Haematologica 1998; 83:660-662 review

Chronic lymphocytic leukemia: from palliative therapy to curative intent

Giovanna Meloni, Francesca Romana Mauro, Anna Proia, Franco Mandelli
Dipartimento di Biotecnologie cellulari ed Ematologia, Università "La Sapienza", Rome, Italy

Abstract

High dose therapy and stem cell transplantation is increasingly being used for treatment of CLL. The present article summarizes available results reported in literature on the use of high dose therapy followed by allogeneic or autologous hemopoietic precursor infusion. Transplant procedures seem a feasible approach, especially autografts, while allogeneic transplant has been associated with a higher mortality rate. Interesting clinical/biological results have been reported for both allogeneic and autologous transplants but prospective large clinical trials are needed to establish their real value. We consider important issues of stem cell transplantation in CLL patients, such as the kind of transplant (allogeneic vs autologous), the optimum timing, the selection of patients, the value and type of purging and, above all, impact on survival.

Key words: chronic lymphocytic leukemia (CLL), allogeneic and autologous stem cell transplantation

Chronic lymphocytic leukemia (CLL) is a clonal hematopoietic disorder with proliferation and accumulation of small lymphocytes, usually of B-cell lineage. It is the most common form of leukemia in the Western hemisphere, accounting for approximately 25 to 30% of all adult leukemias. Median age at diagnosis is 65 years and only less than 10% are younger than 40 years old. Clinical course and prognosis are extremely variable. In most cases CLL is an indolent disease: the annual mortality rate is about 8%, median survival is nearly 6 years, and 20% of patients survive more than 10 years. The disease is, however, incurable with conventional treatments and in the presence of adverse prognostic factors, survival time is less than 3 years, a period not acceptable for younger patients. Therefore, in these patients intensive treatment modalities should be considered for obtaining long-lasting remissions and possibly disease eradication. As a consequence, high dose therapy followed by allogeneic or autologous hemopoietic precursors could be an interesting and attractive approach for this particular category of patients.[1-7].

Correspondence: Giovanna Meloni, MD, Dipartimento di Biotecnologie Cellulari ed Ematologia, Università degli Studi "La Sapienza", via Benevento 6, 00161 Roma, Italy.
Phone: international +39-6-857951 • Fax: international +39-6-44241984.

Allogeneic bone marrow transplantation

So far, allogeneic and autologous bone marrow transplantations (BMT-ABMT) have only been performed in a limited number of CLL patients with poor prognosis. The largest series of allotransplanted CLL patients has been collected by the *European* and the *International Bone Marrow Transplant Registries* (EBMT-IBMTR).[8] Of this cohort of 54 patients, with a median age of 41 years, only 7 were considered to have a disease responsive to chemotherapy at the time of transplant. Conditioning regimen mostly consisted of cyclophosphamide and total body irradiation (Cy+TBI); cyclosporin or methotrexate or both were used as graft-versus-host disease prophylaxis. Hematological remission was achieved in 38 (70%) patients. A total of 23 patients in hematological remission were alive at a median time of 27 months after BMT. Of the 30 deaths, 25 were treatment related and generally due to graft-versus-host-disease (GVHD). The rate of transplant related deaths was much lower (10%) in two single center studies reported by the *Dana Farber Cancer Institute* (DFCI)[9] and the *MD Anderson Cancer Center* (MDACC).[10] These different results are probably due to patient's selection criteria and to the lower incidence of severe GVHD. However, it is noteworthy that in both these studies all but two patients received fludarabine treatment, a potent T-cell suppressive agent. In the DFCI experience 8 CLL patients treated to a minimal disease status with conventional chemotherapy were submitted to a T-cell depleted allogeneic BMT after CY+TBI conditioning regimen; after a median follow up of 1 year, 6 patients remained in remission with no phenotypic or molecular biologic evidence of residual CLL cells in 5 of them. The experience at MDACC was similar to that at the DFCI as far as concerns conditioning regimen and GVHD prophylaxis, but all patients had refractory or relapsing disease at the time of transplant. In this study 10 out of 11 patients were alive after a median follow up of 10 months.

Martinez *et al.*[11] treated six patients (four with advanced chronic lymphocytic leukemia, one follicular center cell lymphoma and one mantle cell lymphoma) with allogeneic stem cell transplantation (SCT). The conditioning regimen included in five cases cyclophosphamide, TB1 and high-dose chlorambucil, without the latter in the patient with follicular lymphoma. Four patients are alive in complete remis-

sion. Additionally, there is no evidence of residual disease by immunologic and molecular techniques in three cases, while one patient has residual disease assessed by molecular methods.

In the recently updated MDACC experience, Khouri *et al*. reported a total of 15 patients, with progressive disease after fludarabine therapy, submitted to allogeneic BMT.[12] Eleven patients (73%) achieved a complete remission (CR), and 8 (53.5%) are still alive after a median follow-up of 35 months. Overall, these data suggest that, despite the high treatment related death rate, BMT is capable of inducing long lasting remissions in refractory CLL patients who otherwise have little possibility of long term survival.

Autologous stem cell transplantation

There are several reports on autotransplantation in CLL,[9,10,13-17] the first one having been produced by the DFCI Group from Boston.[9] Twelve patients with high risk CLL were transplanted in a minimal residual disease status after conventional therapy. The transplant was performed with marrow *ex vivo* purged with monoclonal antibodies anti B1, B5 and J5, after Cy+TBI conditioning regimen. All patients engrafted and most of them achieved molecular and immunological remission. The MDACC Group from Houston transplanted eleven patients in relapse with marrow previously harvested during a fludarabine-induced remission.[10] In 7 cases marrow was purged by a MoAb (anti-CD19) immunomagnetic selection. Although six of the 11 patients achieved a clinical CR with immunological disappearance of the leukemic B-cell clone in 5, a high relapse rate was observed. The EBMT-IBMTR study retrospectively evaluated the results of autologous hematopoietic transplantation in 29 cases of CLL of whom 77% were in clinical remission before transplant.[14] . The conditioning regimen consisted in Cy+TBY in most cases; 18 patients received autologous, ex vivo purged in 16, marrow, 9 patients received autologous peripheral blood stem cells transplantation (PBSCT) and 2 patients both. After a median follow-up of 36 months 23 patients were alive and the 5 year survival probability was 52%. Better results were achieved in patients transplanted with less advanced disease. In our institute in March 1995 we started a program of PBSCT in CLL patients achieving a minimal residual disease status after fludarabine treatment, to test the feasibility and efficacy of this therapeutic strategy.[15] Ten CLL patients with a median age of 44 years (range, 21-56) were candidates for unmanipulated PBSCT after a BEAM (BCNU, etoposide, Ara-c, melphalan) conditioning regimen. All patients were in stage B at the time of fludarabine administration. Median interval from fludarabine therapy to PBSC mobilization was 3 months (range, 2-6). Cyclophosphamide (7 gr/m^2) followed by rhG-CSF (5 µg/kg) was utilized to mobilize PBSC. A sufficient number of PBSC was collected and reinfused in 7 patients while three patients required marrow collection and reinfusion. All patients engrafted and the median time to reach neutrophils >500/µL and platelets >20,000/µL was 12.5 (range, 9-24) and 27.5 days (range, 13-115), respectively. No major toxicities were observed during treatment. One patient developed an acute myeloid leukemia 16 months after transplant and received antileukemic chemotherapy. He died 17 months later because of metastatic lung cancer while in CR from both hematological diseases. All the remaining 9 patients are still alive: 8 are in persisting unmaintained hematological remission after a median follow-up of 15 months (range, 4 to 26).[16] The feasibility of the PBSCT procedure has been recently confirmed by Itala *et al.*[17] After a preparative regimen consisting of Cy+TBI they transplanted 8 patients in a minimal residual disease status. A satisfactory PBSC mobilization was obtained in five cases. After a median follow-up of 10 months, 4 patients still remained in hematological remission. However, several infectious complications were observed. Recently, Scimè *et al.* started a multicenter study using CD34$^+$ cells selected by immunoabsorption technique in CLL patients responsive to fludarabine therapy.[18] The CD34$^+$ cells mobilization was obtained by CY (4 g/m^2) followed by rhG-CSF (5 µg/kg). Eight patients were transplanted after a myeloablative regimen consisting of busulfan (12 mg/kg) and melphalan (140 mg/mq) and all engrafted. At a median follow up of 8 months (range, 3-24) 4 patients were in continuous hematological remission, with no evidence of molecular disease in 2 of them.

Conclusions

Taken together, these data about allogeneic and autologous transplantation in CLL are certainly encouraging because both autologous and allogeneic stem cell transplantation could result in molecular remissions thus giving the possibility of cure. Since transplant procedures in CLL are still experimental approaches, one should first answer the question whether or not, still in CLL, allogeneic is better than autologous transplant and then identify the candidates best suited to each procedure.

Two arguments are in favor of allogeneic transplantation in patients with CLL: the first is the possibility of obtaining a sufficient number of good quality stem cells because the donor's hematopoietic system has not been exposed to cytotoxic agents; the second is that hemopoietic donor cells are uncontaminated by clonal lymphocytes. These advantages combined with the graft-versus-leukemia effect,[19,20] make allogeneic transplantation a more attractive procedure than autografting in terms of disease eradication. The major disadvantage of allotransplantation, however, is the treatment-related mortality that cannot be expected much lower than 20% and could be even higher considering the age of CLL patients. In contrast, autologous transplantation treatment relat-

ed mortality rate may be less than 5%, especially when PBSC are utilized. The major disadvantage of autologous transplantation is graft contamination by malignant cells, although this problem may be overcome by the use of purging techniques to eliminate tumor cells from the graft or by the use of $CD34^+$ cell purification devices. However, the real effect of purging procedures on disease free survival after transplant has still to be evaluated. Taken together these data suggest that we should consider BMT for younger patients with refractory CLL while in all those young patients with advanced disease who achieve a minimal residual disease status after therapy, autograft may represent a less toxic therapeutic choice. There are many questions which remain to be answered, but these preliminary and promising clinical/biological results should be confirmed in large prospective clinical studies with longer follow-up. The path leading from palliative to curative therapy in CLL has been opened and will certainly be explored thoroughly during the next years.

Contributions

GM was primarily responsible for the conception of this review article and the writing of the paper. FRM, AP and FM contributed to the analysis of the literature and writing of the paper.

Funding

Supported by MURST 40%.

Disclosures

Conflict of interest: none.

Redundant publications: no substantial overlapping with previous papers.

Manuscript processing

Manuscript received February 9, 1998; accepted April 30, 1998.

References

1. Rozman C, Montserrat E. Chronic lymphocytic leukemia. N Engl J Med 1995; 333:1052-7.
2. Catovsky D, Murphy RLW. Key issues in the treatment of chronic lymphocytic leukemia (CLL). Eur J Cancer 1995; 31:2146-54.
3. Tura S, Zinzani PL. New target of chronic lymphocytic leukemia treatment. Haematologica 1994; 79:197-9.
4. Robertson LE, Yang O, Keating M, et al. Response assessment in CLL after fludarabine plus prednisone: clinical, pathologic, immunophenotypic and molecular analysis. Blood 1992; 80:28-36.
5. International Workshop on Chronic Lymphocytic Leukemia. Chronic lymphocytic leukemia. Recommendation for diagnosis, staging and response criteria. Ann Intern Med 1989; 110:236-8.
6. Lenormand B, Bizet M, Fruchart C. Residual disease in B-cell chronic lymphocytic leukemia patients and prognostic value. Leukemia 1994; 8:1019-26.
7. Robertson LE, Huh JO, Pugh WC, et al. Response assessment in chronic lymphocytic leukemia after fludarabine: clinical, pathologic, immunophenotypic and molecular analysis. Blood 1993; 80:1695.
8. Michallet M, Archimbaud E, Bandini G, et al. HLA-identical sibling bone marow transplantation in younger patients with chronic lymphocytic leukemia. Ann Intern Med 1996; 124:311-5.
9. Rabinowe SN, Soiffer RJ, Gribben JG, et al. Autologous and allogenic bone marrow transplantation for chronic lymphocytic leukemia: preliminary results. Blood 1993; 82:1366-76.
10. Khouri IF, Keating MJ, Huibert M, et al. Autologous and allogeneic bone marrow transplantation for chronic lymphocytic leukemia. J Clin Oncol 1994; 12:748-58.
11. Martinez C, Martino R, Brunet S, et al. Allogeneic stem cell transplantation for advanced low-grade lymphoproliferative disorders: report of six cases. Haematologica 1996 ; 81:330-4.
12. Khouri IF, Przepiorka D, Van Besien K, et al. Allogenic blood or marrow transplantation for chronic lymphocytic leukemia: timing of transplantation and potential effect of fludarabine on acute graft-versus-host disease. Br J Haematol 1997; 97:466-73.
13. Bastion Y, Felman P, Dumontet C, et al. Intensive radio-chemotherapy with peripheral blood stem cell transplantation in young patients with chronic lymphocytic leukemia. Bone Marrow Transplant 1997; 19:647-51.
14. Michallet M, Archimbaud E, Rowling PA, et al. Hematopoietic stem cell transplant for chronic lymphocytic leukemia [abstract]. Bone Marrow Transplant 1996; 17(suppl 1):S3.
15. Meloni G, Mauro FR, Proia A, et al. Peripheral blood stem cell transplantation in CLL patients in remission after fludarabine therapy: a feasibility study [abstract]. Autologous Marrow and Blood Transplant 1997; 8:177.
16. Meloni G, Mauro FR, De Fabritiis P, et al. Unmanipulated peripheral blood stem cell transplantation in chronic lymphocytic leukemia in remission after fludarabine therapy. Experience in 10 patients [abstract]. Blood 1997; 90:(Suppl 1):4241.
17. Itala M, Pelliniemi T-T, Rajamaki A, Remes K. Autologous blood cell transplantation in B-CLL: response to chemotherapy prior to mobilization predicts the stem cell yield. Bone Marrow Transplant 1997; 19: 647-51.
18. Scimè R, Santoro A, Musso M, et al. Peripheral CD34+ cell autograft in CLL: preliminary results of a cooperative study [abstract]. Blood 1997; 90:(Suppl 1): 4580.
19. de Magalhaes-Silverman M, Donnenberg A, Hammert L, et al. Induction of graft-versus-leukemia effect in a patient with chronic lymphocytic leukemia. Bone Marrow Transplant 1997; 20:175-7.
20. Bertolini F, De Vincentiis A, Lanata L, et al. Allogeneic hematopoietic stem cells from sources other than bone marrow: biological and technical aspects. Haematologica 1997; 82:220-38.