PROCEEDINGS ARTICLE

Challenges for the next decade: allogeneic stem cell transplantation in chronic lymphocytic leukemia

P Corradini¹ and L Farina²

Although hematopoietic stem cell transplantation (allogeneic SCT (allo-SCT)) is the treatment of choice for many aggressive hematological malignancies, the role of allo-SCT in chronic lymphocytic leukemia (CLL) is still a matter of debate and can be considered one of the more important challenges for the next decade. In the era of novel drugs and humanized antibodies, the long-term outcome of patients has improved, and a critical reappraisal of autologous and allo-SCT in CLL treatment is warranted.

Leukemia Supplements (2012) 1, S33–S34; doi:10.1038/leusup.2012.19

Keywords: chronic lymphocytic leukemia; allogeneic; reduced intensity

Although hematopoietic stem cell transplantation (allogeneic SCT (allo-SCT)) is the treatment of choice for many aggressive hematological malignancies, the role of allo-SCT in chronic lymphocytic leukemia (CLL) has remained controversial and can be considered a challenge for the next decade. Now in the era of improved conventional treatment and better prognostication of long-term outcome, a critical reappraisal of autologous and allo-SCT in CLL treatment is warranted. Despite an improved disease-free survival in some patients, prospective, randomized autologous SCT CLL trials failed to demonstrate an overall survival (OS) benefit as compared with conventional therapy.¹ Allo-SCT, although limited by donor availability, can successfully eradicate CLL with adverse prognostic features. In the older CLL patients, nonmyeloablative or reduced-intensity conditioning (RIC) allogeneic transplants are better tolerated than myeloablative transplants with a lower non-relapse mortality.^{2–4} Patients affected by lymphomas or CLL relapsing after two lines of therapy, or autografting, or with refractory disease are often candidates for RIC regimens followed by allo-SCT. All the published series reported a 2-year progression-free survival (PFS) of 50–60%, 40% and 30% in indolent lymphomas or CLL, aggressive lymphomas and Hodgkin's lymphoma (HL), respectively.^{2–13} The long-term efficacy and toxicity of this strategy is still unknown. We report the results of a prospective multicenter phase II trial: 194 relapsed/refractory lymphomas received the same RIC regimen followed by allo-SCT from matched sibling donors. Histologies were as follows: non-HL (NHL) (indolent (low grade (LG)-NHL, $n=68$), including follicular lymphoma ($n=29$), CLL ($n=35$) and others ($n=4$); aggressive lymphoma (high grade (HG)-NHL, $n=87$), including B-cell phenotype ($n=43$), T-cell phenotype ($n=28$), mantle cell lymphoma ($n=16$)) and HL ($n=39$); 133 (68%) of 194 patients had chemosensitive disease, and 100 (52%) of 194 failed previous autologous SCT. The median age was 50 years (range, 20–63 years).

At the last follow-up (median 60 months, range 15–113), 116 patients were alive (59%) and 78 died ($n=47$ for disease progression, $n=30$ for non-relapse mortality, $n=1$ not assessable). The 5-year OS and PFS were 62% and 70% for LG-NHL, 61% and 59% for HG-NHL, and 42% and 19% for HL, respectively. Disease status before allo-SCT significantly influenced long-term

outcome in HG-NHL and HL (chemosensitive vs chemorefractory: 73% vs 32% ($P<0.001$) for HG-NHL; 64% vs 0% ($P<0.002$) for HL), but not in LG-NHL (65% vs 56% ($P=0.43$)). Although the 5-year PFS was significantly different between follicular lymphoma and CLL (85% vs 58%, $P=0.04$), the 5-year OS was not (71% vs 56%, $P=0.13$). The OS and PFS were not significantly different between aggressive lymphoma of B- and T-cell origin (5-year OS: 67% vs 55% ($P=0.51$); 5-year PFS: 63% vs 57% ($P=0.45$)), respectively. Overall, 30 patients died of non-relapse mortality, with a 5-year cumulative incidence of 15%. The incidences of acute and chronic graft-versus-host disease were 34% and 55%, respectively. Interestingly, only 27 of 116 (23%) patients are still receiving immunosuppressive therapy. Our long-term data with a median 5-year follow-up shows that (i) patients with relapsed lymphomas or CLL can achieve long-term remission and are probably cured, (ii) non-relapse mortality is rather low and (iii) disease status before transplant is a critical determinant.

In conclusion, nonmyeloablative or RIC allo-SCT should be considered in high-risk populations early in the disease process, as well as in the setting of relapsed disease. Monitoring of minimal residual disease can be an important tool for early intervention with drugs, cyclosporine withdrawal or donor lymphocyte infusions.^{14–16}

CONFLICT OF INTEREST

PC has received consulting fees from Sanofi, Novartis and lecture fees from Celgene and Genzyme. LF declares no competing interest.

REFERENCES

- 1 Michallet M, Dreger P, Sutton L, Brand R, Richards S, van Os M *et al.*, EBMT Chronic Leukemia Working Party. Autologous hematopoietic stem cell transplantation in chronic lymphocytic leukemia: results of European intergroup randomized trial comparing autografting versus observation. *Blood* 2011; **117**: 1516–1521.
- 2 Khouri IF, Keating M, Körbling M, Przeciorka D, Anderlini P, O'Brien S *et al.* Transplant-lite: induction of graft-versus-malignancy using fludarabine-based nonablative chemotherapy and allogeneic blood progenitor-cell transplantation as treatment for lymphoid malignancies. *J Clin Oncol* 1998; **16**: 2817–2824.
- 3 Corradini P, Doderio A, Farina L, Fanin R, Patriarca F, Miceli R *et al.* Allogeneic stem cell transplantation following reduced-intensity conditioning can induce durable clinical and molecular remissions in relapsed lymphomas: pretransplant

¹Department of Hematology, University of Milano, Milan, Italy and ²Division of Hematology, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy. Correspondence: Dr P Corradini, Department of Hematology, University of Milano, Via G. Venezian 1, Milan 20133, Italy. E-mail: paolo.corradini@unimi.it

- disease status and histotype heavily influence outcome. *Leukemia* 2007; **21**: 2316–2323.
- 4 Escalón MP, Champlin RE, Saliba RM, Acholonu SA, Hosing C, Fayad L *et al*. Nonmyeloablative allogeneic hematopoietic transplantation: a promising salvage therapy for patients with non-Hodgkin's lymphoma whose disease has failed a prior autologous transplantation. *J Clin Oncol* 2004; **22**: 2419–2423.
 - 5 Armand P, Kim HT, Ho VT, Cutler CS, Koreth J, Antin JH *et al*. Allogeneic transplantation with reduced intensity conditioning for Hodgkin and non-Hodgkin lymphoma: importance of histology for outcome. *Biol Blood Marrow Transplant* 2008; **14**: 418–425.
 - 6 Bloor AJ, Thomson K, Chowdhry N, Verfuert S, Ings SJ, Chakraverty R *et al*. High response rate to donor lymphocyte infusion after allogeneic stem cell transplantation for indolent non-Hodgkin lymphoma. *Biol Blood Marrow Transplant* 2008; **14**: 50–58.
 - 7 Khouri IF, McLaughlin P, Saliba RM, Hosing C, Korbling M, Lee MS *et al*. Eight-year experience with allogeneic stem cell transplantation for relapsed follicular lymphoma after nonmyeloablative conditioning with fludarabine, cyclophosphamide, and rituximab. *Blood* 2008; **111**: 5530–5536.
 - 8 Vigouroux S, Michallet M, Porcher R, Attal M, Ades L, Bernard M *et al*. Long-term outcomes after reduced intensity conditioning allogeneic stem cell transplantation for low-grade lymphoma: a survey by the French Society of Bone Marrow Graft Transplantation and Cellular Therapy (SFGM-TC). *Haematologica* 2007; **9**: 627–634.
 - 9 Rezvani AR, Storer B, Maris M, Sorror ML, Agura E, Maziarz RT *et al*. Nonmyeloablative allogeneic hematopoietic cell transplantation in relapsed, refractory, and transformed indolent non-Hodgkin's lymphoma. *J Clin Oncol* 2008; **26**: 211–217.
 - 10 Dreger P, Corradini P, Kimby E, Michallet M, Milligan D, Schetelig J *et al*. Indications for allogeneic stem cell transplantation in chronic lymphocytic leukemia: the EBMT transplant consensus. *Leukemia* 2007; **21**: 12–17.
 - 11 Michallet M, Sobh M, Milligan D, Morisset S, Niederwieser D, Koza V *et al*. Chronic Leukemia Working Party of the EBMT. The impact of HLA matching on long-term transplant outcome after allogeneic hematopoietic stem cell transplantation for CLL: a retrospective study from the EBMT registry. *Leukemia* 2010; **24**: 1725–1731.
 - 12 Khouri IF, Bassett R, Poindexter N, O'Brien S, Bueso-Ramos CE, Hsu Y *et al*. Nonmyeloablative allogeneic stem cell transplantation in relapsed/refractory chronic lymphocytic leukemia: long-term follow-up, prognostic factors, and effect of human leukocyte histocompatibility antigen subtype on outcome. *Cancer* 2011; **117**: 4679–4688.
 - 13 Shea T, Johnson J, Westervelt P, Farag S, McCarty J, Bashey A *et al*. Reduced-intensity allogeneic transplantation provides high event-free and overall survival in patients with advanced indolent B cell malignancies: CALGB 109901. *Biol Blood Marrow Transplant* 2011; **17**: 1395–1403.
 - 14 Dreger P, Döhner H, Ritgen M, Böttcher S, Busch R, Dietrich S *et al*. Allogeneic stem cell transplantation provides durable disease control in poor-risk chronic lymphocytic leukemia: long-term clinical and MRD results of the German CLL Study Group CLL3X trial. *Blood* 2010; **116**: 2438–2447.
 - 15 Logan AC, Gao H, Wang C, Sahaf B, Jones CD, Marshall EL *et al*. High-throughput VDJ sequencing for quantification of minimal residual disease in chronic lymphocytic leukemia and immune reconstitution assessment. *Proc Natl Acad Sci USA* 2011; **108**: 21194–21199.
 - 16 Böttcher S, Ritgen M, Dreger P. Allogeneic stem cell transplantation for chronic lymphocytic leukemia: lessons to be learned from minimal residual disease studies. *Blood Rev* 2011; **25**: 91–96.