Unmanipulated haploidentical blood and marrow transplantation: where we are

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Human leukocyte antigen (HLA)–mismatched/haploidentical blood and marrow transplants (haplo-BMT) from family donors have been intensively studied because of the decreasing family size in mainland China, and also because the Chinese Marrow Donor Program is still not big enough. The protocol for unmanipulated haplo-BMT has been designated as ‘GIAC’ by Dr DP Lu—‘G’ represents granulocyte colony-stimulating factor mobilisation; ‘I’ stands for immunosuppression during pre-conditioning being prolonged and intensified; ‘A’ stands for the use of antithymocyte globulin; ‘C’ means combined use of bone marrow and peripheral blood as the graft. Haplo-BMT with GIAC regimen has been shown to be feasible for many applications as reported in 2004. Under this protocol, haplo-BMT has achieved comparable outcomes in terms of severe acute graft-versus-host disease (GVHD), chronic GVHD, relapse, treatment-related mortality (TRM), disease-free survival (DFS), and overall survival with HLA-identical sibling transplantation. The probabilities of DFS at 2 years in haplo-BMT setting were 70.7%, 49.6%, 22.2% in standard-risk, high-risk, advanced disease groups, respectively. As the third party cells, cord blood co-infusion could significantly reduce the incidence and severity of acute GVHD, and also 100-day TRM. The majority of refractory cytomegalovirus, Epstein-Barr virus and aspergillus infections can be controlled by adoptive cellular therapy. Many patients who early relapsed after BMT and failed, or are ineligible for standard therapy, have been salvaged with dendritic cell-primed cytokine-induced killer cells. With these new strategies, the lower TRM and improved DFS have been attained. Therefore, it is better to consider haplo-BMT for the patients with otherwise incurable haematological malignancies at earlier stage, when matched sibling or unrelated donors are not available.

Introduction

Allogeneic blood and marrow transplantation (allo-BMT) is the only or most important curative therapy for a majority of haematological malignancies. A lack of human leukocyte antigen (HLA)–matched sibling or unrelated donor, however, has restricted its application. This is particularly relevant in mainland China with shrinking family sizes. Related HLA-mismatched/haploidentical BMT (haplo-BMT) is a feasible alternative since almost every patient has at least one haplotype-sharing parent, child, or sibling available. The main obstacles of haplo-BMT are graft failure, graft-versus-host disease (GVHD) and infections.

Development of haploidentical blood and marrow transplantation

The first series of unmanipulated haplo-BMT was successfully performed by Ji in 1999 in mainland China, with granulocyte colony-stimulating factor (G-CSF)–primed bone marrow (BM) and antithymocyte globulin (ATG). Acute GVHD (aGVHD) was the main cause of death. Then, a modified protocol with anti-CD25 monoclonal antibody and sequential immunosuppressants was employed for a much larger cohort of patients. It was characterised by high engraftment rates, a low incidence of GVHD, and good event-free survival in the patients with leukaemia. A clinical study by this group has demonstrated that total body irradiation is not necessary in unmanipulated haplo-BMT, and this has resulted in lower transplant-related mortality (TRM). The same group was the first to report that killer cell immunoglobulin-like receptors mismatching in donor-recipient pair could increase engraftment, and decrease both the rates of severe aGVHD and relapse in Chinese. This was followed by a series of study regarding effects of G-CSF on donor T lymphocytes and GVHD, immune reconstitution after haplo-BMT as well.

In early 1990s, DP Lu explored to induce immune tolerance and modulate allogeneic reaction in related mismatched BMT by ‘third-party cell’ co-infusion, in-vitro T-cell depletion, and mixed autologous and haplo-BMT. In 1991, his team pioneered haplo-
The role of haploidentical blood and marrow transplantation in the treatment of haematological malignancies

From a large cohort of patients with haematological malignancies after haplo-BMT, more than 99% of recipients had haematological reconstitution. The overall 2-year DFS rates were 70.7%, 49.6%, 22.2% in standard-risk, high-risk, advanced diseases, respectively (Fig 1). For acute myeloid leukaemia, 2-year DFS rates were 78.5%, 57.3%, 21.9%, in standard-risk, high-risk, advanced disease, respectively. For acute lymphoblastic leukaemia, 2-year DFS rates were 74.2%, 35.0%, 14.4%, in standard-risk, high-risk, advanced disease, respectively. Therefore, it is better to perform haplo-BMT from family donor for the patients with otherwise incurable leukaemia at earlier disease stage, when matched sibling or unrelated donors are not available.

For patients with chronic myeloid leukaemia (CML) in accelerated phase (AP) or blastic crisis (BC) without matched either sibling or unrelated donors, the results of haplo-BMT were respectable. Two-year cumulative DFS rates were 71.4%, 37.9% and 33.3% in second chronic phase (CP2), AP, BC, respectively. Therefore, when CML has progressed to advanced stages, haplo-BMT is an alternative option for the patients without matched donors. It is preferable to perform haplo-BMT after regaining haematological remission (CP2).

The success of haplo-BMT was also extended to patients with myelodysplastic syndromes. The overall post-BMT 3-year DFS, OS and relapse rate for this group of patients were 80%, 82%, 12% in our institute. In the haplo-BMT group, the 3-year OS rate (90.1%) was comparable to patient groups receiving BMT from HLA-identical siblings (81.2%) or from matched unrelated donors (89.6%). Hence myelodysplastic syndrome is another good candidate disease for allo-BMT and haplo-BMT, since this is the only curative modality.

BMT by using ‘third-party cells’, such as foetal liver and thymus cells with certain success. In a murine model, Zhang and Lu has demonstrated that the animals transplanted with three mixed BM (A+B+C→A) were able to survive longer, due to milder GVHD, compared with the mice transplanted with one allogeneic BM only (B→A). Lu first reported success in mixing BMT of ex-vivo T-depleted autologous BM with maternal haploidentical BM in human. The patient has achieved leukaemia-free survival with grade I aGVHD since 1991.
Improvement of haploidentical blood and marrow transplantation outcome with new strategies

Cellular therapy methods have been explored to further improve the outcomes of haplo-BMT. The use of cord blood (CB) as co-infused third party cells during haplo-BMT setting to induce immune tolerance has been examined. The cumulative incidences of grade II-IV aGVHD after CB co-infusion was reduced from 38.4% to 16.4% (P=0.008). This was particularly relevant for the reduction in the incidence of severe (grades III-IV) aGVHD in the CB group versus control group (9.2% vs 22.4%; P=0.043). Such improvements led to a reduction in the 100-day TRM of 1.8% in the CB group versus 10.4% in the control group (P=0.053).

Cytomegalovirus (CMV) and Epstein-Barr virus (EBV) reactivation after BMT can result in life-threatening complications such as interstitial pneumonia and post-transplant lymphoproliferative disease. About two thirds of haplo-BMT recipients had CMV reactivation as measured by quantitative polymerase chain reaction. An eradication of circulating CMV DNA could be achieved in 94% of cases by pre-emptive therapy with either ganciclovir or foscarnet. However, the incidence of CMV disease remained significant (10.8%), and 6.5% of patients died of CMV disease. For refractory CMV and EBV disease, 56% of patients with refractory CMV–cytotoxic T-lymphocyte (CMV-CTL) therapy, 62% of patients with EBV viramia/disease achieved complete response (CR), and 36% of them had partial response (PR). Patients with CMV viramia had better response than those with EBV disease. With EBV-CTL therapy, 62% of patients with EBV viramia/disease attained CR, while the remaining patients had PR.

Invasive aspergillosis is associated with high mortality in severely immunocompromised patients. Some patients with refractory invasive aspergillosis can be treated with aspergillus-specific cytotoxic T-lymphocytes alone. With this modality, 10% of patients can achieve resolution of their infection, while 60% of them improved significantly.

Dendritic cell-primed cytokine-induced killer cells (DC-CIK) is a novel and emerging therapeutic option to manage the patients who had early relapse after allo-BMT and responded poorly to immunosuppressant withdrawal, chemotherapy, and donor lymphocyte infusion. With DC-CIK treatment, two thirds of patients achieved durable CR again.

Conclusion

Unmanipulated haplo-BMT with current protocol is a feasible approach which promised high engraftment rates, reasonable TRM risks, and stable DFS comparable to transplant from identical sibling. Therefore, it has become an important alternative option for patients who need urgent BMT in the absence of matched donors. With the new strategies mentioned above, further improved outcome of allo-BMT has been attained. Much lower incidence of aGVHD and TRM have been achieved by using CB as the third party cells; and the majority of refractory CMV, EBV and fungal infections can be better controlled by adoptive cellular therapy. Furthermore, many patients who early relapsed after allo-BMT, and either failed or are ineligible to standard therapy can be salvaged by immunotherapy with DC-CIK.

References


