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Editorial Open Access

Role of Allogeneic Stem Cell Transplant in Chronic Lymphocytic Leukemia and its Implications in Current Era

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Editorial

CLL is the most prevalent adult leukemia in the western countries with 18,960 new cases diagnosed in 2016 and estimated mortality of 25% per year [1]. It is an extremely heterogeneous disease with the clinical course varying from patients who never require therapy to a rapidly progressive and fatal malignancy in others. While most patients treated with fludarabine, cyclophosphamide and rituximab achieve 3-years OS of 87%, there is a high risk CLL group that has a dismal prognosis with a 4-years OS of less than 20% when they are treated with chemo immunotherapy [2,3]. High risk CLL is defined by presence of non-response or early relapse (within 12 months) after purine analogues, relapse within 24 months after having achieved a response with purine analogue-based combination therapy or autologous transplantation, and patients with p53 mutation or del(17p) requiring treatment. In 2007 the European Group for Bone Marrow Transplantation (EBMT) recommended that patient with high risk disease should be considered for allogeneic stem cell transplant [4].

Novel Therapies for Relapse/Refractory CLL

The prognosis of relapsed/refractory CLL has changed dramatically since the approval of B-cell receptor (BCR) and B-cell lymphoma2 (bcl-2) inhibitors and allo-HCT is now relegated to later stages of the disease. Ibrutinib has been studied in CLL patients with relapse/refractory disease, it has an estimated 60-month PFS and OS of 43% and 57% respectively, the overall response rate (ORR) was 86%, with only 10% of patients achieving CR. For patients with del(17p) the 60-month OS was 32% and the median PFS was 26 months [5]. Idelalisib + rituximab has a 12-months OS of 92% in the relapse setting (including patients with 17p deletion, TP53 mutation, and IGHV mutations), the ORR was 81% and all them partial responses [6]. Finally, venetoclax was studied in relapse/refractory patients with 17p deletion. The 12-month PFS was 72% and the 12-month OS was 86.7%, the ORR was 74%, with 54% of partial responses and 16% of complete response or CR with incomplete recovery of blood counts [7].

Despite the good outcomes of the BCR and BCL2 inhibitors, the long term efficacy and toxicity are unknown, complete remissions are uncommon, and the curative potential is unlikely.

Allogeneic Transplant for Relapse/Refractory CLL

In spite of the FDA approval of these new drugs, patients who are refractory or have relapse after being treated ibrutinib and venetoclax have a dismal prognosis with a median OS of 3.1 months after discontinuing ibrutinib [8]. In such patients, non-myeloablative allo-HSCT may still offer the best possible chance of long term remission and cure [9]. Multiple retrospective studies have described a long term PFS of 50% [9-15]. The Center for International Blood and Marrow Transplant Research reported the outcomes of 1338 patients who received an allo-HSCT (RIC=912, myeloablative=426) between 2001 and 2011 and showed that the 3-year probability of survival was significantly higher for the RIC allo-HSCT group (58% ± 2% versus 50% ± 3%, P<0.001)[16]. In addition, the non-relapse mortality (NRM) with MAC can be unacceptably high in the range of 10-40% [17-23.] The median age of newly diagnosed CLL patient ranges from 65–70 years, which makes RIC the preferred conditioning regimen in allo-HSCT [24].

The factors associated with an inferior OS and event-free survival after allo-HSCT in CLL patients are high hematopoietic cell transplant co-morbility index (≥ 3 score), age (≥ 65 years old), and donor HLA match (HLA mismatched) [9,11,25].

Kharfan-Dabaja et al. published in 2016 clinical practice recommendations on behalf of the American Society for Blood and Marrow Transplantation (ASBMT), which now recommend allo-HCT in the absence of response or if there is evidence of disease progression after B cell receptor (BCR) inhibitors in standard risk patients, this group is defined as absence of Del17p/TP53 mutation, complex karyotype and del11q.

For high-risk CLL defined as presence of Del17p/TP53 mutation and presence of complex karyotype, allo-HCT is recommended in four circumstances: in patients who failed to 2 lines of therapy and showed an objective response to BCR inhibitors or to a clinical trial; in patients who fail to show an objective response or progress after BCR inhibitors, but show an objective response to BCL-2 inhibitors or clinical trials; patients who fail to show an objective response or progress after BCL-2 inhibitors; and in patients with Richter transformation who have an objective response to anthracycline-based chemotherapy.

ASBMT also recommends reduce-intensity conditioning regimen, filgastrim mobilized peripheral blood stem cells transplant, the use of MRD for monitoring disease after allo-HCT and to look for CLL or monoclonal B cell lymphocytosis in siblings who are identified as suitable donors [26].

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