



Is Allogeneic Hematopoietic Cell Transplantation Still an Option for Chronic Lymphocytic Leukemia in the Era of BTK Inhibition?

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Chronic lymphocytic leukemia (CLL) remains the most common adult leukemia in Western countries. Over the last several decades, there has been an evolution in therapeutic options from single-agent alkylating agents to purine analog-containing regimens, as well as chemo-immunotherapy combinations. Despite the high initial response rates reported with conventional chemo-immunotherapy [1,2], patients invariably relapse and may subsequently develop resistance to further conventional therapy. Unfortunately, there is no evidence to date that conventional therapy is curative. Allogeneic hematopoietic cell transplantation (HCT) has been evaluated as a treatment option to improve prognosis, specifically in patients with poor-risk features or in those with refractory disease [3-9]. Allogeneic HCT can be curative in the treatment of CLL due to the allo-immune graft-versus-leukemia effect [10-12]. Recently, there have been several new small molecule inhibitors gaining accelerated approval by the United States Food and Drug Administration (FDA) to manage difficult-to-treat CLL patient populations, including PI3K delta inhibitors and Bruton's tyrosine kinase inhibitors [13,14]. With this new armamentarium, is there still a role for HCT in CLL?

Relatively fewer patients with CLL become eligible for HCT for many reasons. CLL is largely a disease of the elderly population, with a median age at diagnosis of 71 years and with approximately 70% of patients diagnosed above the age of 65 years [15]. The disease may be initially indolent with a long natural history, so there is reluctance to commit patients to a treatment approach with significant morbidity and potential mortality. Due to declining organ function and medical comorbidities often encountered in this age group, the risks of allogeneic HCT become substantial. Furthermore, often at the time of referral to a transplant facility, patients have been heavily pretreated and may have developed reduced performance status and treatment-related toxicities [16]. It is well known that the success of allogeneic HCT decreases as the number of cytotoxic pre-transplant therapies increase. Nonetheless, allogeneic HCT remains a reasonable option for eligible patients with previously treated disease, criteria for poor-risk disease [17,18], patients with early relapse, and those with chromosome 17p deletion (17p-) requiring treatment [19].

Especially problematic are the patients with 17p-, as outcomes remain poor with currently available treatment regimens. Patients with 17p- CLL have a median survival time of approximately 1.5 years after first-line treatment with fludarabine alone or in combination with cyclophosphamide [20]. In fact, 17p- is an independent prognostic variable predicting for overall survival in CLL [21] and is responsible for more rapid progression of disease [22]. *P53* is a tumor suppressor gene located on the short arm of chromosome 17, which becomes inactivated by deletion and/or point mutation in many human malignancies [23-29]. The wild-type *p53* gene protein product signals apoptosis and acts as a checkpoint regulator of cells entering into the synthesis phase (S-phase) of DNA replication. Additionally, *p53* can contribute to the cytotoxic action of many cytostatic agents and radiation by triggering apoptosis in response to DNA damage [30]. *P53* mutations have been identified in 7% of newly diagnosed patients and up to 47% of patients with relapsed or refractory disease. This mutation is associated with worse outcomes, short treatment free intervals, reduced median survival, and poor response to chemotherapy.

Allogeneic HCT has shown promising results with durable responses demonstrated on long-term follow up. This approach is also potentially curative for high-risk disease. Among a number of cohorts reported, overall survival rates at 2 years are in the range of 50 to 70% [4,7,8,31,32]. Patients with poor risk cytogenetics do not influence HCT outcomes as compared with conventional treatments, however complete responses are lower with refractory disease at the time of HCT [7,9]. Allogeneic HCT is not without complications. Acute and chronic graft-versus-host disease (GVHD) remain the major contributors for morbidity and mortality following allogeneic HCT. More recent data using reduced-intensity conditioning for allogeneic HCT in CLL show incidences of acute GVHD in the range of 40% and extensive chronic GVHD in the range of 20 to 60% and are the likely contributors of non-relapse mortality rates observed in the range of 15 to 20% at 2 years.

Now enter the era of ibrutinib, the first available selective and irreversible small-molecule Bruton's tyrosine kinase (BTK) inhibitor.

Citation: Simmons JD, Pantin J (2014) Is Allogeneic Hematopoietic Cell Transplantation Still an Option for Chronic Lymphocytic Leukemia in the Era of BTK Inhibition?. *Int J Cancer Clin Res* 1:003e. doi.org/10.23937/2378-3419/1/1/1003

Received: September 01, 2014; **Accepted:** September 05, 2014; **Published:** September 08, 2014

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BTK is a member of the Tec kinase family and is positioned early within the B-cell antigen receptor (BCR) signaling cascade [33,34]. This is an essential mediator of BCR signaling in transformed B-cells and inhibiting this pathway promotes apoptosis and inhibits proliferation, migration and adhesion of malignant lymphocytes. Ibrutinib is a highly active, well-tolerated oral therapy with substantial activity across B-cell histologies, including CLL [35,36]. Recently the FDA expanded the approved use of ibrutinib to treat patients with CLL carrying 17p- and the drug received a "Breakthrough Therapy" designation for this use [37]. The recent approval was based on data from the international, multicenter, phase 3, RESONATE trial which reported the outcomes of patients with relapsed or refractory CLL or SLL treated with either ibrutinib or the anti-CD20 antibody ofatumumab. The patients treated with ibrutinib as a single-agent had significantly lengthened PFS on followup at 9.4 months (median not reached with ibrutinib vs. 8.1 months with ofatumumab; HR 0.215, 95% CI, 0.146 to 0.317; $P < 0.0001$) and OS (HR 0.434; 95% CI, 0.238 to 0.789; $P = 0.0049$) compared to those treated with ofatumumab. The trial was stopped early for efficacy after a pre-planned interim analysis showed ibrutinib-treated participants experienced a 78% reduction in risk of disease progression or death [14]. More importantly, at 12 months, the overall survival rate in the ibrutinib arm was 90%. Of the 127 participants with 17p-, those treated with ibrutinib experienced a 75% reduction in risk of disease progression or death [14]. In a prior phase Ib/II study, previously treated or relapsed/refractory patients with CLL taking ibrutinib demonstrated an overall response rate of up to 71% with an additional 15-20% of patients showing a partial response [36]. The responses noted were independent of clinical and genomic risk factors present before treatment, including 17p- and the responses were durable with the estimated PFS, 75% with an OS of 83% at 26 months.

Allogeneic HCT and ibrutinib are now both demonstrated options to provide long-term disease control and to improve survival in patients with high-risk CLL, and in patients with relapsed disease or who are refractory to traditional chemo-immunotherapy. Ibrutinib is an extremely effective agent with clinically demonstrated response rates that remain durable in a patient cohort that remains very complex and difficult to treat. Although long-term mature data describing outcomes with ibrutinib treatment for CLL are not yet available, 80 to 90% overall response rates at 1 year compare favorably to outcomes with allogeneic HCT at similar follow up without the debilitating events of GVHD. Ibrutinib may not yet become the silver bullet and resistance to its mechanism of action has been shown [38]. However, this once a day small molecule inhibitor can be argued as a veritable alternative to HCT as salvage therapy in high-risk relapsed/refractory patients with CLL. Additional time will be required to allow the ibrutinib data to mature to determine if responses remain durable for extended periods when compared to HCT, and until then we may likely see more complicated patients with greater debilitation being referred for transplant evaluation.

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