CHRONIC MYELOID LEUKEMIA

Allogeneic transplantation for chronic myelogenous leukemia

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Keywords: CML, transplantation

Related donor transplantation

Over the last quarter century investigators have demonstrated that allogeneic hematopoietic cell transplantation (HCT) can cure chronic myelogenous leukemia (CML). Early reports suggested the efficacy of related donor transplant after a myeloablative preparative regimen containing total body irradiation (TBI) [1–3]. Subsequent studies have identified variables which improve outcome such as transplant in early chronic phase, younger recipient age, donor/recipient compatibility at the major HLA loci and male donor gender [4,5]. Myeloablative regimens which do not contain TBI have also proven effective in transplant for CML [6]. The use of peripheral blood progenitor cells as a source of stem cells for transplant mobilized with G-CSF is comparable in most respects to non-mobilized related donor marrow, although long-term studies may uncover differences in the incidence of chronic GVHD and in the risk of relapse [7].

Adult unrelated donors

Alternative sources of stem cells for CML patients without a suitably HLA-matched related donor have been developed. Adult, volunteer unrelated donors (URD) can be obtained through the National Marrow Donor Program (NMDP) and other registries for many, but not all, otherwise eligible patients. Factors predicting success of transplant are comparable in the unrelated and related donor setting [8–10]. Large, retrospective analyses have identified certain donor-recipient disparities such as mismatch at HLA-C as a predictor of poor outcome, while DNA-based methodology has identified certain single and multiple allele mismatches with adverse effects on outcome in URD transplant for CML [11].

Umbilical cord blood

Umbilical cord blood (UCB) has been identified as a source of hematopoietic stem cells for transplantation [12]. Furthermore, UCB may be particularly useful in the unrelated donor transplant setting since HLA-typed, frozen and stored cells are usually available within 1–2 days through international registries, can be used to repopulate hematopoiesis in adults as well as children, and may (arguably) tolerate a greater degree of HLA mismatch with the recipient than hematopoietic stem cells obtained from adult volunteer URD [13,14]. The role of UCB transplant in CML is promising, but not yet fully explored.

Donor Leukocyte Infusions

Although a clinically relevant “graft-versus-leukemia” (GVL) effect was first detected over 20 years ago [15], the importance of this effect in transplant therapy for CML has recently been underscored. Early attempts at ex-vivo T-cell depletion after related donor HCT for CML resulted in a reduced incidence of acute GVHD, but an unexpected, extraordinarily high incidence of relapse. Analyses of a large International Bone Marrow Transplant Registry (IBMTR) data set demonstrated a correlation between development of GVHD and protection from CML relapse [16].

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ISSN 1024-5332 print/ISSN 1607-8454 online © 2005 Taylor & Francis
DOI: 10.1080/10245330512331389764
Subsequently, Kolb et al. have demonstrated the efficacy of donor leukocyte infusions (DLI) to suppress persistent or recurrent malignant clones after allogeneic HCT [17–19]. Predictably, such infusions may provoke or exacerbate GVHD.

Nonmyeloablative preparative regimens
These clinical observations, underpinned by considerable preclinical data [20], prompted investigators to develop less intensive and often non-myeloablative (NMA) preparative regimens for allogeneic HCT therapy of CML. These NMA regimens are intended to minimize toxicity while exploiting the GVL effect [21–25]. Current results suggest that HCT with a NMA preparative regimen is a feasible treatment option for individuals not eligible for more standard preparative regimens. The incidence of nonrelapse mortality may be lower; however non-engraftment, GVHD, infection and disease persistence or recurrence still complicate — transplants [26].

Current clinical results
Analysis of long-term results using a large data set from the Center for International Blood and Marrow Transplant Research (CIBMTR) reveals an approximately 60% incidence of overall survival at 10 years for over 3300 first chronic phase CML patients receiving related donor HCT between 1978 and 1997 and 50% for over 1300 similar patients receiving transplants from alternative donors. The incidence of relapse at 10 years for these two groups is approximately 20%. Of note, the overall survival curve does not plateau. Important late-occurring causes of death include GVHD, infection and relapse [27].

Late effects and quality of life
Late effects and quality of life after allogeneic HCT therapy for CML are important issues in a field where effective alternative therapy is developing rapidly [28]. A retrospective analysis of late effects in 248 CML transplant recipients who had survived at least 2 years was very informative [29]. Compared to siblings, survivors had a high prevalence of long-term health-related complications including endocrine, ocular, oral health, gastrointestinal, musculoskeletal, neurosensory and neuromotor impairment. In a non-overlapping study of 46 CML transplant recipients, investigators observed a high incidence of late cognitive deficits and an increase in psychosexual problems compared to the general population [30]. Of interest, in a third study CML patients and physicians reported an improved Quality of Life (QOL) Index score, decreased signs and symptoms of depression and less alcohol consumption at 12 months following transplant compared to the study patients’ immediate pretransplant baseline [31].

The imatinib era
The development of the selective Bcr-Abl tyrosine kinase inhibitor imatinib (STI-571, Gleevec) has fundamentally changed therapy of CML. Imatinib, given orally on a daily basis as first-line therapy in newly diagnosed chronic phase CML patients, results in hematologic, cytogenetic and molecular remissions in the majority of cases [32]. Relapses occur and can often be attributed to mutations in the BCR-ABL gene [33]. It is possible that such mutations can be treated successfully with a second generation of tyrosine kinase inhibitors possessing higher binding affinities for the ABL kinases [34–37]. These exciting developments call into question the historical first-line role of allogeneic HCT therapy for CML.

Transplant in the imatinib era
Recently, investigators have demonstrated that imatinib can be used effectively to treat CML relapse after allogeneic HCT [38]. By 6 months after imatinib therapy for post-transplant relapse, 9 of 10 patients achieved cytogenetic remission, and the BCR-ABL transcript could not be identified in 7 of these patients. Of note, patients achieving cytogenetic remission also converted to complete donor chimerism. These early results raise the issue of substituting imatinib therapy for DLI in the post-transplant relapse setting.

In small, uncontrolled trials, imatinib has also been administered as prophylaxis during the first 100 days following transplant for poor prognosis CML [39]. Early results suggest that this approach is feasible, but requires reduced doses of imatinib and tacrolimus and resulted in reversible hematologic suppression. The investigators suggest that an “adjuvant” strategy incorporating imatinib in the early post transplant regimen may reduce risk of relapse in high-risk individuals.

Imatinib has also been used to prepare patients for subsequent NMA HCT therapy of CML. In a recently reported study, CML patients receiving pretransplant imatinib had equivalent time to engraftment and transplant related mortality compared to equivalent patients not pre-treated with imatinib [40]. Of note, the incidence of molecular remission in the imatinib pre-treatment group (83%) was significantly higher than that in the group not pre-treated with imatinib (40%) \( P=0.11 \). Such approaches might be useful to reduce the leukemia load prior to NMA HCT.

Current results suggest that the majority of chronic phase patients receiving imatinib as first-line therapy will achieve a complete cytogenetic remission without
undue toxicity. On the other hand, a recent study suggests that patients achieving a complete cytogenetic remission with imatinib have a lower incidence of molecular remission, less durable molecular remissions and a higher level of residual disease in molecular remission (determined by replicate RT-PCR testing) than comparable patients treated with allogeneic HCT [41]. Furthermore, some CML patients will not respond to imatinib or will develop imatinib resistance, and the role of newer agents with increased binding activity to the ABL-kinase domain in the treatment of imatinib-resistant CML is not yet fully understood. Early transplant in patients unlikely to have a durable response to imatinib may be indicated, and methods to predict those who will benefit from early transplant are needed.

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