Role of Allogeneic Hematopoietic Stem-Cell Transplantation in Chronic Lymphocytic Leukemia

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The use of combination chemotherapy and chemoimmuno-therapy for the treatment of chronic lymphocytic leukemia (CLL) has resulted in dramatically improved complete remission (CR) rates and prolongation of remission of disease. However, there is no evidence to date that these treatments are curative; all patients invariably experience relapse and subsequently develop resistance to chemotherapy.\(^1\) CLL is an indolent disease, but once patients become fludarabine refractory, their prognosis is dismal, with a median survival time of less than 1 year.\(^2\)

In other hematologic diseases, the rational for hematopoietic stem-cell transplantation (SCT) has been demonstrated in randomized clinical trials demonstrating a survival advantage after SCT compared with chemotherapy. To date, no such studies have been performed in CLL, but a number of phase II studies have been performed in CLL to determine whether SCT has curative potential. High-dose therapy with autologous SCT is feasible in CLL but does not seem to be curative, and the major problem remains relapse of disease and late toxicities.\(^3,4\) Myeloablative allogeneic SCT is associated with a high morbidity and mortality; registry data demonstrate that treatment-related mortality (TRM) is unacceptably high, with rates of up to 50% reported.\(^5\) Despite the high TRM, patients who do survive can have long-term disease control, with actuarial overall and event-free survival rates of almost 40% at 5 years. The major advantage of the use of allogeneic SCT seems to be the potential for a graft-versus-leukemia (GVL) effect. A strong GVL effect has been noted, with patients developing acute or chronic graft-versus-host disease (GVHD) having near complete protection from relapse.\(^6\)

Most patients with CLL are too elderly to consider high-dose therapy and SCT because the median age of presentation is between 65 and 70 years. More than 90% of younger patients will die as a result of their CLL,\(^7\) unlike older patients who often die of comorbidity not associated with CLL. Therefore, there has been considerable interest in the use of reduced-intensity conditioning SCT approaches, which may be more suitable to allow the use of SCT in older patients with CLL. The approach could allow the use of SCT in older patients, decrease the TRM,\(^8\) and still allow exploitation of the GVL effect to induce long-term remission or even cure. Despite encouraging initial results, the follow-up of most clinical trials of reduced-intensity conditioning SCT has been too short to assess whether this approach could cure CLL.

In the current issue of *Journal of Clinical Oncology*, long-term follow-up is reported in 82 CLL patients who underwent reduced-intensity conditioning SCT using total-body irradiation (2 Gy) with or without fludarabine, with 52 patients using related donors and 30 patients using unrelated donors.\(^9\) At 5 years, 50% of patients were alive and 39% were free of disease, but this success did not come without a high price. The nonrelapse mortality rate remains high at 23%, and GVHD remains a considerable problem. Almost 50% of patients developed chronic extensive GVHD. The median duration of immunosuppressive treatment for GVHD was 25 months, with some patients requiring more than 5 years of treatment, and one patient in four remains on immunosuppressive therapy. In the present study, presence of bulk disease and presence of comorbidity were risk factors for poor outcome.\(^9\)

Although there are always concerns regarding some degree of patient selection in nonrandomized clinical trials comparing SCT with alternative therapy, 87% of the patients in the study by Sorror et al\(^9\) had documented fludarabine-refractory disease, so it seems highly unlikely that such durable responses could have been obtained in this patient population without the use of SCT. There is still plenty of room for improvement, and longer follow-up is required to determine whether there really is a plateau on the overall and event-free survival curves. Questions remain regarding appropriate patient selection for consideration of SCT and the timing of SCT in the clinical course of the disease, the ideal conditioning regimen, optimal post-transplantation immunosuppressive therapy, and how best to exploit the GVL effect without concomitant morbidity from GVHD. Whereas improved disease control might be achieved by increasing the intensity of the conditioning regimen, this might also lead to increased TRM and increased GVHD. Specific immune manipulation of the donor cells to engender more GVL is currently under investigation but remains experimental. In all hematologic disorders, improved outcomes after allogeneic SCT are seen when patients undergo transplantation earlier in their disease course and before their disease has become refractory. It is intriguing to speculate whether results could be improved by judicious selection of high-risk patients before the disease becomes fludarabine refractory, so that patients could undergo SCT without bulk disease. In CLL, as in all other diseases, the role of SCT must always be considered by comparing the risk of undergoing SCT with the risk from the underlying disease. SCT is clearly not an appropriate option for patients with indolent disease, but relatively younger patients with poor prognosis can be identified for whom SCT may offer a chance of cure. Recently, major advances have been made in establishing prognostic factors that help to identify patients who are likely to follow an aggressive course or in whom
chemotherapy resistance will reduce the likelihood of durable responses to chemotherapy. It remains unclear whether a GVL effect can overcome these poor prognostic biomarkers of disease. Whereas patients with unmutated immunoglobulin gene rearrangements have poorer outcome after autologous SCT, this adverse event can be overcome by the GVL effect. In the present report, expression of high levels of CD38 and presence of high-risk cytogenetic factors were not associated with poor outcome, but further study will be required to assess this. A working party has established European Group for Blood and Marrow Transplantation guidelines outlining the indications for SCT in CLL. The guidelines conclude that there is evidence for the efficacy of allogeneic SCT in CLL and that this is indicated in high-risk CLL patients. The consensus of the working group was that allogeneic SCT is recommended early in the disease course for young patients with CLL who do not achieve CR or who experience progression within 12 months after purine analogs and in patients who experience relapse within 24 months after having achieved a response with purine analog–based combination therapy or autologous transplantation. Precisely what other factors are defined as high risk remains unclear, but patients with p53 deletions or mutations are considered candidates in first remission. Ongoing prospective clinical studies will be required to determine the specific risk factors that identify patients at sufficiently high risk to merit use of allogeneic SCT in first CR. The Cancer and Leukemia Group B and the Blood and Marrow Transplant Clinical Trials Network plan to examine the role of reduced-intensity conditioning SCT in patients with relapsed disease, as well as in high-risk patients in first response. Inherent in this approach is the correlative science that is planned in collaboration with the CLL Research Consortium.

Future approaches to the management of this disease must always take into account the balance between the increased morbidity and mortality of SCT in CLL and the curative potential that these approaches potentially offer. In the absence of any other treatment modalities currently capable of improving outcome in this disease, the treatment of choice for younger patients with poor-risk CLL may indeed be allogeneic SCT. Therefore, continued enrollment of appropriate patients into well-designed clinical trials is vital for further progress.

**Author's Disclosures of Potential Conflicts of Interest**

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**References**