

Stem Cell Transplantation for Chronic Myeloid Leukaemia

John M. Goldman

The various approaches to treatment have been reviewed recently^(1,2). It is clear now that allogeneic haemopoietic stem cell transplantation (allo-SCT) can cure selected patients with CML, but the risks of morbidity and mortality associated with the transplant procedure remain. Furthermore, a significant number of patients will relapse within three years of a transplant procedure that seemed otherwise to have been successful. Some of the factors that influence the results of allo-SCT are listed in **Table 1**. Autografting (auto-SCT) undoubtedly has the capacity to induce Ph-negativity in a high proportion of patients, but the evidence that auto-SCT prolongs life is not yet totally convincing. Thus a number of critical questions relating to the use of SCT remain unanswered. For example, for a patient with a suitable donor, when should the transplant be performed? How should alternative donors be selected? Should the allograft be performed with blood or marrow stem cells, or both? Should some patients receive a trial of interferon- α (IFN- α) first? How should relapses be treated? Should all other patients be offered autograft procedures? If so, how and when? Various groups have tried to construct treatment flow diagrams or algorithms applicable for patients not entered into prospective studies. The algorithm currently in use at the Hammersmith Hospital in London is shown in **Figure 1**.

Allografting

Selected patients can be offered high dose therapy followed by transplantation of allogeneic hematopoietic stem cells. The best outcome is achieved if patients are transplanted while still in chronic phase and preferably within one year of diagnosis⁽³⁾. The suggestion that prior treatment with IFN- α increases the probability of treatment failure after allografting⁽⁴⁾ was not confirmed by a retrospective study carried out by the International Bone Marrow Transplant Registry based on relatively large numbers of patients⁽⁵⁾. However, a recent analysis from the German Multi-Centre Study Group suggested that patients who received IFN- α immediately before the allograft had a higher treatment-related mortality than those for whom IFN- α was stopped at least 90 days before transplant.

For patients transplanted with stem cells from HLA-identical donors, leukemia-free survival (LFS) at five years is 40-65%. Younger patients fare better than older patients. Splenic irradiation prior to transplant confers no significant benefit⁽⁶⁾. The possible sequelae of allografting are legion; the relative frequency of chronic sinusitis has only recently been emphasized⁽⁷⁾.

The relative risk of treatment failure for patients with good risk leukaemia (which includes CML in chronic phase) transplanted with marrow cells from 'well-matched' alter-

native donors (i.e. phenotypically HLA-matched family members or unrelated donors) is 2.1 compared with HLA-identical sibling donor transplants⁽⁸⁾. The LFS at five years for CML patients is 30-50%, but subset analyses can define sub-populations who survive better than average, for example younger patients who are CMV seronegative and who receive transplants from genotypically matched unrelated donors⁽⁹⁾. Clinical results are optimal if donor and recipient are matched for HLA-DRB1 by molecular methods⁽¹⁰⁻¹²⁾. A successful transplant has been reported using umbilical cord blood stem cells for a patient in chronic phase and in blastic transformation^(13,14).

The details of the actual transplant procedure vary between different centres. Conditioning with busulfan and cyclophosphamide give results equivalent to the more conventional cyclophosphamide and total body irradiation; the risk of relapse may be lower in those who achieve high plasma levels of busulfan⁽¹⁵⁾. Currently, there is uncertainty also about whether CML patients should receive allografts with stem cells derived from blood or marrow. In general, engraftment is more rapid with blood-derived stem cells, but the incidence of chronic graft-versus-host disease (GVHD) seems to be higher. It may be appropriate to use marrow as source of stem cells for allografts for patients in

Table 1

(A) Factors that may impact on transplant-related mortality after allo-SCT

- Patient factors
 - Age
 - CMV serostatus
- Disease factors
 - Duration of chronic phase
 - Phase
- Donor factors
 - Gender match
 - Histocompatibility
- Transplant factors
 - Conditioning
 - Nucleated cell dose
 - GVHD prophylaxis

(B) Factors that may impact on risk of relapse post-transplant

- Disease factors
 - Phase
- Donor factors
 - Gender
 - Histocompatibility
- Transplant factors
 - Cell dose
 - GVHD prophylaxis

ALGORITHM FOR TREATING CML - 1999

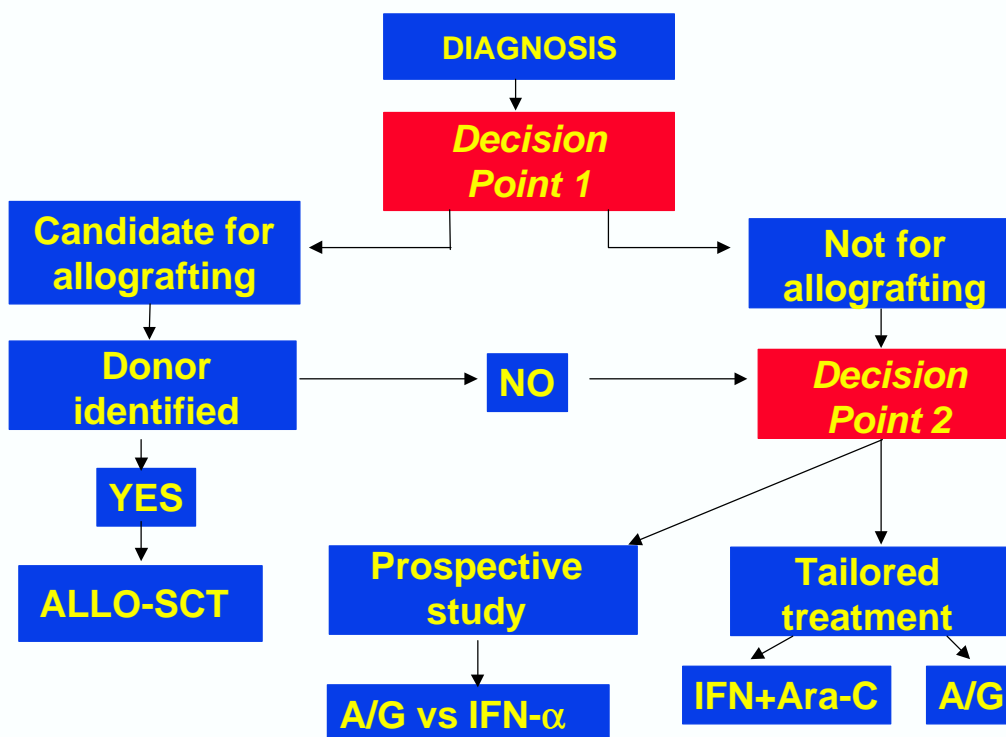


Figure 1. A suggested flow chart for planning treatment for a newly diagnosed CML patient aged under 60 years.

It is suggested that the clinician in collaboration with the patient attempts to decide within 4 weeks of diagnosis whether the patient is or is not in principle a candidate for treatment by allogeneic transplantation. If the patient has an HLA-identical sibling donor, he or she proceeds to transplant within 6 months of diagnosis. If a phenotypically HLA-matched unrelated donor is identified, the advisability of transplant is again evaluated and the patient may proceed to transplant within 6 months. If however the optimal donor is deemed unsuitable or no suitable donor is identified, the patient should be considered for initial treatment with IFN- α (plus or minus cytarabine) or for an autograft procedure.

first chronic phase, but to use blood stem cells for patients with more advanced disease.

Some groups use some form of T-cell depletion but most use cyclosporin A and methotrexate for prevention of GVHD. Even in patients who survive long term without untoward sequelae, *in vitro* assays that address primitive progenitor cells reveal incomplete recovery of marrow function⁽¹⁶⁾.

Most groups monitor patients closely post-transplant. Routine cytogenetic studies of marrow are informative, but hypermetaphase FISH is at least one order of magnitude more sensitive⁽¹⁷⁾. For patients who remain Ph-negative, the use of RT-PCR may be highly informative. In general patients with a high or rising number of BCR-ABL transcripts in their blood post-transplant will progress to cytogenetic and subsequently to hematologic relapse⁽¹⁸⁾. The risk of relapse is relatively high if donor bone marrow is depleted *in vitro* of T-cells. Using non-T-cell depleted donor marrow, the risk of relapse for 177 consecutive related donor transplants for CML performed in Minneapolis was 20% at 5

years; the corresponding figure for 106 unrelated donors transplants was 3%⁽¹⁹⁾. Relapses were seen up to 9 years post-transplant. Early transplant, chronic GVHD post-transplant, and use of unrelated donors were associated with significantly lower risks of relapse.

Graft-versus-leukemia and donor lymphocyte infusions (DLI)

In no hematologic malignancy is the effectiveness of adoptive immunotherapy more convincing than in patients with CML in relapse after allogeneic bone marrow transplantation who receive DLT. The overall response rate in 70-80%⁽²⁰⁾; the response rate may be higher in those who receive DLT in molecular or cytogenetic relapse compared with those whose leukemia has progressed to hematologic relapse⁽²¹⁾. Efforts have been made to reduce the toxicity of DLT, which consists mainly of induction of GVHD and myelosuppression, by transfusing lymphoid cell preparations depleted of CD8+ cells⁽²²⁾, or by transfusing initially only

very low doses of T-cells on an escalating dose schedule⁽²³⁾. Both approaches seem promising and warrant further study. For patients who do not respond to DLT, use of peripheral lymphoid blood cells in conjunction with interleukin-2 may be successful⁽²⁴⁾.

The immunological basis for the GVL reaction remains enigmatic (reviewed in ref 25). Human T-cells can recognize CML-specific oligopeptides of appropriate length presented by MHC class molecules⁽²⁶⁾ or longer oligopeptides processed intracellularly and presented at the surface of leukaemia cells⁽²⁷⁾. Thus GVL may recognise tissue-specific minor histocompatibility antigens expressed in this manner. Dendritic cells from CML patients, which are Ph-positive, can induce CD8+ cytotoxic T-cells specific for leukemic cells (28).

Autografting

Retrospective analyses suggest but do not prove that high-dose chemotherapy followed by autografting with blood or marrow stem cells can prolong survival for patients in chronic phase^(29,30). Since it is now widely accepted that some Ph-negative stem cells survive at the time of diagnosis in most if not all patients, efforts have been made to develop autografting techniques that favor reconstitution with Ph-negative hematopoiesis (reviewed in ref 31). Myeloid cells mobilized and collected from patients who have responded to IFN- α can be used for autografting with success. The Genoa group has reported the results of collecting nucleated cells from the peripheral blood after recovery from treatment with high-dose chemotherapy (idarubicin, cytarabine and etoposide)⁽³²⁾; similar results were achieved in Houston and elsewhere⁽³³⁾. The probability of harvesting Ph-negative myeloid cells is greatest if the procedure can be undertaken in previously untreated patients⁽³⁴⁾. Patients autografted with Ph-negative stem cells may achieve Ph-negative hematopoiesis, which is durable in some cases. Prospective randomized studies to define the precise role of autografting in the management of CML have been initiated on both sides of the Atlantic.

It may be possible to isolate from the marrow of CML patients enough Ph-negative progenitor cells for an autograft on the basis of their lack of DR expression; this may be most readily achieved in early chronic phase⁽³⁵⁾. Other groups have attempted to isolate Ph-negative progenitor cells by incubating blood or marrow cells *in vitro* with agents designed specifically to kill or suppress the proliferation of Ph-positive cell progenitors. Sensitized T-cells or natural killer cells are theoretically attractive agents for this purpose⁽³⁶⁾. Antisense oligodeoxynucleotides and ribozymes have been tested with some success *in vitro*; the former may act by a non-specific mechanism. Of great interest in this domain is the apparently selective action of a new ABL-specific tyrosine kinase inhibitor designated STI-571⁽³⁷⁾. It specifically inhibits the proliferation of CML but not of other myeloid cell lines and of CFU-GM and BFU-E from CML patients. It can induce haematological remission in CML patients treated in chronic phase and is also active in myeloid blastic transformation.

Treatment strategy for the newly diagnosed patient

For newly diagnosed patients under the age of 60 years, the various options for treatment may pose a major challenge. The decision to offer an allograft early after diagnosis to a relatively young patient with an HLA-identical sibling is probably straightforward, but for other patients questions arise in relation to upper age limit, the selection of 'alternative' donors, and the precise timing of transplant in the absence of HLA-identical siblings. The issue has been addressed by Gratwohl and colleagues, who have developed a 'risk score' that can predict within broad limits the probability of survival and transplant-related mortality for individual patients⁽³⁸⁾. For older patients or those with poor-risk disease, allografting with a non-myeloablative conditioning regimen may substantially reduce the chance of transplant-related mortality⁽³⁹⁾. For patients not eligible for any form of transplant procedure, initial treatment with IFN- α is becoming the standard approach, but how to assess response remains controversial. Prospective studies comparing the use of IFN- α with autografting have recently been launched on both sides of the Atlantic. For patients not entered into one or other prospective study, the use of a treatment algorithm is may be useful (Fig. 1).

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