Bone Marrow Transplantation (2008) 42, S73–S75

www.nature.com/bmt

REVIEW

Blood and marrow transplantation in the People's Republic of China

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Syngeneic BMT was first performed successfully in China in 1964. In 1981, allogeneic BMT was applied in an acute leukemia patient with success. Since then, the number of BMTs has been increasing gradually, especially since the 1990s. More than 2000 stem cell transplants per year have been performed in recent years in more than 50 BMT units in mainland China. A survey of 16 BMT units from 1986 to 2005 indicates that the predominant types of transplantation performed are identical sibling (36%), related mismatched/haploidentical (11.2%), unrelated (7.5%) and autologous (44.5%) and that the distribution of disease entities and prevalent diseases being transplanted are AML (31%), ALL (16.1%), CML (19.1%) and lymphoid malignancy (22.2%). The number of transplants from unrelated donor or related mismatched/haploidentical donor has increased significantly in the past 5 years. BM and G-CSF-mobilized peripheral blood are used about equally often as a source of hematopoietic stem cells, or they are used in combination. Umbilical cord blood is used least often. Leukemias for allogeneic and lymphoid malignancies for autologous BMT continue to increase, but the increase in BMT for CML has been slow since 2004. By the end of 2007, HLA data were available on more than 700 000 individuals in the Chinese Marrow Donor Program, and 800 stem cell donations have been carried out from these. Related HLA-mismatched/haploidentical BMT has achieved comparable outcomes in terms of severe acute GVHD, chronic GVHD, relapse, treatment-related mortality, disease-free survival (DFS) and overall survival (OS) with HLA-identical sibling transplantation in the author's two BMT units. Cord blood co-infusion as the third-party cells could significantly reduce the incidence and severity of acute GVHD, steroid-refractory acute GVHD and extensive chronic GVHD without an increase in leukemia relapse and could improve DFS and OS.

Bone Marrow Transplantation (2008) **42,** S73–S75; doi:10.1038/bmt.2008.123

Keywords: unrelated; haploidentical; SCT

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Introduction

The first BMT was successfully performed at Peking University People's Hospital by D-P Lu in early 1964. A young woman was cured of her severe aplastic anemia by syngeneic BMT and is still living and healthy. The first allogeneic BMT was employed to treat acute leukemia with success in 1981 by D-P Lu, and since then the number of BMTs in China has increased gradually, especially after the late 1990s. As the family size is decreasing in China, more and more alternative donors such as related HLA mismatched/haploidentical donor or HLA matched unrelated donor have been used for transplants since the 1990s. The unique regimen for haploidentical BMT designed by D-P Lu has been applied successfully and adapted by the BMT units nationwide, and the clinical results are quite reproducible. Double-unit cord blood transplantation (CBT) was first performed successfully in China by D-P Lu for a high body weight adult with advanced acute leukemia.

China has a population of approximate 1300 million. There are at least 50 active BMT units all over the country, as shown in Figure 1. More than 2000 transplants were performed each year in recent years. A transplant survey from 16 BMT units has been carried out from 1986 to 2005. The predominant types of transplantation performed are identical sibling (36%), related mismatched/haploidentical (11.2%), unrelated (7.5%) and autologous (44.5%), as shown in Figure 2. The distribution of disease entities and prevalent diseases being transplanted is AML (31%), ALL (16.1%), CML (19.1%) and lymphoid malignancy (22.2%), as shown in Figure 3. The number of transplants from unrelated donor or related mismatched/haploidentical donor has increased significantly in the past 5 years. BM and G-CSF-mobilized peripheral blood are used about equally often as a source of hematopoietic stem cells, or they are used in combination. Cord blood (CB) is used least often. Leukemias for allogeneic and lymphoid malignancies for autologous BMT continue to increase, but the increase in BMT for CML has been slowed down since 2004.

The cumulative incidences of II–IV acute GVHD are 32 and 40% in identical sibling transplant and related mismatched/haploidentical transplant, respectively. The 2-year cumulative incidences of chronic GVHD are 56 and 55% in identical sibling transplant and related mismatched/haploidentical transplant, respectively. Around 7% of recipients have hepatitis viral infections including hepatitis A, B and C.

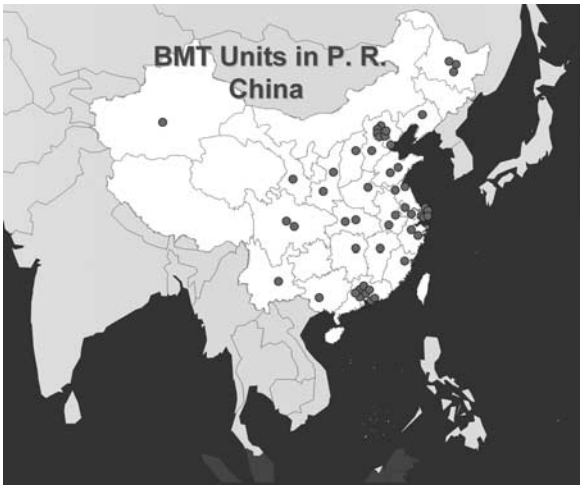

Figure 1 BMT units in the People's Republic of China.

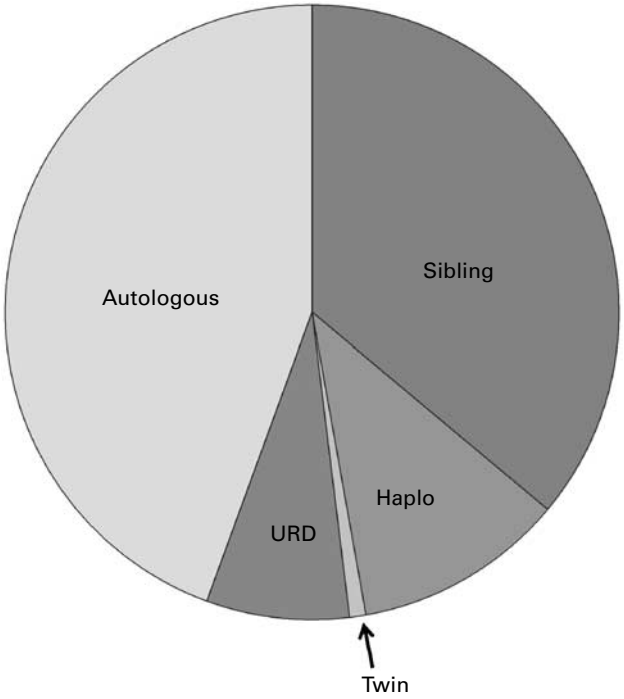

Figure 2 Types of BMT (data from 16 BMT units for the period 1986–2005).

We have participated in international and regional registries such as the Center for International Blood and Marrow Transplant Research and the Asian Pacific Blood and Marrow Transplantation Group.

Unrelated BMT

Chinese Marrow Donor Program (CMDP) was initiated in 1992 and started service for the public in 2001. By the end of 2007, more than 700 000 of HLA data were available, and 800 stem cell donations have been carried out from CMDP. It expects to have 1 million HLA data by 2010.

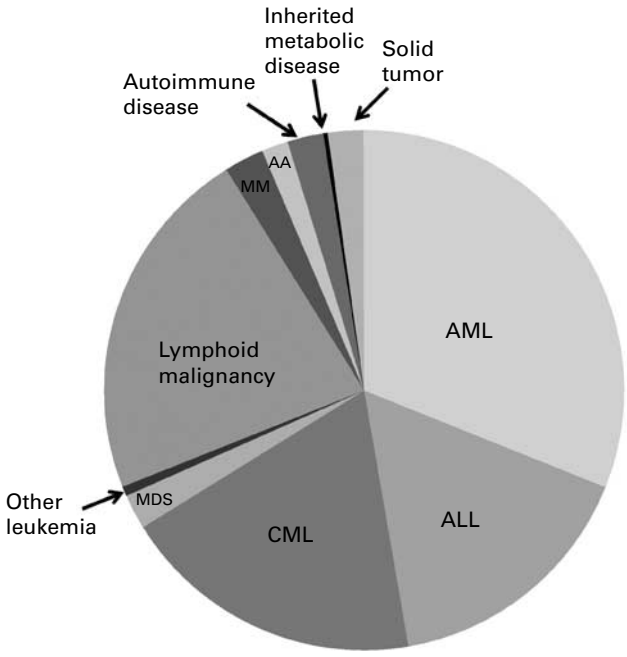

Figure 3 Distribution of disease entities being transplanted (data from 16 BMT units for the period 1986–2005).

CMDP under the Chinese Red Cross Society has 30 branch registries, 25 HLA labs, 3 high-resolution HLA labs and 1 quality control lab. There are more than 200 search requests per month with 60% of preliminary matching rate. CMDP is also actively involved in international collaborations. More than 300 preliminary searches for more than 20 countries have been carried out. The stem cells from CMDP have been successfully donated to the United States, Singapore, Switzerland, Korea and the United Kingdom. The main suppliers of unrelated hematopoietic stem cells in mainland China are CMDP (peripheral blood only) and Tzu Chi Stem Cell Center (peripheral blood or BM).

The disease-free survival (DFS) and overall survival (OS) of unrelated BMT have been improved. At least two factors are related to the improvement: first, refined and more reliable DNA typing techniques leading to better donor selection and, second, advances in transplant technique and supporting care, including conditioning regimen and GVHD prophylaxis.

Related HLA-mismatched/haploidentical BMT

HLA-mismatched/haploidentical transplants from family donors have been intensively studied because of the decreasing family size in China, and because the CMDP is still not big enough. The protocol for HLA-mismatched/haploidentical BMT has been designated as GIAC: 'G' represents G-CSF mobilization; 'I' stands for immunosuppression during pre-conditioning being prolonged and intensified; 'A' stands for the use of ATG; 'C' means the combined use of BM and peripheral blood as the graft. HLA-mismatched/haploidentical BMT has been shown to

be feasible for many applications as reported by Han *et al*.[1] Related HLA-mismatched/haploidentical BMT under the above protocol has achieved comparable outcomes in terms of severe acute GVHD, chronic GVHD, relapse, treatment-related mortality, DFS and OS with HLA-identical sibling transplantation as reported by Lu *et al*.[2] With related haploidentical BMT, the probabilities of DFS at 2 years were 77, 49 and 21% in standard-risk, high-risk and advanced disease groups, respectively.[3] Therefore, for patients with otherwise incurable hematological malignancies in need of urgent BMT, a family haploidentical donor can be beneficial when compared with an extended search for a matched unrelated donor.

To reduce severe GVHD in related HLA-mismatched/haploidentical BMT, several strategies such as T-cell depletion and third-party cell co-infusion have been employed by the authors since the late 1980s with success. In a retrospective case–control study, CB as the third-party cells was used in haploidentical BMT to induce immune tolerance. The results indicate that CB co-infusion could significantly reduce the incidence and severity of acute GVHD, steroid-refractory acute GVHD and extensive chronic GVHD without an increase in leukemia relapse. The nonrelapse mortality is much lower, and improved OS and DFS have been obtained with CB co-infusion.[4]

Cord blood banks and CBT

The Ministry of Public Health has authorized the establishment of 10 cord blood banks, and the banks in Beijing, Tianjin, Shandong, Guangdong and Zhejiang have all reached considerable size. There is no government financial support for either the public bank or the private part of the cord blood bank. By the end of 2006, there were eight cord blood banks in China, and four of them got licenses from the Ministry of Public Health. More than 250 pieces have been used for transplants.[5]

CB has been applied in China for transplantation with a single unit or double units and co-infusion as the third-party cells in mismatched/haploidentical BMT. Liu and Lu compared the outcomes of CBT with unrelated BMT in Peking University People's Hospital. The results showed that CBT yielded lower platelet engraftment and less severe acute GVHD. The 2-year DFS rates were 52.9 and 53.5%, respectively, for unrelated BMT and CBT.[6]

In 2000, the first case of double CBT was successfully performed in Beijing and reported in Tokyo at the International Symposium on Hematopoietic Stem Cell Transplantation.[7] The patient was diagnosed with advanced ALL and his body weight was 95 kg. The engraftment was prompt and he is still living with good health 7 years after CBT. Since May 2000, 26 patients have received double CBT. No significant differences on engraftment, OS and DFS were seen in the patients who received either single-unit or double-unit CBT.[5] Double CBT is widely practiced now elsewhere in the world and in China; however, the indications need to be refined.

Conflict of interest

Neither author declared any financial interests.

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