Allogeneic Hematopoietic Cell Transplantation

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Allogeneic hematopoietic cell transplantation (alloHCT) represents a treatment option for multiple myeloma (MM) patients. As shown in several studies, alloHCT is highly effective, but it is hampered by a high toxicity, mainly related to the graft-versus-host disease (GVHD), a complex immunological reaction ascribable to the donor's immune system. The morbidity and mortality associated with GVHD can weaken the benefits of this procedure. On the other side, the high therapeutic potential of alloHCT is also related to the donor's immune system, through immunological activity known as the graft-versus-myeloma effect.

Keywords: Allogeneic ; myeloma ; immunotherapy

1. Introduction

Multiple myeloma (MM) accounts for 1% of all malignant diseases and 10% of all hematological malignancies [1]. Novel agents have been incorporated in the treatment of MM over the last two decades [2][3]. This has led to an improvement in the duration of disease response and overall survival (OS) for this group of patients [2][3][4].

According to the American Society for Transplantation and Cell therapy (ASTCT) and European Society for Blood and Marrow Transplantation (EBMT) guidelines, the use of high-dose chemotherapy followed by autologous hematopoietic cell transplantation (autoHCT) is the standard of care for transplant-candidate patients with newly diagnosed MM [5][6]. The implementation of novel agents has led to improvements in outcomes after first-line autoHCT [2][3][4][7]. For these reason, Allogeneic hematopoietic cell transplantation (alloHCT) is currently performed in selected patients in relapse or progression after first-line therapy. AlloHCT as consolidation after first-line induction therapy is still indicated as a clinical option in selected patients [5][6].

According to the last reports provided by the Center for International Blood and Marrow Transplant Research (CIBMTR) and EBMT, MM remains the most common indication for autoHCT in the United States and Europe. However, the proportion of MM patients treated with alloHCT is decreasing. A total of 360 patients with plasma cell disorders underwent alloHCT in 2017. In comparison to 2016, this proportion decreased by 17% [8][9][10]. AlloHCT is a treatment with curative potential in MM due the immune-mediated graft-versus-myeloma (GVM) effect [9][10][11][12][13]. Nevertheless, alloHCT is also associated with considerable therapy-related mortality (TRM), impact on quality of life, and disease relapse. The use of reduced intensity conditioning (RIC) regimens, the refinement of graft-versus-host disease (GVHD) prophylaxis, donor selection, and supportive care has improved alloHCT results [14][15][16]. However, with the development of novel therapeutic strategies, the role of alloHCT in MM requires a critical review [17][18][19]. In this review, we summarize the evidence behind alloHCT in MM and we suggest a possible role of newer therapies in this setting.

2. Current Recommendations and Patient Selection

International recommendations regarding the use of alloHCT for MM are not consistent. EBMT guidelines suggest upfront alloHCT as a clinical option for standard-risk patients and as standard of care for high-risk patients whenever a HLA-identical donor is available [5]. Additionally, alloHCT is indicated as a clinical option for relapsed/refractory disease after autoHCT. ASTCT guidelines considered alloHCT as a clinical option only for relapsed/refractory disease or plasma cell leukemia (first-line or relapsed/refractory setting). Finally, in a consensus conference from the EBMT, ASTCT and International Myeloma Working Group, more specific indications were given for alloHCT in the relapsed/refractory setting: patient with early relapse (less than 24 months) after primary therapy that included an autoHCT and/or high-risk features (cytogenetics, extramedullary disease, plasma cell leukemia, or high lactate dehydrogenase) [20].

However, these recommendations do not come from randomized trials and are largely based on experts' opinions. Moreover, the use of newer drugs at relapse was not considered at that time. Currently, alloHCT as first-line consolidation is not representing a clinical option considering the good results obtained with triplet induction treatment followed by

autoHCT and lenalidomide maintenance [21]. The definition of high-risk myeloma is a dynamic concept. Different stratifications have been developed over the years depending on genetic/clinical stratification but also on drug resistance. The revised risk stratification for myeloma identifies a class of patients (stage III) with serum 2-microglobulin level >5.5 mg/L and high-risk cytogenetic (del(17p) and/or t(4;14) and/or t(14;16)) or high LDH level with a poor 5-year PFS and OS of 24% and 40%, respectively [1]. Considering the poor survival, the toxicity of an alloHCT could be accepted in this setting. Ideally, alloHCT should always be performed in the context of clinical trials for MM patients considering the existing low level of clinical evidence. Whenever an alloHCT is performed, reduced-intensity conditions should be preferred considering the good and consistent results available in the literature, the low toxicity and the fact that the majority of these patients have already received myeloablative autologous transplants. Haploidentical donors represent an acceptable option whenever HLA-identical donors are not available [22][23]. Since the chemosensitive disease and disease burden of alloHCT are two important prognostic factors, disease reduction (at least a partial remission) should be pursued before alloHCT. No consolidation/maintenance therapies are currently recommended. In case of disease relapse, no standard recommendations could be made. The choice of therapy should be tailored depending on patient status, previous treatments and time from alloHCT.

3. Conclusions and Future Perspectives

AlloHCT represents a potentially curative option for MM in the new drugs era. AlloHCT can be considered as an immunological platform for subsequent salvage therapies, such as lenalidomide therapy. Its high toxicity is the reason why this procedure is not offered to all patients. Its use should be currently considered in the relapsed setting for those patients who are fit with clinically and biologically high-risk disease features. AlloHCT can be potentially associated with newer drugs and should not be considered as the last therapeutic available option. Chimeric antigen receptor T cells, bispecific antibodies, immunoconjugates or immune modulating monoclonal antibodies could be synergic with a new immune system and their use should be tested in the future. Additionally, it is possible that these newer strategies alone or in combinations will substitute the need of performing alloHCT for this disease. In fact, redirecting the patient's own immune system against myeloma instead of balancing the effects of a graft-versus-tumor and graft-versus-host diseases seems to be a safer and more predictable therapeutic intervention.

While the use of alloHCT for MM is decreasing, it has a curative potential. Following international consensus, it should be reserved for high-risk patients who failed the first line of therapy (including autoHCT). The use of alternative donors (haploidentical followed by PTCy) is expanding alloHCT indications. The use of newer drugs should be exploited to reduce the disease before alloHCT. However, little is known regarding the potential effects of these drugs on allografting. Reducing the toxicity of transplants through the improvement of conditioning regimens should be pursued in the coming years. Future trials should be possibly focused on post-transplant minimal residual disease evaluations to allow early disease treatment. Additionally, a better biologic characterization of post-transplant disease relapse should guide which therapeutic strategy could be the most effective.

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