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Current Trends in Allogeneic Hematopoietic Stem Cell Transplantation

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Editorial

Hematopoietic stem cell transplantation (HSCT) has proven to be a curative treatment strategy for patients with many malignant and non-malignant hematological disorders, including leukemia, lymphomas and aplastic anemia, and indications are still expanding.

Since the first human bone marrow transplant in the 1950s, over 1 million procedures have been completed worldwide, and the number of transplants performed each year is now close to 70.000.

Allogeneic HSCT is a procedure that restores stem cells that have been destroyed by a preparative regimen including chemotherapy with or without total body irradiation delivered before stem cell infusion to optimize tumor cell kill and immunosuppress the recipient to prevent graft rejection. In addition, allogeneic HSCT recipients receive immunosuppressive agents, namely calcineurin inhibitors, for a prolonged period of time after transplant to mitigate the graft-versus-host reaction.

Allogeneic HSCT has undergone profound changes in recent years, and significant advances have improved the outcome of transplantation.

First, several studies have documented a substantial reduction of non-relapse mortality over the past decade [1]. A consistent number of changes in the transplantation practice have contributed to improve the outcome of HSCT recipients.

The use of reduced-intensity preparative regimens has made possible the extension of HSCT to older patients and patients with relevant comorbidities once considered ineligible to the transplant [2]. The development of HLA molecular typing technologies has facilitated the identification of well-matched unrelated donors thereby contributing to improve the outcome of patients receiving grafts from unrelated volunteer donors [3].

Our approach to the treatment of infectious complications may benefit of new agents. CMV infection is now based on pre-emptive antiviral therapy including foscarnet, ganciclovir and valganciclovir, but new drugs, for instance letermovir, brincidofovir and maribavir should be introduced in the daily clinical practice very shortly.

The advent of mold-active antifungal agents has reduced significantly the mortality due to fungal infections [4,5]. Epidemiological trends of invasive fungal infections in HSCT document a consistent rise of mold over yeast infections, and justify the use of mold-active agents for prophylaxis and pre-emptive therapy of patients who develop fungal infections [4].

Graft-versus-host disease (GVHD) due to alloreactive T cells infused with the stem cell inoculum, is a major hindrance to the success of HSCT, contributing substantially to morbidity and transplant-associated mortality. Nevertheless, a recent study has documented that the proportion of patients with grades III-IV acute GVHD appears to have decreased over time with a concomitant reduction in the involvement of the three organs, skin, gut and liver [6]. Even more importantly, two different studies showed an improved overall survival and treatment-related mortality [6,7]. Certainly, these achievements reflect improvements in supportive care and treatment of infectious complications in HSCT recipients, although it has been postulated that these results reflect the increased utilization of tacrolimus-based GVHD prophylaxis [6].

The second major change in HSCT practice, is the shift towards the preferential utilization of alternative donors, in particular haploidentical family donors. Infact, haploidentical HSCT has the potential to offer the possibility of a transplant to those patients who might benefit from this therapeutic procedure but do not have a suitable family or unrelated donor.

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Based on the 2015 European Bone Marrow Transplant survey report, 12% of allogeneic HSCT were performed in Europe utilizing haploidentical donors and similar results have been reported in USA (12.5%), while the Chinese Registry reported that 52% of the allogeneic HSCT were haploindentical transplants [8]; in Italy, 32% of allogeneic HSCT reported in 2016 were haploidentical HSCT. The remarkable increase of HSCT from haploidentical donors is mainly due to the introduction of different strategies able to mitigate GVHD reaction while preserving immune responses to infections and patient's underlying malignancy.

Since T cells are responsible of causing GVHD, early attempts were made by removing T cells from the graft, however ex-vivo T-cell depletion was associated to an extremely high risk of graft rejection an severe infections due to the significant delay of immune reconstitution [9,10]. The selective depletion of αβ+ T cells represents one of the most recent and promising approach of graft manipulation: while αβ+ T cells are responsible of the initiation of GVHD, γδ+ T cells are known to facilitate immune reconstitution preserving antiviral function and activity against leukemic cells [11,12]. The preliminary results are extremely promising, particularly in children with low non-relapse mortality and favorable overall survival [13].

Two main T-cell-replete platforms have been developed. The GIAC protocol, developed by the Peking group, is based on four components: G-CSF stimulation of the donor, Intensified immunosuppression including cyclosporin, mycophenolate and methotrexate, Antithymocyte globulin, Combination of peripheral blood stem cells and bone marrow [14]. The second protocol, developed by the Baltimora group, is based on the administration of post-HSCT cyclophosphamide (PT/Cy) [15]. Hematopoietic stem cells are resistant to high dose Cy due to the presence of high levels of aldehyde dehydrogenase, the enzyme primarily responsible for detoxification of Cy, while Cy given after the transplant targets donor alloreactive T cells reducing the risk of graft rejection and GVHD [16]. Similarly, TREG cells, considered necessary to prevent GVHD, are resistant to PT/Cy-induced cytotoxicity due to high levels of aldehyde dehydrogenase [16,17]. Based on these biological assumptions, several clinical trials have analyzed the outcomes of patients receiving haploidentical transplants after PT/Cy, showing excellent results in many malignant disorders which compare favorably with the results obtained with HSCT from matched sibling and unrelated donors [18,19].

To conclude, the "scenario" of HSCT is rapidly moving: transplant-related toxicities are progressively better controlled and a greater proportion of patients who might benefit from this procedure, may receive a transplant, due to the wide application of haploidentical transplants.

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