Allografting for indolent lymphoid neoplasms

Division of Hematology, Vancouver Hospital & Health Sciences Centre, Vancouver, Canada

Summary

Background: Allogeneic bone marrow transplantation (BMT) has been used in patients with low-grade lymphoma (LGL) and chronic lymphocytic leukemia (CLL) with the goal of achieving long-term disease-free survival.

Patients and methods: Twenty-nine patients with these diagnoses (LGL = 19, CLL = 10) received allogeneic BMT between September 1995 and January 1999. Median age was 42 (range 20–52) years. Twenty-three of twenty-nine patients (79%) were Ann Arbor or Rai stage IV at the time of transplant; twenty-four (83%) had never achieved complete remission (CR). Donor source was HLA-matched sibling (20), unrelated (8) and syngeneic (1).

Results: Seventeen patients are currently alive, a median of 29 months (range 1–85) post-BMT with a median KPS of 90%. Twenty-three of twenty-seven evaluable patients (85%) achieved CR post-BMT. Six patients had refractory/recurrent disease. Death occurred related to transplant complications in eight patients and underlying disease in four. Overall and event-free survival for the whole group is 51% and 44%, respectively.

Conclusions: Allogeneic BMT for young patients with advanced stage LGL or CLL is a feasible strategy that can result in achievement of long-term disease-free survival.

Key words: allogeneic bone marrow transplantation, indolent lymphoid neoplasms

Introduction

The development of therapy that will prolong survival for patients with the indolent lymphoid neoplasms follicular and small lymphocytic lymphoma and chronic lymphocytic leukemia (CLL) remains a challenge. Newer therapies including nucleoside analogues, combined with patient selection and refined supportive care have impacted upon disease-free periods and quality of life but thus far have not altered the natural history of these diseases, with median survival remaining in the order of a decade [1–4].

Allogeneic hematopoietic stem-cell transplantation shows promise for these patients [5–14], where, as in other selected malignancies, the immunological anti-tumor effect may be an important component of long-term disease control [15–19].

This report summarizes results for 29 patients with these diagnoses who received allogeneic bone marrow transplantation (BMT) at the Leukemia/BMT Program of British Columbia between September 1985 and January 1999.

Patients and methods

Inclusion criteria

Patients with a diagnosis of low-grade lymphoma or CLL were considered for allogeneic BMT following failure of primary therapy or at disease progression, if they met current program organ function guidelines for allogeneic transplant, and had a suitable donor (related or unrelated). Age limit was less than 50–55 years for related and less than 45–50 years for unrelated donor BMT.

Patient characteristics

Fifteen patients were female, fourteen male. Median age at transplant was 42 (range 20–52) years. Median interval from diagnosis to BMT was 21 (range 4.4–154) months. Nineteen patients had low-grade lymphoma, including thirteen with follicular small cleaved cell, four with follicular mixed, and two with small lymphocytic. Ten patients had CLL, including seven with B-cell, two with T-cell, and one with T-cell prolymphocytic leukemia.

Stage and disease status

Twenty-three of twenty-nine patients (79%) were Ann Arbor or Rai Stage IV at the time of transplant, four patients were stage III, and two patients stage II. Most proceeded to BMT at first recurrence (9 patients or 31%) or with primary refractory disease (9 patients or 31%). Complete remission had never been achieved prior to transplant in 83% (24 patients).

Prior therapy

Median number of lines of prior therapy was 2 (range 0–6). Prior therapy included nucleoside analogues and/or others in 38% (11 patients), and alkylating agents ± prednisone in 59% (17 patients). One patient with a syngeneic donor proceeded to transplant as primary therapy.
The majority (twenty patients) received marrow from HLA-matched siblings; one patient had a syngeneic donor and eight received marrow from HLA-matched unrelated donors.

Conditioning regimen
This included cyclophosphamide and total body irradiation for most patients (n = 26). Three patients who had had prior dose limiting radiation received busulfan-based chemotherapy only conditioning.

Graft-versus-host disease prophylaxis
Twenty-two patients received standard short course cyclosporine and methotrexate, two patients cylosporine and methylprednisolone, four patients regimens including T-cell depletion, and one patient (syngeneic donor) none.

Statistical analysis
Standard criteria were used to evaluate BMT-related events including regimen-related toxicity, acute and chronic graft-vs.-host disease (GVHD). Survival analysis (Kaplan–Meier) was employed to estimate overall and event-free survival (with death, relapse, or second BMT as events) and to calculate the actuarial probabilities of transplant-related mortality, acute and chronic GVHD, and relapse. Univariate analysis was performed to examine for factors associated with survival, transplant-related mortality and relapse.

Results
Seventeen patients (59%) are alive at a median follow-up of 29 months (range 6–85). Overall and event-free survival is 51% (95% confidence interval (95% CI): 26%–71%) and 44% (95% CI: 23%–64%), respectively.

Engraftment
Median (range) days to ANC > 0.5 x 10^9/l, WBC > 1.0 x 10^9/l, and platelets > 20 x 10^9/l was 18.5 (10–33), 18.0 (10–32), and 26.5 (10–68), respectively. One patient had failure to engraft following a TCD marrow transplant from an unrelated donor and subsequent recovery of oligoclonal host hematopoiesis post T-replete marrow transplant from the same volunteer unrelated donor. No patient had secondary graft failure.

Toxicity
The majority (20 patients, 69%) had acceptable regimen-related toxicity, i.e., ≤ grade 2 (Bearman criteria). Six patients had grade 3, and three grade 4. Death was related to transplant complications in eight patients.

Graft-versus-host disease
Actuarial incidence of acute (grade 2–4) and chronic GVHD was 54% (95% CI: 37%–74%) and 66% (95% CI: 45%–86%), respectively. Twenty-two patients had ≤ grade 2 acute GVHD, three patients grade 3 and four patients grade 4.

Disease response
Eighty-five percent (23 of 27 evaluable patients) achieved complete remission post BMT, including seven patients with primary refractory disease. Two patients had resistant disease and died at days +69 and +326. One patient had disease evident at day +152 and died day +166 from multiple causes and one relapsed at day +1299 and died at day +1432 from disease. Two patients relapsed at days +182 and +799 and are alive at +613 and +826 days, respectively.

Discussion
Allogeneic BMT has been performed infrequently for low-grade lymphoma and CLL in comparison to other malignancies that are incurable with conventional therapy. This likely relates to the older median age at diagnosis, and a reluctance to employ therapy with a higher up front mortality risk in disorders with a relatively long median survival.

However, a substantial inroad toward survival prolongation has not occurred with conventional therapies, and there is mounting evidence to support the importance of graft-versus-tumor effect in these diseases [15–19], making a strong case for expanded consideration of allogeneic BMT in this population.

Feasibility of allogeneic BMT has been demonstrated in this and other series [5–14]. Regimen-related toxicity appears comparable to that experienced with allogeneic BMT for other diagnoses. Increased pulmonary toxicity has been reported from registry data [8], and will require further evaluation in prospective series. A potential effect of nucleoside analogues to down-modulate acute GVHD has been postulated [14]; if this bears true with further study, inclusion of nucleoside analogues may be an important component of pre-BMT therapy or the conditioning regimen itself.

Since the majority of patients with low-grade lymphoma and CLL are considered ineligible for allogeneic BMT due to age or donor considerations, the use of non-myoeloblatie conditioning regimens with allogeneic hematopoietic stem cell transplant is of great interest [20]. This approach has been adopted by a number of groups and its role should become apparent in the next few years.

Initial results appear optimistic for improved overall survival and the possibility of long-term disease-free survival for selected patients with low-grade lymphoma and CLL undergoing allogeneic BMT. However, median follow-up of a decade or more will be necessary to fully assess the impact of allogeneic strategies in these disorders in view of their well established long natural history.
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References


Correspondence to:
Dr C. Toze
Division of Hematology
Vancouver Hospital & Health Sciences Centre
950 West 10th Avenue
Vancouver, BC V5Z 4E3
Canada