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Review

Donor lymphocyte infusion after allogeneic stem cell transplantation

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ABSTRACT

Allogeneic stem cell transplantation (allo-SCT) is considered the cornerstone in the treatment of several malignant and not malignant hematological diseases. However, relapse of hematological disease after allo-SCT is considered the most challenging point in the field. The risk can be reduced through optimal patients, donor and disease selection before allo-SCT, but harnessing donor immune system is an appealing way to treat or avoid disease relapse. Donor lymphocyte infusion (DLI) is a simple and effective therapy after allo-SCT. In this paper, the efficacy of DLI will be analyzed in different hematological diseases, focusing also on their therapeutic or pre-emptive use.

Contents

1. Introduction

During the last decades, allogeneic stem cell transplantation (allo-SCT) is considered a cornerstone in the treatment of several malignant and not malignant hematological diseases. The number of allo-SCT is still growing [1]. In this

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complex procedure, we have to face 2 relevant points: first, toxicity both in terms of morbidity and mortality, mostly linked to infections and acute or chronic graft versus host disease (aGVHD and cGVHD), and second the relapse of underlying disease.

The toxicity of allo-SCT is slightly but progressively in reduction as demonstrated in at least 2 papers from Genova's [2] and Seattle's teams [3]. Nevertheless, the 1 year mortality rate of allo-SCT is around 10–15%, and even higher in specific setting of patients with poor performance status, comorbidities, advanced disease, and grafted from alternative donors.

The relapse of hematological disease after allo-SCT is perceived as a *Damocles' sword* by patients and physicians, with higher risk of relapse early after transplantation, because of the majority of relapses are in the first year. Although this risk can be reduced at different levels before allo-SCT acting on patients, donor and disease selection, the key point has been the comprehension of the role of donor T cells infused with bone marrow and, in higher number, with peripheral blood stem cells that can react against tumor cells. Therefore, the step forward was to use of donor T cells as an adoptive immunotherapy after transplantation. Donor lymphocyte infusion (DLI) is, so far, a simple and effective post-allo therapy.

In this review, the results of DLI treatment were analyzed, focused, when possible, on the last 5 years search. Exhaustive reviews were published before 2010 [4–6].

2. Brief history and mechanism of efficacy

The first report on DLI was published in 1990 by HJ Kolb. In this report, 3 patients with chronic myeloid leukemia (CML), relapsed after allo-SCT, were treated with DLI and interferon alpha, obtaining a complete cytogenetic response. The data on the efficacy of DLI in CML patients were confirmed by the same and other Authors [7–9]. More recently, the efficacy and toxicity of DLI were retrospectively compared to the use of tyrosine kinase inhibitor in this setting. The response was not significantly different, but the relapse rate and the leukemia free survival were significantly better after DLI [10].

After these promising results, DLI was extensively used in other hematological malignancies such as acute leukemia, lymphomas, and myeloma. At present, considering that the majority of CML patients did not receive allo-SCT, DLI is mainly used in other hematological diseases.

The mechanism of action of donor lymphocytes has been studies by Bachireddy and Wu. They analyzed the mechanism of DLI and if there are biological factors predictive of response in CML. Patients relapsed after allo-SCT were treated with CD4+ DLI. In this analysis, responding patients had lower tumor burden in bone marrow and, only in responders, the number of CD3+ and CD8+ T cells in the marrow but not in the peripheral blood was higher. Moreover, the immunological status before DLI was significantly different in the responders that showed a higher T and B infiltration in the marrow, with in particular the CD8+ infiltrate higher than 4%. The Authors also observed that CD3+ T cells in responders expressed a set of genes inducing cell exhaustion, due to chronic antigenic stimulation, which was reverted after DLI. Finally, in responders there was an up-regulation of PD-1 suggesting an increased T-cell activation after DLI [11,12].

Although these results outlines in the mechanism of efficacy of DLI, probably they are not exportable to other hematological diseases. However, in more "solid" diseases such as lymphomas, the role of tumor infiltrating T-cells could play an important role and guide the use of DLI.

3. Modalities of administration

DLI has been used in 3 clinical settings: therapeutic (for proven relapsed/progression), pre-emptive/prophylactic in patients considered to be at high risk of relapse, and in case of mixed chimerism.

4. Therapeutic DLI (tDLI) in acute myeloid leukemia (AML)/myelodysplastic syndromes (MDS)

In this subset of patients, hematological disease is clinically present, and tDLI can be administered to induce a complete remission. Most of papers in literature reported data on response, survival, and toxicity. Overall, the prognosis of AML and MDS is poor when relapsed after allo-SCT. Excluding CML because allo-SCT is now applied only in a minority of patients, the response rate and survival in relapsed AML and MDS after DLI is around 35% and from 15% up to 56%, respectively (Table 1).

Takami et al. reviewed the data from Japanese Society for Hematopoietic Cell Transplantation on 143 AML patients relapsed after allo-SCT and treated with DLI. The 1-, 2-, and 5-year OS were 32%, 17%, and 7% respectively. In multivariate analysis, 2 factors influenced the survival: CT at time of DLI and time from allo-SCT and relapse longer than 5 months. Using these factors, the Authors separated the cohort in 3 groups: the most favorable group consisting of patients in CR, independently from time to relapse (2-year OS 100%), followed by patients not in CR with a long time between allo-SCT and relapse (2-year OS 12%), and the worst group compounding patients not in CR and early relapse (2-year OS 4%) [24].

A recent Center for International Blood and Marrow Transplant Research (CIBMTR) study analyzed the outcome of 1788 patent relapsed after allo-SCT. Overall, almost 70% of these patients were treated: 37% with chemotherapy (CT) alone, 11% DLI ± CT, and 21% second allo-SCT ± CT ± DLI. Thirty-two percent of patients treated with DLI survived more than 1 year, but one third of them received a second allo-SCT. The 1-year overall survival (OS) was 23%. In multivariate analysis, the treatment offered to the patients did not modify the survival, which was significantly influenced by longer time from allo-SCT to relapse (cut off 1 year), reduced intensity (RIC)/nonmyeloablative conditioning (NMAC), age (cut off 41 years), unfavorable cytogenetic, active acute GVHD, and alternative donor (mismatched unrelated and cord blood). In particular, the 1-year OS for patients relapsing after more than 1 year from all-SCT and receiving DLI was 44% [19].

Guièze et al. described the outcome of 147 MDS patients relapsed after allo-SCT. The 2-year OS for all patients was 16%, but it was significantly different if they received an immunotherapy (second allo-SCT or DLI) or CT alone or