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Allogeneic hematopoietic cell transplantation with fludarabine-based reduced-intensity conditioning as treatment for advanced chronic lymphocytic leukemia

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B-cell chronic lymphocytic leukemia (CLL) is the most frequently diagnosed leukemia in the western world, yet remains essentially incurable. Although initial chemotherapy response rates are high, patients invariably relapse and subsequently develop resistance to chemotherapy. The prognosis of CLL is particularly poor when adverse indicators such as 17p- and 11q-chromosomal aberrations [1], un-mutated status of the variable region of the immunoglobulin heavy chain gene [2,3], and increased expression of surface CD38 [3] and ZAP 70 [4,5] antigens are present. For the moment, allogeneic hematopoietic cell transplantation (alloHCT) remains the only potentially curative treatment for patients with CLL. Early studies of myeloablative allogeneic hematopoietic cell transplant in younger CLL patients established durable remissions with a promising survival plateau; however, significant transplant related mortality (TRM) was observed (25–50%) [6,7]. Due to the advanced age distribution of CLL patients, reduced intensity conditioning (RIC) regimens have been exploited to decrease TRM and increase availability of alloHCT [8,9]. Using the RIC approach, TRM dropped even for older and heavily pre-treated patients, while OS/PFS remained comparable to myeloablative regimens, raising questions about the role of the graft versus leukemia effect in long term disease control. The two-year progression-free survival in various studies ranges from 34–67% with TRM reported between 15 and 30% [8–10].

This study analyzed data from a consecutive case-series of 27 patients with CLL/SLL who underwent RIC alloHCT at City of Hope from 2001 to 2008. Transplant was offered to CLL/SLL patients who had refractory disease or poor prognostic factors based on the literature at the time of treatment. After 2007, EBMT criteria were used to determine transplant eligibility [11]. Donor selection was based on the availability of an HLA-identical family donor, or alternatively from an HLA-matched unrelated donor based on molecular typing of HLA A, B, C, DR, and DQ loci.

Patient demographics are detailed in Table 1. The population was relatively high-risk: 15 patients (55.6%) had bulky adenopathy (>5cm in largest diameter), 9 patients (33%) were fludarabine-refractory, 14 patients (53.9%) had gross involvement of the bone marrow (> 30% bone marrow involvement), 10 patients (37.0%) had progressive disease or failed induction therapy at the time of transplant. The choice of reduced intensity conditioning regimen and GVHD prophylaxis were based on the institutional guidelines at the time of

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transplant and physician discretion but majority of the patients (78%) received fludarabine/melphalan conditioning with or without rituximab.

The median follow-up for surviving patients was 25.1 months (range: 5.8–81.5). The 100-day mortality was 7.4% (2 of 27 patients), with one death from disease progression and one from infection. All patients but one engrafted; the patient with primary graft failure underwent a successful second matched unrelated transplant on day 67. Three patients lost graft function after initial engraftment due to disease progression in the bone marrow. The incidence of acute GVHD was 70.4% (19/27) with 11 patients at grades I/II and eight at grades III/IV. Sixteen of 25 evaluable patients (64.0%) suffered from chronic GVHD, seven with limited and nine with extensive disease. The best response post-transplant was complete remission in 19 patients (70.4%), partial response in 4 (14.8%), stable disease in one (3.7%) and progression in three (11.1%). Assessment of response was based on National Cancer Institute-sponsored Working Group guidelines for CLL [13]. As of the analytic date, 14 of the 19 patients who achieved CR remain alive and in remission at last contact. Four CR patients expired as a result of cGVHD and infectious complications and one patient eventually died of disease progression. Of the four PR patients, one died of disease progression, two died of infection, and one was living with residual disease.

As assessed by the Kaplan-Meier method, overall survival (OS) was 80.0% (95% CI: 63.6, 89.6 at 1 year and 64.0% (95% CI: 49.3, 75.4) at 2 years and progression-free survival (PFS) was 72.8% (95% CI: 57.8, 83.2) at 1 year and 62.4% (95% CI: 48.6, 73.4) at 2 years (Figure 1A–B.) Patients who were alive at the time of analysis were censored at the last contact date. Non-relapse-related mortality and relapse/progression were considered competing risks for mortality. The cumulative incidence of relapse/progression was 15.4% (95% CI: 5.6, 34.3) at 2 years (Figure 1C) and the cumulative incidence of non-relapse mortality (NRM) was 24.7% (95% CI: 9.4–45.7) at 2 years (Figure 1D). Our study demonstrates promising rates of progression-free survival and incidence of relapse/progression; in a population with a median age over 50 and a high rate of bulky disease and chemoresistance, this outcome suggests that cure can be achieved by RIC alloHCT, even in these heavily pre-treated patients. Our experience also confirms observation by other investigators that CLL has a relatively low relapse rate compared to other malignancies, with relapse/progression events decreasing over time – suggesting a plateau and supporting the role of the graft-versus-leukemia effect in the disease control (8,9,10).

The significance of disease/treatment features was assessed using log-rank comparison of the univariate Kaplan-Meier survival. Differences between cumulative incidence curves in the presence of a competing risk were tested using the Gray method. The following risk factors were analyzed to assess their predictive value: cytogenetic abnormalities (good/normal, poor risk [1]), bulky lymphadenopathy (yes, no), fludarabine-refractory disease (yes, no), degree of bone marrow involvement (<30%, ≥30%) and presence of chronic GVHD (yes, no). The presence of poor risk cytogenetic abnormalities, bone marrow involvement and presence of chronic GVHD did not influence the outcome. The log-rank results of the univariate Kaplan-Meier survival analysis showed a positive association between absence of bulky lymphadenopathy ($p=0.0001$) and chemosensitive disease (0.06) with a trend towards improved PFS (Figure 1E–F).

Based on the available data, we saw no significant correlation between poor risk cytogenetic features and outcomes. While our patient population is relatively small this finding concurs with studies demonstrating that allogeneic transplant can overcome the detrimental effects of negative prognostic indicators such as 17p and 11q deletion, [14]. This is particularly important as immunochemotherapy alone has been associated with limited efficacy and disappointing outcome in patients with poor cytogenetic features [1,15]. Expanding the

indications for alloHCT to include patients with poor cytogenetic risk factors earlier in the disease course, before they become truly chemorefractory, may improve transplant outcomes and rates of treatment-related complications.

By survival analysis, we found that fludarabine-refractory disease and bulky lymphadenopathy at the time of transplant were associated with a trend toward inferior progression-free survival ($p=0.06$ and 0.0001 respectively), associations supported by Sorror *et al.* [9] in a study with a large percentage of chemoresistant patients. In our population fludarabine-refractory disease may be a surrogate for bulky disease as a predictor of poor prognosis, since 8 of 9 fludarabine-refractory patients also had bulky lymphadenopathy. Fludarabine-refractory disease could predict intrinsic resistance to GVL activity or, alternatively, could be a marker of aggressive disease that progresses too rapidly to be controlled by even an active immune response. In the latter case the use of non-myeloablative conditioning might possibly result in insufficient cytoreduction, which could interfere with engraftment and may not allow time for development of GVL. For patients with less-than-optimal disease control at the time of transplant, potential ways to improve the efficacy of reduced intensity regimens that are being investigated include aggressive debulking prior to transplant, reduced intensity rather than purely non-myeloablative preparative regimens, immunomodulation with monoclonal antibodies and/or donor lymphocyte infusion following the transplant, and incorporation of novel agents with activity against CLL.

Although there is no doubt that alloHCT can improve the prognosis of selected poor-risk patients, its place in the treatment algorithm for the general CLL population is still unclear. In the absence of randomized and large prospective studies, the biggest challenges in CLL alloHCT therapy remain patient selection and timing of transplant during the disease course. New emerging therapies can potentially enable refractory patients to attain response as a bridge to more effective stem cell transplantation or enhance its curative potential as part of conditioning regimens. These issues can be properly addressed only by prospective clinical trials. Until then, the data from retrospective and prospective studies provided by the cooperative groups and large transplant centers, including City of Hope, remain valuable sources of information.

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Figure 1. Outcomes

For all panels survival probability and cumulative incidence are plotted as functions of time from transplant in years. Tick-marks indicate censoring. **Panel A** shows overall survival (OS), defined as time from stem cell infusion to death from any cause. **Panel B** shows progression-free survival (PFS), defined as time from stem cell infusion to recurrence, progression or death from any cause, whichever occurred first. **Panel C** shows the cumulative incidence of relapse/progression calculated with non-relapse mortality as a competing risk. **Panel D** shows the cumulative incidence of non-relapse mortality calculated with relapse/progression as a competing risk. **Panel E** plots PFS in the presence and absence of bulky lymphadenopathy: solid line = absence of, and dashed line = presence of. **Panel F** plots PFS in the presence and absence of chemorefractory disease: solid line = absence of, and dashed line = presence of.

Table 1
Summary of Patient/Disease/Transplant Characteristics

Reported as number of patients (percent) or median (range). N=27 for total population

Variable	N (%) or median (range)
Patient Age at Transplant (Years)	52.5 (38–68)
Patient Gender	
Female	9 (33.3)
Male	18 (66.7)
Donor Type	
Matched Related Donor	15 (55.6)
Matched Unrelated Donor	12 (44.4)
Stem Cell Source	
Bone Marrow	3 (11.1)
Peripheral Blood Stem Cell	24 (88.9)
Chemosensitivity	
Refractory * to fludarabine	9 (33.3)
Chemosensitive	18 (66.7)
Time from Diagnosis to HCT (Months)	53.4 (12.8–123.3)
Disease Status at Transplant	
Induction Failure	1 (3.7)
Partial Remission	16 (59.3)
Progressive	9 (33.3)
Stable	1 (3.7)
% Bone Marrow Involvement at HCT	
<30% Involvement	12 (46.1)
30% Involvement	14 (53.9)
Unknown	1
Cytogenetic Risk	
Good	3 (11.1)
Normal	10 (37.0)
Poor/Complex	8 (29.7)
Not Done	6 (22.2)
Bulky Lymphadenopathy at HCT (>5 cm)	
Yes	15 (55.6)
No	12 (44.4)
# of prior chemotherapy regimens	3 (2–10)
ZAP-70 overexpression at HCT	
Yes	7 (25.9)
No	4 (14.8)
Not Done	16 (59.3)
CD-38 overexpression at HCT	
Yes	11 (40.7)

Variable	N (%) or median (range)
No	2 (7.4)
Not Done	14 (51.9)
Conditioning Regimen	
Fludarabine / Melphalan ± Rituxan	21 (77.8)
Fludarabine / CTX / Rituxan	5 (18.5)
Fludarabine / TBI	1 (3.7)
GVHD Prophylaxis	
Tacrolimus / Sirolimus ± MTX	12 (44.4)
Tacrolimus / MTX	3 (11.1)
Cyclosporine / Cellcept ± MTX	12 (44.4)

* Chemorefractory disease is defined as treatment failure (< PR) or disease progression within 6 months of the last antileukemic therapy [12].