SCIENTIFIC PAPER

Blood and marrow transplantation in mainland China

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As of 1981, allogeneic bone marrow transplantation (allo-BMT) was applied in an acute leukaemia patient with success. Since then, the number of BMT has been increasing gradually, especially since the 1990s. Approximately 2000 BMTs per year have been performed in recent years in more than 100 BMT units in mainland China. A recent survey of 12 major BMT units indicates that the predominant types of transplantation performed are identical sibling (38.6%), related mismatched/haploidentical (19.4%), unrelated (17.2%), and autologous (24.5%). The indications of major disease entities are acute myeloid leukaemia (32.8%), acute lymphoblastic leukaemia (20%), chronic myeloid leukaemia (CML) [18.9%], and lymphoid malignancy (13.5%). The number of transplants from unrelated donor or related mismatched/haploidentical donor has been increasing significantly in recent 6 years. Granulocyte colony-stimulating factor–mobilised bone marrow plus peripheral blood are routinely used as a source of stem cells for haploidentical BMT. Umbilical cord blood is used less often. Although the total number of patients who received allo-BMT continues to increase, the increase in BMT for CML has been flattened since 2004. By the end of 2008, more than 960 000 volunteer's human leukocyte antigen (HLA) data are available in Chinese Marrow Donor Program (CMDP), and more than 1100 stem cell donations have been performed from it. Stem cells for unrelated BMT in mainland China are mainly from Taiwan Tzu Chi Stem Cell Center and CMDP. Related HLA-mismatched/haploidentical BMT has reached fairly good outcomes in terms of severe acute graft-versus-host disease (GVHD), chronic GVHD, relapse, treatment-related mortality, disease-free survival, and overall survival, which are comparable with HLA-identical-sibling BMT in the author's BMT units. Syngeneic BMT started successfully in 1964 and has still very good outcomes in more than 23 BMT units from the statistics of Chinese Society of Blood and Marrow Transplantation.

General survey

Blood and marrow transplantation (BMT) in People's Republic of China (PRC) has been developing steadily in the past 10 years. There has been growth in the number of BMT procedures, and more remarkably, the number of BMT units. The total number of BMT being performed is approximately 2000 per year, including 1000 allogeneic BMT (allo-BMT) at the end of September 2008. The distribution of the number performed in those major BMT units is shown in Figure 1. The total number of BMT units in PRC has increased to about 100, notwithstanding the strict regulation of authorising BMT units by the government. The increase in the number of allo-BMT being performed in the year 2008, compared to that in 1998, however, lags behind the increase in the number of BMT units (Fig 2). This is because the medical insurance cannot sufficiently cover the rural area. Moreover, BMT-related medical skill and experience, and the related medical and laboratory support required are tremendous. Hence, patients are often gravitated to hospitals with better track record and more experienced doctors. An additional reason for the slowing of growth in BMT number is the use of imatinib mesylate in patients with chronic myeloid leukaemia (CML).[1]

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Status of allogeneic blood and marrow transplantation from human leukocyte antigen–identical sibling or unrelated donor

Human leukocyte antigen (HLA)–identical sibling BMT forms the major part of BMT performed in PRC. Although family, mostly sibling, donors are most often used, unrelated donors from the Chinese Marrow Donor Program and from Taiwan Tzu Chi Stem Cell Center have been increasingly used. These unrelated donors, especially those from

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中國大陸的造血幹細胞移植

1981年異基因骨髓移植（BMT）治療急性白血病在北京獲得成功。之後，BMT的例數在中國大陸逐漸增加，尤其是上世紀九十年代以後更有長足發展。近年，中國大陸超過100個BMT中心每年約進行2000例BMT。最近一項來自12個主要BMT中心移植情況的調查顯示，主要的移植類型有HLA同胞相合移植（38.6%），親緣部分相合／單倍體相合移植（19.4%），非血緣移植（17.2%）及自體移植（24.5%）。主要的移植適應症包括AML（32.8%）、ALL（20%）、CML（18.9%）及淋巴系統惡性腫瘤（13.5%）。最近6年，非血緣及親緣部分相合/單倍體相合移植的例數明顯增加。G-CSF動員的骨髓加外周血已作為親緣部分相合／單倍體相合移植的常規造血幹細胞來源。臍帶血移植應用最少。雖然白血病進行異基因BMT的例數持續增加，但CML接受BMT的例數自2004年起增加趨勢明顯放緩。至2008年底，中國造血幹細胞捐獻者資料庫（CMDP）已有960 000多份HLA配型資料入庫，實現捐獻1100多例。大陸非血緣BMT的幹細胞來源主要為臺灣慈濟幹細胞中心和CMDP。在作者的BMT中心，親緣部分相合／單倍體相合移植在嚴重急性GVHD、慢性GVHD、復發率、治療相關死亡率、無病生存率及總生存率方面均取得了與同胞相合移植相似的結果。同基因BMT於1964年在北京獲得成功，來自中華造血幹細胞移植協會（CSBMT）的報告顯示多於23個移植中心的同基因BMT的結果仍然非常令人鼓舞。

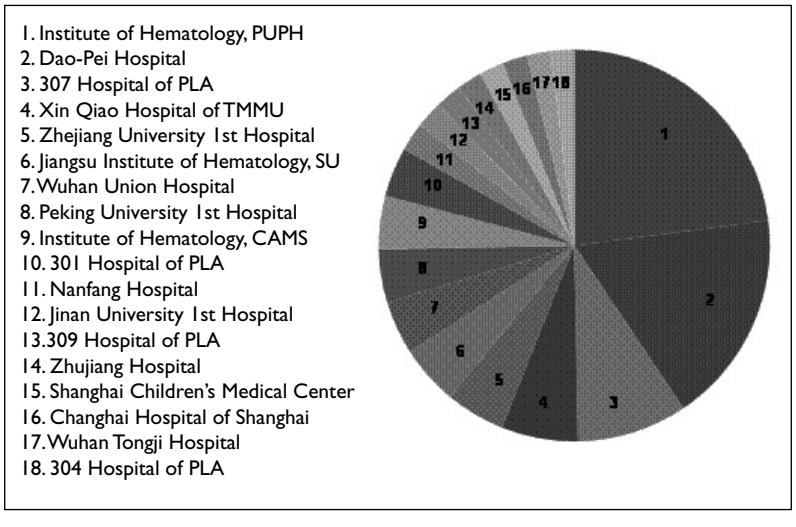

FIG 1. Distribution of the number of blood and marrow transplantation (BMT) performed in major BMT units in mainland China from January 2008 to September 2008

Taiwan, are very much appreciated by the patients, who are desperately in need of unrelated BMT. The indications for allo-BMT are mostly haematological malignancies, especially AML, ALL with poor prognosis, or CML in accelerated or blastic phase. The general overall survival is around 75 to 85%, depending upon the disease stages of the patients. There is a tendency in PRC that patients with less-advanced or less-complicated disease are treated in 'developing' BMT units, while the more difficult and challenging cases are referred to more mature and developed BMT units.

Haploidentical blood and marrow transplantation

The first large-scale haploidentical BMT (haplo-BMT) program in PRC was developed by Dr Shuquan Ji.[3,4] The stem cell used was granulocyte colony-stimulating factor (G-CSF)–mobilised bone marrow (BM), while antithymocyte globulin (ATG) and total body irradiation (TBI) constituted the conditioning regimen.

A report of haplo-BMT with larger number of patients, conditioned with a non-TBI regimen, was subsequently published by Lu et al.[5] This protocol still employed G-CSF and ATG, and was characterised by prolonged and strengthened immunosuppression, and a combined use of BM and peripheral blood (PB) as sources of stem cells. The rationale for prolonged immunosuppression before stem cell infusion was based on the experience of ameliorated graft-versus-host disease (GVHD) following haplo-BMT recipient with severe combined immunodeficiency disease cases. A combination of BM and PB stem cells was also found to be desirable for a number of reasons. Firstly, they can provide more stem cells than a single source. Secondly, mesenchymal cells and other stroma cells are harvested from the BM. Finally, compared to a single stem cell source, more immuno-modulating cells can be obtained. This protocol was coined by the present author as GIAC protocol, and is used widely in PRC.[6]

Related haplo-BMT has achieved fairly good outcomes in terms of severe acute GVHD (aGVHD), chronic GVHD (cGVHD), relapse, treatment-related mortality (TRM), disease-free survival (DFS), and overall survival which are comparable with HLA-identical sibling BMT procedures performed in parallel in the same BMT unit. This achievement was recognised with the First Prize of the Beijing Science and Technology Award in 2006.

Measures against complications in blood and marrow transplantation

Cytotoxic T lymphocytes (CTL) are used in PRC against refractory cytomegalovirus and Epstein-Barr virus reactivations/infections. The CTL are prepared in collaboration with the University of Florida (Long-Ji Chang) and Vectorite Biomedica Inc. (Taiwan). The results have been encouraging and might be helpful not only in the treatment, but also in the prophylaxis of severe clinical infections.

Leukaemia relapse is also a major complication

after BMT. The immunotherapy with dendritic cell–primed cytokine-induced killer cell (DC-CIK) has been used in relapsing patients after allo-BMT. The encouraging results indicate that donor DC-CIK is a safe and effective means in the treatment of early leukaemia recurrence after allo-BMT. This is especially useful for patients who have failed, or are ineligible for, immunosuppressant withdrawal, chemotherapy, and donor lymphocyte infusion.[7]

Cord blood and its utility

Cord blood banks for public use are developing slowly in our country without financial support from the government. However, due to the rapid development of the two stem cell donor programs in mainland China and Taiwan, as well as the growth of haplo-BMT, transplants from unrelated cord blood are less often performed. One additional obstacle is the slow platelet engraftment, translating to higher costs associated with more platelet infusion post-BMT.

The use of cord blood as third-party haematopoietic cells was suggested and widely used in our institute. Our group pioneered the predecessor form of this treatment in the usage of foetal liver and thymus cells to facilitate related mismatched BMT.[8] Double-cord blood transplant was started by the author as early as 2000.[9-11] It is gratifying to note that the first two patients who received double cord blood transplant are still alive and well.

Our preliminary clinical study has shown that using cord blood as the third party cells could significantly reduce the incidences of aGVHD (especially severe aGVHD) and also curtail 100-day TRM in haplo-BMT.[12]

Syngeneic blood and marrow transplantation

Syngeneic BMT (syn-BMT) has been applied for the treatment of many malignant or non-malignant haematological disorders. It is associated with insignificant GVHD, much less TRM, and lower relapse rates compared to autologous BMT. However, the limited number of cases performed in each single BMT centre precluded meaningful statistical analysis. To address this issue, the Chinese Society of Blood and Marrow Transplantation (CSBMT) had performed a collaborative survey among the BMT centres in CSBMT.

From January 1964 to December 2008, a total of 77 syn-BMTs were performed in 23 BMT centres. The diagnosis included severe aplastic anaemia (SAA, 22 cases), AML (23 cases), ALL (14 cases), CML (9 cases), lymphoma (3 cases), myelodysplastic syndrome (4 cases), large granular lymphocytosis (1 case), and neuroblastoma (1 case). Main pre-conditioning regimens were CY/TBI or BU/CY for malignant diseases, none or CY/ATG for SAA. The median follow-up time was 32 months (1 month to 44 years).

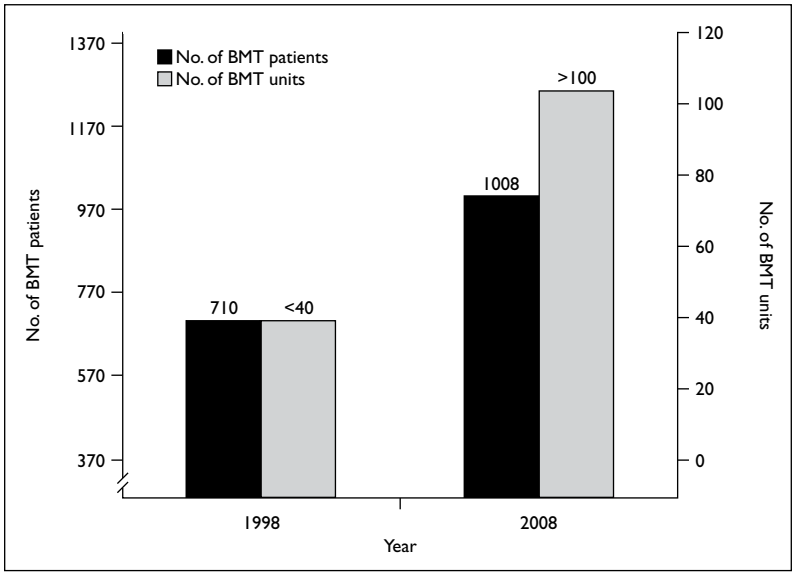

FIG 2. Increase in number of allogeneic blood and marrow transplantation (allo-BMT) in comparison with BMT units in 10 years

All patients achieved engraftment and three of them experienced late rejection. Of 77 patients, six had grade I to II aGVHD. All aGVHD was controlled with low-dose steroid. No cGVHD was noted. No transplant-related death occurred. Among patients with non-malignant disorders, 87% of cases achieved durable DFS. The longest survivor is alive and well 44 years after syn-BMT. Among patients with malignant diseases, 69% achieved disease-free survival.

Syn-BMT is a safe and effective therapeutic option for both acquired non-malignant and malignant haematologic disorders. Syngeneic donor, if available, should be the first choice.

Conclusion

Bone marrow transplantation has been developing continuously in mainland China. Concurrent developments were seen in the fields of matched-sibling BMT, matched-unrelated BMT, cord blood banking and transplantation, as well as haplo-BMT. Advanced clinical techniques such as CTL treatment for viral complications, as well as special protocol for haplo-BMT and cord blood cells as the third party cells are being developed. Along with the growth of economy and improved scientific research, PRC holds great promise as an emerging force in the field of BMT. It is natural that CSBMT will play an important role in the collaboration and advancement of BMT among Chinese worldwide.

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