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ORIGINAL RESEARCH REPORT

Reduced intensity is preferred over myeloablative conditioning allogeneic HCT in chronic lymphocytic leukemia whenever indicated: A systematic review/meta-analysis

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Abstract
Despite availability of new and more effective therapies for chronic lymphocytic leukemia, presently this disease remains incurable unless eligible patients are offered an allogeneic hematopoietic cell transplant. Recent published clinical practice recommendations on behalf of the American Society for Blood and Marrow Transplantation relegated the role of for allogeneic hematopoietic cell transplantation to later stages of the disease. To our knowledge, no randomized controlled trial has been performed to date comparing myeloablative versus reduced intensity conditioning regimens in chronic lymphocytic leukemia patients eligible for the procedure. We performed a systematic review/meta-analysis to assess the efficacy of allogeneic hematopoietic cell transplantation when using myeloablative or reduced intensity conditioning regimens. We report the results in accordance to the Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines. Based on lower non-relapse mortality and slightly better overall survival rates, reduced intensity conditioning regimens appear to be

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the most desirable choice whenever the procedure is indicated for this disease. It appears highly unlikely that a RCT will be ever performed comparing reduced intensity vs. myeloablative allogeneic hematopoietic cell transplantation in chronic lymphocytic leukemia. In the absence of such a study, results of this systematic review/meta-analysis represent the best available evidence supporting this recommendation whenever indicated in patients with chronic lymphocytic leukemia.

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Introduction

Increased availability of novel and more effective therapies for chronic lymphocytic leukemia (CLL) have disrupted traditional treatment algorithms even when high-risk disease features are present [1–5]. A decade ago, the European Society for Blood and Marrow Transplantation (EBMT) published a consensus paper with guidelines indicating optimal timing for allogeneic hematopoietic cell transplantation (allo-HCT) for CLL, recommending the procedure for patients who showed evidence of relapse within 12 months of receiving purine analogue-containing therapy of after failing an autologous hematopoietic cell transplant (HCT) [6]. Moreover, presence of *TP53* mutation and/or Del17p was considered then an indication to offer allo-HCT in the front-line setting [6]. While acknowledging that failure of purine analogue-based regimens remains to this date a prognostic predictor of aggressive clinical behavior, emergence of therapies such as ibrutinib, idelalisib, venetoclax, or others, have proven to be effective in these cases and/or in the presence of other adverse prognostic features [1–5]. For instance, treatment using ibrutinib in heavily pretreated CLL patients (median of 4 prior lines of therapy), including post-nucleoside analogue failures (95%) showed overall response rates (ORR) of 90% and 30-month progression-free survival (PFS) of 70% [1,2]. Moreover, venetoclax, an oral, small-molecule BCL2 inhibitor, showed impressive ORR of 79%, mostly partial responses (PR) in a multicenter phase 2 study in Del17p CLL with relapsed or refractory disease [4].

Recent published clinical practice recommendations for allo-HCT for CLL on behalf of the American Society for Blood and Marrow Transplantation (ASBMT) have relegated the role of allo-HCT to later stages of the disease [7]. To our knowledge, no randomized controlled trial (RCT) has been performed to date (and perhaps will never be) comparing myeloablative (MAC) versus reduced intensity (RIC) conditioning allo-HCT regimens in CLL. In fact, RIC regimens are already more commonly used by virtue of necessity considering that CLL patients are generally of advanced age and they have existing comorbidities which would preclude them from receiving MAC regimens. Non-randomized comparisons using registry data from the Center for International Blood and Marrow Transplant Research (CIBMTR) showed a better 3-year probability of survival with RIC allo-HCT regimens (58% vs. 50%, $p < 0.001$) [8]. Here, we describe results of a systematic review and meta-analysis which aimed at assessing the totality of evidence pertaining to efficacy of RIC or MAC allo-HCT in patients with CLL. For the purposes of this analysis, we included non-

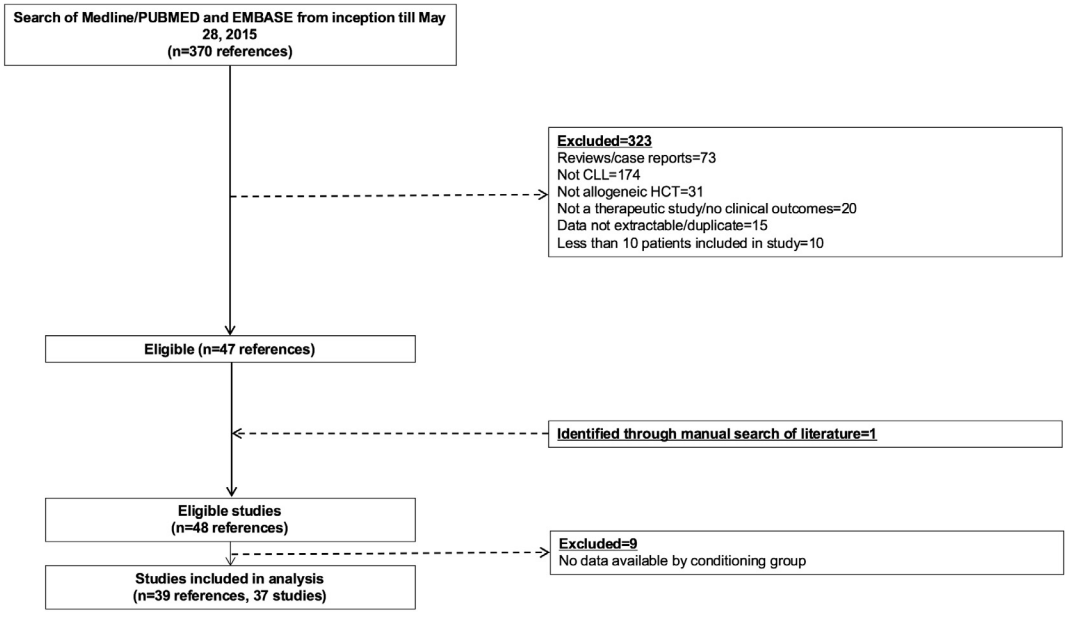

Fig. 1 Study selection process.

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