SCIENTIFIC PAPER

Haematopoietic stem cell transplantation in Taiwan: past, present, and future

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In Taiwan, haematopoietic stem cell transplantation (HSCT) has been used to treat patients with haematological diseases since 1983. Thereafter till 2007, there were 2537 patients who had undergone HSCT in more than 15 hospitals. Their diseases included acute myeloid leukaemia in 27.8% of cases, non-Hodgkin's lymphoma 23.3%, acute lymphoblastic leukaemia 12.8%, chronic myeloid leukaemia 11.9%, severe aplastic anaemia 8.7%, and multiple myeloma 4.1%. Most of the cases received myeloablative conditioning regimens. More than 15% of cases received non-myeloablative regimens, and the mean age of these cases was at least 10 years older than those who received myeloablative regimens. The types of graft included peripheral blood (60.4%) and bone marrow (32.0%). A total of 35% of patients received autologous grafts. Of 1557 allogeneic HSCT patients, 338 (21.7%) received grafts from unrelated donors. Cord blood transplantation has been successfully performed in paediatric patients with thalassaemia major and with a large body size, and adult patients. The incidence of acute graft-versus-host disease was relatively low in Taiwan. On the contrary, a relatively higher proportion of hepatitis B carrier in the recipients had led to a higher incidence of reactivation hepatitis, which was markedly decreased following lamivudine prophylaxis. In conclusion, HSCT has become a routine therapy for major medical centres in Taiwan. Our unique experiences in the past decades also contributed to the progress of HSCT. With the establishment of professional association and patient supportive groups, we hope we can fully improve our daily practice and clinical as well as basic research in HSCT.

Introduction

Haematopoietic stem cell transplantation (HSCT) was performed in Taiwan since 1983. At that time, only two major medical centres—Taipei Veterans General Hospital (Taipei VGH) and National Taiwan University Hospital (NTUH)—had facilities and abilities to do this kind of therapy.[1] Nowadays in Taiwan, HSCT has become a routine therapy practised in more than 16 hospitals, with about 300 cases receiving transplant annually. The evolution of HSCT in Taiwan also followed the footsteps of world's trend. Peripheral blood stem cell transplantation (PBSCT) was performed since 1994, and non-myeloablative transplantation started since 1999.[2] In-vivo T-cell depletion using antithymocyte globulin (ATG) for high-risk HSCT was done since 2000, and cord blood (CB) transplantation for paediatric and adult patients was done since 1995 and 2005, respectively.

Demographics of Taiwan patients receiving haematopoietic stem cell transplantation

From the survey of Taiwan Bone Marrow Transplant Registry in 2007, there were 2537 patients who had undergone HSCT in more than 16 hospitals since 1983. The disease entities of HSCT patients included acute myeloid leukaemia (AML) in 27.8% of cases, non-Hodgkin's lymphoma (NHL) 23.3%, acute lymphoid leukaemia 12.8%, chronic myeloid leukaemia (CML) 11.9%, severe aplastic anaemia (SAA) 8.7%, multiple myeloma (MM) 4.1%. Hodgkin's disease, myelodysplastic syndrome and inherited genetic/metabolic diseases contributed the rest. The number of CML patients receiving HSCT is rapidly decreasing at present, most likely due to application of target therapy; whereas the number of MM patients is increasing.

Types of graft and sources of donors

A total of 35% of HSCT recipients received autologous grafts, mainly for those with MM and NHL, while the remaining 65% of HSCT were allogeneic transplantation. Peripheral blood stem cell (PBSC) graft was first used in 1994[3] and become the major graft type both in autologous and allogeneic transplant. The number of patients using bone marrow (BM) graft is decreasing and is mainly reserved for paediatric patients and those with non-

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台灣造血幹細胞移植：過去、現在與未來

台灣從1983年開始應用造血幹細胞移植來治療血液疾病，到2007年止，已在超過16間醫院中累計進行2537病例，涵蓋的疾病依多寡分別為：急性骨髓性白血病（27.8%）、淋巴瘤（23.3%）、急性淋巴白血病（12.8%）、慢性骨髓性白血病（11.9%）、重度再生不良性貧血（8.7%）及多發性骨髓瘤（4.1%）。所用的移植前處方大多數為傳統骨髓破壞方式，而接受非骨髓去除性方法的病患佔15%，平均年齡比接受傳統處方者多10歲。幹細胞來源包括60%週邊血液及32%骨髓。移植物來源為33%是自體，而異體移植中，非親屬捐贈者佔21.7%，且有增加的趨勢。臍帶血移植主要用於海洋性貧血及部份大體重的小兒病患，目前已開始應用於成人病患。在台灣，移植後發生急性移植物對抗宿主疾病的發生率較西方報告低，但高比率的B肝帶原移植者，移植後易發生猛暴性肝炎，目前使用lamivudine已可有效控制。結論，造血幹細胞移植已普遍在台灣各醫院進行，先前一部份的研究經驗已對造血幹細胞移植的進展有所貢獻，現階段期望藉由各院間及國際的合作，進一步提昇研究及照護品質。

malignant haematological diseases. The grafts of all patients were derived from PBSC in 60.4% of cases, BM in 32.0% and others in 7.6%.

Grafts from unrelated donors

Unrelated BM transplantation was first performed in Taipei VGH with the graft from Hong Kong Bone Marrow Donor Registry in 1993. Later in 1994, the Buddhist Tzu Chi Stem Cell Center (BTCSCC, formerly Tzu Chi Bone Marrow Donor Registry) was established, and had collected over 320 000 volunteer donors by the end of 2008. Thereafter, almost all of unrelated donors were provided via BTCSCC.[4,5] The estimated matching rate is about 50 to 60% in our population. Up to now, more than 520 matched unrelated HSCT have been successfully performed in Taiwan, accounting for 21.7% of HSCT cases. In recent 2 years, it is worthily noted that more than half of cases receiving allogeneic HSCT used unrelated donors in Taipei VGH and NTUH.

Cord blood transplantation

In Taiwan, CB transplantation has been performed since 1995, with major indications including paediatric patients with acute leukaemia, SAA and mucopolysaccharidosis. Recently, it was successfully applied in paediatric recipients with thalassaemia major.[6] On the other hand, CB transplant in adult patients or those children with large body size was not successfully performed until 2004 after using dual-unit CB. Cord blood grafts come from non-profit organisation, such as BTCSCC and Sun Yat-Sen Cancer Center Cord Blood Bank, as well as commercially run CB bank, such as StemCyte Cord Blood Bank. The number of CB transplantation is increasing in recent 2 years, up to a total of 120 cases till February 2009.

Specific issues in post-transplant complications

Lower prevalence of acute graft-versus-host disease

In comparison with western countries, most analyses regarding Taiwan HSCT recipients revealed a lower prevalence of grade II-IV acute graft-versus-host disease (GVHD) even in unrelated transplant. Possible explanation included the routine usage of isolation rooms with laminar airflow and a relatively low level of genetic diversity in histocompatible antigens.[7] This finding, however, needs further validation in a more large-scale survey.

Viral hepatitis

Taiwan is one of the endemic areas for hepatitis B virus (HBV) infection, with a 15% of surface antigen carrier rate in general population. Up to 80% of Taiwan HSCT patients had abnormal liver function tests after transplantation,[8] and most of them could be attributed to reactivation of viral hepatitis, especially HBV infection.[9-11] Several important studies have significantly contributed to the care of HSCT patients and will be reviewed in the same issue by Hsiao LT from Taipei VGH.[12]

Infections

Tuberculosis

In a retrospective study of 350 HSCT recipients, Ku et al[13] revealed that pulmonary tuberculosis (TB) developed in eight cases during a 6-year follow-up period. Four cases were fatal with a relatively shorter duration between HSCT and the onset of infection than non-fatal cases. All eight patients received allogeneic HSCT and seven of them developed TB during treatment for GVHD. The estimated relative risk of pulmonary TB after HSCT was 13.1-fold higher than the general population in Taiwan.

Cytomegalovirus infection

In Taiwan, more than 90% of adult HSCT recipients and donors were seropositive to cytomegalovirus (CMV) infection. However, the overall incidence of CMV disease infection after HSCT has been reported as about 5% at Taipei VGH and at Kaohsiung Medical University Hospital. With the increasing use of more potent immunosuppressive agents and HSC selection measure, there were several observations recently. Lin et al[14] found an increased incidence (20%) of CMV infection after CD34+-selected PBSCT for high-risk aggressive NHL patients.

Varicella zoster

In a retrospective survey of 161 HSCT recipients who received myeloablative conditioning, post-transplant varicella zoster virus (VZV) infection occurred in 29 (18%) patients. The median onset of infection was 6.5 months post-transplant, with 82% of cases occurring within the first year of transplant. Two risk factors associated with VZV infection were the presence of GVHD in allogeneic transplants and leukaemia as the underlying disease in autologous transplants.[15]

Specific issues in long-term post-transplant complications

Pulmonary dysfunction

In the study regarding pulmonary function change of Taiwan CML patients, only modest pulmonary dysfunction was found in long-term survivors who received human leukocyte antigen (HLA)–matched allogeneic HSCT. Associated factors included gender, smoking, bronchiolitis obliterans, and GVHD. Bronchiolitis obliterans was the most important factor to cause both clinical symptoms and impaired pulmonary function.[16] In another study regarding the effect of conditioning regimens, myeloablative conditioning treatment was found to have greater impact on 1-sec forced expiratory volume, forced vital capacity, and diffusing capacity of the lung for carbon monoxide than non-myeloablative one.[17]

Second malignancies including post-transplant lymphoproliferative disorder

Over the past 24 years, 11 (4.3%) out of 262 HSCT patients between the ages of 15 and 53 years at Taipei VGH developed second malignancies, including five for oral cancer, each one for ovarian cancer, breast cancer, gastric cancer, oesophageal cancer, myelodysplastic syndrome and post-transplant lymphoproliferative disorder (unpublished data). In the recent data from NTUH, Epstein-Barr virus–induced post-transplant lymphoproliferative disorder developed in 12 cases of 577 patients after allogeneic haematopoietic HSCT with an overall incidence of 2.51% at 1 year. Independent risk factors included grades II-IV acute GVHD, CMV antigenemia and the use of ATG. Of note, eight of 12 cases had pulmonary involvement with an extremely aggressive course and poor response to current therapy.[18] An additional case was also found after receiving CB transplantation.[19]

Pregnancy

Over the past 24 years, 13 (7.2%) of 181 HSCT patients between the ages of 15 and 30 years at Taipei VGH, including four cases of SAA, six cases of leukaemia, two cases of lymphoma, and one case of myelodysplasia, had uneventful pregnancy and deliveries after transplant (unpublished data). All of the delivered children are both physically and mentally healthy after 20 years' follow-up. One patient with AML even received 1575cGy dose of total body irradiation (TBI) as conditioning regimen. Our study revealed that recovery of ovarian function and normal pregnancy are still possible after receiving conditioning regimens incorporating TBI and high-dose cyclophosphamide.[20]

Taiwan Bone Marrow Transplant Registry

Taiwan Bone Marrow Transplant Registry was established in 2006, with the purpose to collect demographic information of HSCT patients from all hospitals in Taiwan and to develop and promote clinical research cooperation among medical centres and hospitals. With these, it is anticipated to promote clinical and basic research related to issues special in Taiwan and local area, and improve health care quality of Taiwan HSCT recipients.

Conclusions

Haematopoietic stem cell transplantation has become a routine therapy for major medical centres in Taiwan. Our unique experiences in the past two decades also contributed to the progress of HSCT. With the establishment of professional associations and patient supportive groups, we hope we can improve our daily practice, as well as clinical and basic research in HSCT.

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