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Hematopoietic stem cell transplantation for chronic lymphocytic leukemia

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Abstract

Purpose of review—Although hematopoietic stem cell transplantation (HSCT) is the treatment of choice for many aggressive hematologic malignancies, the role of HSCT in chronic lymphocytic leukemia (CLL) has remained controversial. Now in the era of improved conventional treatment and better prognostication of long-term outcome, a review of autologous and allogeneic HSCT in CLL treatment is warranted.

Recent findings—Despite an improved disease-free survival in some patients, multiple, prospective, randomized autologous HSCT CLL trials fail to demonstrate an overall survival benefit as compared to conventional therapy. Allogeneic bone marrow transplantation, although limited by donor availability, can successfully eradicate CLL with adverse prognostic features. In the older CLL patients, nonmyeloablative allogeneic transplants are better tolerated than myeloablative transplants. Nonmyeloablative allogeneic transplants are less effective in heavily diseased burdened patients.

Summary—Outside of a clinical protocol, autologous HSCT for CLL cannot be justified. Nonmyeloablative allogeneic transplantation should be considered in high-risk populations early in the disease process, when disease burden is most easily controlled. Alternative donor selection using haploidentical donors and posttransplantation cyclophosphamide has the potential to vastly increase the availability of curative therapy in CLL while retaining a low treatment-related toxicity.

Keywords

allogeneic; autologous; chronic lymphocytic leukemia; hematopoietic stem cell transplantation

INTRODUCTION

The treatment of chronic lymphocytic leukemia (CLL) with hematopoietic stem cell transplantation (HSCT) is not novel; the first CLL autologous HSCT series published in 1993 [1] was interestingly preceded by an allogeneic HSCT CLL trial report in 1988 [2].

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Conflicts of interest

There are no conflicts of interest.

Despite the subsequent years of investigation thereafter, HSCT for CLL remains controversial. Given recent advances in non-HSCT CLL treatment and better prognostication of long-term outcome, a review of HSCT for CLL is warranted.

The diagnosis of CLL is established by the presence of at least 5000 cells/ μ l (5×10^9 cells/l) circulating clonal, morphologically mature-appearing small B lymphocytes [3], expressing extremely low levels of surface immunoglobulin, κ or λ light chains, and the associated antigens CD19/CD20, CD23 with CD5 [4]. Of the estimated 15 000 new CLL cases in the United States, 40% are diagnosed before age 65 [5¹¹], and approximately 35% of the estimated 4000 deaths occur in patients younger than 75 years.

Importantly, CLL patients exhibit heterogeneous survival rates [6], and especially in early-stage patients, the CLL clinical grading systems (Rai or Binet) poorly predict overall survival and disease aggressiveness [7–9]. Among the array of prognostic CLL laboratory studies currently available, immunoglobulin variable region heavy chain (IGHV) mutation status [10,11,12¹²,13] and interphase fluorescence in-situ hybridization (FISH) DNA analysis appear to be the most prognostic predictors of outcome [7,14,15]. Therefore, currently, patients with either advanced-stage disease or those with early but high-risk prognostic disease are often referred for HSCT.

AUTOLOGOUS HEMATOPOIETIC STEM CELL TRANSPLANTATION IN ADVANCED-STAGE CHRONIC LYMPHOCYTIC LEUKEMIA

In 2004, excitement for autologous HSCT grew: a retrospective analysis comparing 66 CLL patients treated with autologous HSCT to 291 CLL patients treated conventionally found an overall survival benefit for high-risk (unmutated IGHV) patients treated with HSCT [16]. Interestingly, this positive HSCT signal was identified despite a greater than two-fold likelihood (74 versus 33%) of having received a fludarabine-based regimen for the non-transplanted cohort. However, in 2011, several prospective autologous HSCT in advanced disease failed to confirm this survival advantage signal.

Michallet *et al.* [17¹³] published the European intergroup randomized CLL trial comparing autografting versus observation. Between 2001 and 2007, 223 people enrolled in this phase III trial based on advanced clinical stage (Binet stage A progressive, B, or C) at the time of first treatment. Patients in a complete response, nodular partial remission, or a very good partial remission (VGPR) after first-line or second-line treatment were randomized to HSCT versus observation. Importantly, although the majority of patients (71%) received fludarabine/alkylator-based therapy, only 4% received purine analogue/rituximab-based treatment, and for the majority of patients, interphase FISH risk analysis was unavailable. Richter syndrome patients were excluded. All patients had peripheral blood stem cells harvested. Those randomized to autologous HSCT received either a cyclophosphamide/total body irradiation (TBI) or a BEAM (carmustine, etoposide, cytarabine, and melphalan) preparative regimen. Although the event-free survival (EFS) at 5 years favored the autografting arm 42 versus 24% ($P < 0.001$), after a median follow-up of 43.7 months, no difference was seen in the estimated 5-year overall survival (OS) 85.5 versus 84.3% ($P = 0.77$).

In a similar study, Sutton *et al.* [18[■]] published the results of a prospective, multicenter, European, randomized trial comparing autologous transplantation intensification in previously untreated adults with CLL. The prerequisite of enrollment for the 241 participants entered onto this phase III trial between 2001 and 2007 was untreated, advanced clinical-stage (Binet stage B or C) CLL. Richter syndrome patients were excluded. After initial therapy (miniCHOP $\times$ 3/fludarabine $\times$ 3), patients in complete response were randomized to observation versus autologous HSCT, whereas noncomplete response patients received salvage chemotherapy (DHAP; dexamethasone, cytosine arabinoside, cisplatin) and then were randomized to autologous transplantation versus 3 monthly course of fludarabine/cyclophosphamide. HSCT randomized patients received a cyclophosphamide/TBI preparative regimen. For those in a complete response after initial therapy, the EFS was nearly doubled in the transplanted patients. However, the 3-year estimated OS rates were the same, 97.8% in the observation arm and 95.7% in the transplant arm ($P = 0.73$). For those not achieving an initial complete response, not only was no difference in the estimated 3-year OS rate observed with an OS of 81.7% in the transplant arm and 87.0% in the fludarabine/cyclophosphamide arm ($P = 0.69$), but also no difference was found in the EFS between the these two subgroups. Interphase FISH analysis and IGHV mutational status, obtained in the majority of patients, did not identify a population whose OS was improved by transplantation.

Brion *et al.* [5[■]] published the results of the Groupe Ouest Est d'Etude des Leucemies Aigues et Maladies du Sang LLC 98 trial. This prospective, multicenter, randomized trial evaluated on an intent-to-treat basis the benefit of autologous HSCT using a cyclophosphamide/TBI preparative regimen in untreated, advanced clinical-stage (Binet stage B or C) CLL as compared to conventional treatment. Eighty-two evaluable patients were enrolled between 1999 and 2004. The conventional treatment plan ($n = 39$) was 6 monthly courses of miniCHOP, and then based on response, either six additional courses of miniCHOP or three to six courses of weekly fludarabine. For the autologous HSCT cohort ($n = 43$), the planned therapy consisted of 3 monthly miniCHOP courses followed by immediate HSCT for patients with a VGPR or complete response; patients with only a partial response or stable disease were planned to received one to three courses of fludarabine until VGPR or complete response to be followed by HSCT. In the conventional arm, 77% received their planned therapy and 67% underwent transplant in the HSCT arm. On an intent-to-treat analysis, the median progression-free survival (PFS) favored autologous transplant. However, no difference in median survival was shown: 104.7 months in the chemotherapy only arm and 107.4 months in the autologous transplant arm. Interphase FISH risk analysis was unavailable in these patients, and although IGHV mutational status was collected, a survival analysis was not performed based on mutational status.

Do these recent analyses eliminate autologous transplantation for CLL as a standard of care? In our opinion: yes. Importantly, concurrent to these trials' accrual, the importance of rituximab in CLL management emerged. In a large, randomized trial of FCR versus fludarabine/cyclophosphamide, which included untreated patients with Binet stage C or active Binet stages A/B, a 3-year OS of 87 versus 83% was found in favor of the FCR arm [19[■]]. This overall excellent 3-year survival rate without HSCT should dissuade future

studies of autologous HSCT in CLL. Moreover, the current prognostic predictors of outcome were not controlled in these autologous HSCT trials, but, given the reduced efficacy of FCR in del(17p) patients [19²²,20²³], it is unlikely that any benefit would be found in autologous-transplanted, molecularly high-risk individuals.

However, it is in the high-risk population in which T-cell mediated cytotoxicity via an autologous-engineered or an allogeneic source holds promise. Porter *et al.* [21] reported the clinical outcome of a chemo-refractory, del(17p) CLL patient treated with autologous T-cells genetically modified to express anti-CD19. The case patient, 10 months after treatment, was in remission [21]. Although the long-term disease control and late toxicities of this particular therapy are not yet known, it is such innovative therapy that further dissuades autologous HSCT as a standard of care in CLL.

ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION IN CHRONIC LYMPHOCYTIC LEUKEMIA

In 2007, the European Group for Blood and Marrow Transplantation published their consensus indications for allogeneic HSCT in CLL: ‘... allo-SCT is a reasonable treatment option for younger patients with nonresponse or early relapse (within 12 months) after purine analogues, relapse within 24 months after having achieved a response with purine-analogue-based combination therapy or autologous transplantation, and patients with p53 abnormalities requiring treatment...’ [22].

As previously mentioned, allogeneic HSCT dates to 1991, when Bandini *et al.* [2] reported 26 patients who received a myeloablative allogeneic or syngeneic HSCT for refractory CLL; in two patients biologic studies showed no residual disease; however, toxicity was high. Over the ensuing years, evidence for a graft-versus-CLL effect solidified [23–26]. However, in the CLL population, myeloablative allogeneic HSCT is limited by toxicity and donor availability. In fact, likely secondary to recipient age, the CLL transplant-related morality of approximately 50% associated with myeloablative conditioning and high rates of acute graft versus host disease (GVHD) dissuaded many from pursuing allogeneic HSCT [23].

NONMYELOABLATIVE HEMATOPOIETIC STEM CELL TRANSPLANTATION IN HIGH-RISK CHRONIC LYMPHOCYTIC LEUKEMIA

The advent of nonmyeloablative transplantation (NMA) greatly reduced the morbidity and mortality of transplantation in older patients [27–29] and rekindled allogeneic transplantation interest for an older CLL patient population. However, as the safety of HSCT was enhanced by NMA, high incidences of nonengraftment, poor disease control, and infectious deaths necessitated a change in strategy – early intervention.

In non-CLL patients, pre-NMA disease burden affects long-term disease control. Warlick *et al.* [30] published the outcomes of 84 transplanted myelodysplastic patients, of whom 38% received a nonmyeloablative regimen. They observed, in high disease burden patients (at least 5% marrow blasts), a relapse rate of 28 versus 50%, when comparing myeloablative allogeneic to NMA-treated patients, and a trend toward an improved disease-free survival

(DFS) in NMA recipients who received pretreatment. Likewise, in CLL patients, high disease burden attributes not only to a decrease in DFS but graft rejection.

In 2006, the Dana-Farber Cancer Institute described the outcome of 46 NMA-treated CLL patients, of whom 57% had progressive chemoresistant disease at time of transplantation. Although adverse cytogenetics did not predict PFS or OS, for those patients in complete response/partial response at NMA, the 2-year PFS and OS was 60 and 84% compared to 15 and 34%, respectively, for those with progressive disease or induction failure. Likewise, CLL marrow cellularity was predictive of outcome; the 2-year PFS for patients with greater than 5% bone marrow CLL cellularity was 8%, compared with 63% for all others, and patients with 5% or less bone marrow involvement were nearly 11 times more likely to achieve at least 75% chimerism [31]. Additionally, others have found nonmarrow disease burden as measured by large lymph node size (>5 cm) to be associated with a doubling of relapse risk, and in confirmation, the German CLL study group CLL3X trial of NMA in poor-risk CLL also found EFS not to be affected by the presence of del(17p), but was adversely affected by uncontrolled disease at time of transplant [32^{***}].

Additional pretransplant factors other than disease burden may affect CLL NMA outcomes. In their review of 86 NMA CLL patients with low-volume relapsed/refractory CLL, Khouri *et al.* [33^{***}] demonstrated that both pretransplant hypogammaglobulinemia and CD4 cell counts less than 100 cells/ μ l had a major influence on survival. Given the importance of pretransplant factors, NMA is most likely to achieve the highest incidence of engraftment and the highest DFS if utilized early in the clinical course, before the development of refractory, bulky disease and treatment-induced toxicity.

NONMYELOABLATIVE HEMATOPOIETIC STEM CELL TRANSPLANTATION AND GRAFT VERSUS HOST DISEASE

Chronic GVHD, a well recognized cause of late morbidity and mortality after standard myeloablative allogeneic and NMA HSCT, increases with older donor and recipient age [34^{*},35^{***}]. This is especially important in CLL patients, given their older age and their most likely donor source, a similarly-aged sibling. In a recent review, Gribben *et al.* [36^{***}] referenced acute and chronic GVDH rates ranging from 10 to 56% and 21 to 58%, respectively for NMA CLL patients.

More recent reviews have similar findings. The German CLL study group CLL3X trial, which utilized multiple NMA preparative regimens with and without in-vivo T-cell depletion, reported a cumulative incidence of chronic and extensive chronic GVHD at 2 years of 73 and 55%, respectively, resulting in an overall nonrelapse mortality rate of 52%. Importantly, 53% of these deaths were attributable to either acute or chronic GVHD [32^{***}]. In the previously cited MD Anderson article of 86 NMA CLL patients, in which the majority of patients received a fludarabine/cyclophosphamide/rituximab preparative regimen with tacrolimus and methotrexate GVHD prophylaxis, a 1-year nonrelapse mortality of 17.4%, a 37% incidence of acute grade II–IV acute GVHD, and a 56% cumulative incidence of extensive chronic GVHD at 60 months was reported [33^{***}].

FUTURE ALLOGENEIC DIRECTIONS: ALTERNATIVE DONOR ALLOGENEIC TRANSPLANTATION AND POSTTRANSPLANTATION CYCLOPHOSPHAMIDE

To date, there has been limited experience with either umbilical cord blood or human leukocyte antigen (HLA) haploidentical stem cell transplantation for CLL. A major limitation of umbilical cord blood transplantation (UCBT) in adults is inadequate stem cell dose with a single-cord blood unit [37]. This obstacle has been overcome to some extent by infusing two separate units of cord blood. Although one of the units is eventually rejected by the other, the extra dose of stem cells helps provide for faster engraftment and earlier protection from infection. Two recent articles have shown that UCBT can be performed safely in patients with CLL [38,39].

Historically, the major limitation of HLA haploidentical stem cell transplantation has been intense bidirectional alloreactivity resulting in high incidences of graft failure or severe GVHD [40,41]. Depletion of mature T cells from the graft reduces the risk of GVHD at the expense of increased incidences of graft failure and infection [42]. Recently, the group at Johns Hopkins developed a method for selective in-vivo depletion of alloreactive cells using high-dose, posttransplantation cyclophosphamide [43]. NMA, HLA haploidentical bone marrow transplantation (BMT) with high-dose, posttransplantation cyclophosphamide is associated with low incidences of fatal graft failure and severe chronic GVHD. In a recent multicenter phase II trial of NMA, HLA haploidentical BMT for adults with leukemia or lymphoma, graft failure occurred in only one of 50 patients; the incidences of acute grades II–IV, grades III–IV, and chronic GVHD were 32, 0, and 13%, respectively, and a 1-year, nonrelapse mortality of only 7%. This study establishes the safety of HLA haploidentical BMT after reduced intensity conditioning, making this approach a viable option for CLL patients who lack an HLA-matched donor [44].

CONCLUSION

Who should be considered for NMA allogeneic transplantation? Curative NMA should be considered in physically fit CLL patients in first response who exhibit high-risk features [an unmutated IGHV status associated with del(11q)/del(17p)] and in those physically fit CLL patients with early relapsed disease after highly active therapy before the development of tumor resistance.

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KEY POINTS

- Autologous hematopoietic stem cell transplantation (HSCT) is not superior to conventional chronic lymphocytic leukemia (CLL) therapy.
- Autologous HSCT should not be offered as a standard-of-care treatment option in CLL.
- A graft-versus-leukemia effect exists in CLL.
- Allogeneic HSCT is curative therapy even in high-risk CLL.
- Nonmyeloablative allogeneic HSCT is most effective when utilized early in the disease process before chemoresistance is established and other treatment toxicities have occurred.