Journal of Bone Marrow Research
ISSN: 2329-8820

Mellen and Nyle, J Bone Marrow Res 2013, 1:5
DOI: 10.4172/2329-8820.1000130

Short Communication Open Access

A Short Review on Allogeneic Stem Cell Transplant in Leukemic Patients

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Abstract

To identify potential barriers to reduced-intensity conditioning (RIC) allogeneic stem cell transplantation (ASCT) in patients with chronic lymphocytic leukemia (CLL) we performed a retrospective review of patients referred for transplant consultation at our center. Of the 209 patients evaluated, a substantial proportion of patients who were appropriate candidates for RIC-ASCT were unable to attain disease control to proceed (18.3%) with this therapy.

Introduction

Chronic lymphocytic leukemia (CLL) is the most common hematologic malignancy in the Western world, representing 30% of leukemia [1]. Utilization of new combinations of chemotherapeutic agents, as well as the introduction of biologic agents, and the identification of prognostic markers that have led to better risk stratification and more tailored treatments have led to longer remissions, but CLL is still considered incurable outside the transplant setting [2]. Treatment for young and otherwise healthy patients has traditionally involved fludarabine, typically in combination with other agents [3]. A comprehensive assessment of certain genetic and molecular markers, including fluorescent in-situ hybridization (FISH) has shown that outcomes of fludarabine-based therapies can be predicted by these markers, and that alternative therapies should be considered in certain patients with high risk markers, including del (17p13.1) and del (11q22.3) [4]. Reduced-intensity conditioning (RIC) allogeneic stem cell transplant (ASCT) is one such option. In spite of RIC ASCT being the only potentially curative option available for CLL, relatively few patients who are referred for transplant evaluation eventually go on to receive one. According to our institutional data, approximately 15-20 percent of patients who are referred for transplant ultimately receive one. The purpose of this study was to quantify how many patients are evaluated versus how many eventually receive a transplant, to evaluate differences between patients who received a transplant and those who did not, and to attempt to elucidate why this therapeutic option is not pursued more frequently.

From January 2003 to August 2009, 209 patients with CLL were referred to our center for a transplant evaluation. Of those, 34 (16.3%) ultimately underwent transplantation. For patients who did not receive a transplant, it was not indicated according to standard of care at the time of consult in 37 patients (21.1%), and for 32 patients (18.3%), transplant was indicated but patients were unable to obtain disease control in order to proceed. Twenty patients (9.6%) were awaiting transplant at the time of analysis and were excluded from comparisons described below.

The differences between patients who went on to transplant and those who could not obtain remission were analyzed more closely. The median age at the time of transplant consultation in the group who received a transplant was 55 years (range: 35 to 69 years), and the median age in the group that could not obtain remission was 58 (range: 29 to 70 years). The group that could not be transplanted received a median of 2.5 prior treatment regimens before transplant evaluation (range: 0 – 7 treatments), compared to a median of 2 prior treatment regimens (range: 0 – 6 treatments) in those who were able to go on to transplant (p = 0.099). Twelve patients in the transplant group (35.5%) had fludarabine-resistant disease at the time of consultation in contrast to 21 patients (65.2%) who could not be transplanted (p=0.026). Of the 34 patients who underwent transplantation, 12 had a complex karyotypic (≥ 3 cytogenetic abnormalities on metaphase analysis) and 22 had 0 to 2 karyotypic abnormalities. This contrasts with the 31 patients with evaluable metaphase cytogenetics who could not attain remission: 19 had a complex karyotype and 12 did not (p = 0.048). If we looked at this as a continuous measure, the median number of karyotypic abnormalities in subjects unable to go to transplant was 4 (range: 0 to 6) vs. a median of 2 karyotypic abnormalities in those who went on to transplant (range: 0 to 6). When interphase cytogenetic abnormalities were further analyzed, notable differences were observed based on presence of high-risk cytogenetic abnormalities [del (17p13.1) or del (11q22.3)], but these differences were not statistically significant; this could be a result of the limited number of subjects. Of interest, we did observe a significant differential in del (17p13.1) chromosomal anomalies in a patient examining this as a continuous variable, where the median was 2%, which is considered normal (range: 0 – 94.5%) in those going on to transplant vs. about 22%, which is considered positive (range: 0 – 100) in those who were unable to be transplanted (p = 0.0477).

In addition to these markers, we found that ECOG performance status was significantly associated with ability to go on to transplant (p = 0.039). Receipt of 4 of more prior therapies versus 3 or fewer was also a significant factor (p = 0.02). These factors were also significant in univariate logistic regression models along with the previously discussed factors of interest (% del (17p13.1), fludarabine refractoriness, and presence of complex karyotype). Other clinical factors such as age, gender, and stage (actual as well as low vs. high) were not statistically significantly related to ability to go on to transplant. An all subsets approach yielded a multivariable model with factors including performance status (p=0.03), % del(17p13.1) (p=0.029), and history of 4+ prior treatment regimens (p=0.017); while this was considered the best-fitting model, there was still considerable variability that was not explained, indicating that larger studies that can explore other potential

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Received July 25, 2013; **Accepted** July 31, 2013; **Published** August 02, 2013

Citation: Mellen D, Nyle H (2013) A Short Review on Allogeneic Stem Cell Transplant in Leukemic Patients. J Bone Marrow Res 1: 130. doi: 10.4172/2329-8820.1000130

factors are required to better understand and predict a CLL patient's ability to go on to receive a transplant.

RIC-ASCT was introduced as a way to minimize the toxicity of transplant but preserve the graft-versus-leukemia effect. Long-term disease-free survival periods are being reported, even in patients with high-risk features such as IGHV unmutated disease or Del (17p13.1) [5-8]. At our center, the majority of patients who did not undergo transplantation did not have an indication for transplant at the time of evaluation, which, in many cases, reflected previous standards of care prior to the understanding of the poor prognosis of patients with high-risk karyotypic and fludarabine-refractory CLL. An inability to obtain disease control in order to proceed to transplantation was the second most common reason transplantation was deferred. These data reflect the difficulty in some cases of determining the appropriate timing for allogeneic transplantation in CLL and the risk of delaying a transplant referral in patients with high-risk disease. Currently, the presence of Del (17p13.1) is the only cytogenetic indication for transplant in first remission in patients with CLL. Purine-analog resistance is included among the criteria, and its importance is underlined by the relative inability of this population of patients to mount an adequate response to salvage treatment to go on to transplant [9]. Additionally, the presence of complex karyotypic on metaphase cytogenetics may be an important factor in predicting whether a patient will have a sufficient response to salvage therapy to undergo subsequent allogeneic SCT [10]. Clonal evolution, the acquisition of new karyotypic abnormalities during the disease course, has been associated with resistance to therapy and shortened survival, and it is observed almost exclusively in patients with unmutated IGHV [11,12]. The propensity towards clonal evolution, as defined by IGHV mutation status, may play a key role in determining which patients should be evaluated for transplant earlier in their disease course, particularly since allogeneic transplant has been demonstrated to overcome the adverse prognostic effect associated with unmutated IGHV, although data that our group has published suggests that it may not overcome the adverse effect associated with complex karyotype [13,14]. The significance of fludarabine resistance at the time of transplant evaluation with respect to the ability to subsequently go on to transplant underscores the need to continue to search for more effective salvage therapies in CLL.

Conclusion

Notably, this study was performed before clinical trials with novel therapeutic agents, such as ibrutinib or GS1101, were available. The clinical successes of these agents further complicate the decision of when to refer a patient for a transplant [15,16]. Nonetheless, appropriate timing of transplant referral and availability of effective salvage therapy are critical to the successful long-term management of patients with fludarabine-refractory CLL.

Acknowledgements

This work is supported by The Leukemia and Lymphoma Society, The National Cancer Institute -P50 CA140158, PO1 CA95426, PO1 CA81534, 1K12 CA133250.

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