status failing to respond to Glivec or interferon, not eligible for conventional myeloablative regimen, with a matched related or unrelated donor available.
References


relapse after post allogeneic bone marrow transplantation. Blood 1996;87:2195-204.


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\(^{1}\) Juvenile chronic myeloid leukemia  
\(^{2}\) Patients treated at the Souraski Medical Center  
\(^{3}\) Abrupt withdrawal of cyclosporine A. UPN denotes Unique patient number, GVHD graft vs host disease and CSP cyclosporine A.  
\(^{4}\) Graded according to IBMTR severity indices.
MUD - Matched unrelated donor
UPN - Unique patient number
NST - Non-myeloablative stem cell transplantation
TABLE 2. Mobilized blood stem cells used for transplantation on days 0 and +1 in patients undergoing NST for CML in first chronic phase

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Kaplan-Meier actuarial survival and disease-free survival of patients with CML in 1st chronic phase treated with non-myeloablative stem cell transplantation (NST)
Figure 2
Kaplan-Meier actuarial probability of overall incidence of acute GVHD (>grade I) and severe GVHD (≥grade III) in patients with CML in 1st chronic phase treated with NST

- >grade I: Probability 75%; 95% C.I. 68–92%
- >grade III: Probability 29%; 95% C.I. 2–47%
Figure 3
Kaplan-Meier actuarial probability of chronic GVHD in patients with CML in 1st chronic phase treated with non-myeloablative stem cell transplantation (NST)
Nonmyeloablative allogeneic stem cell transplantation for the treatment of chronic myeloid leukemia in first chronic phase

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