SCIENTIFIC PAPER

Long-term outcome of allogeneic human leukocyte antigen–matched sibling-donor peripheral blood stem cell transplantation in leukaemia patients

JL Tang 唐季祿
M Yao 姚 明
MY Lu 盧孟佑
BS Ko 柯博升
DT Lin 林東燦
KH Lin 林凱信
YC Chen 陳耀昌

Between 1993 and July 2008, a total of 354 leukaemic patients received either allogeneic bone marrow transplantation (BMT) [n=180] or peripheral blood stem cell transplantation (PBSCT) [n=174] from human leukocyte antigen–matched sibling donors. Graft-versus-host disease (GVHD) prophylaxis consisted of cyclosporin A and methotrexate. When comparing with BMT group, patients in the PBSCT group received much higher nucleated cells and CD34+ cells, and had much faster recovery of the neutrophil and platelet counts. The probability of developing acute GVHD was slightly higher in PBSCT patients (P=0.02). The probability of chronic GVHD (cGVHD) in PBSCT was much higher in PBSCT (70±5.4%, extensive 48±6.5%) than in BMT (25±4.7%, extensive 10±3.4%; P<0.001). Chronic GVHD was associated with long-term impairment of life quality and decreased quality-adjusted survival. In standard-risk leukaemia, use of PBSCT was associated with higher cGVHD, transplant-related mortality and a trend for decreased overall survival. The results suggest that allogeneic PBSCT is associated with high incidence of cGVHD in Chinese patients and its long-term risk and benefit remains to be defined in early stage of leukaemia.

Introduction

Since first introduced in 1995,[1,2] there was a rapid increase in the use of peripheral blood stem cell transplantation (PBSCT) as an alternative to traditional bone marrow transplantation (BMT).[3,4] Granulocyte colony-stimulating factor (G-CSF) mobilisation can harvest much more haematopoietic progenitor and stem cells, resulting in faster recovery of neutrophils and platelets, reduced febrile neutropenic episodes, and shortened hospital stay. In most studies, the incidence of acute graft-versus-host disease (aGVHD) with PBSCT is similar to that reported for BMT. Some studies do not indicate a difference in chronic GVHD (cGVHD), but others suggest a substantially higher incidence of cGVHD with PBSCT.[4-7] Use of allogeneic PBSCT (allo-PBSCT) reduced early morbidity and mortality in comparison with results of BMT in some but not all studies. However, the majority of these studies had relatively short follow-up periods. In this brief review, we conducted a retrospective analysis comparing the differences of long-term outcome between allo-PBSCT and allogeneic BMT (allo-BMT) over a 15-year period in a single institute with emphasis on the incidence of GVHD, overall survival (OS) and leukaemia-free survival (LFS).

Key words
Graft vs host disease; Leukemia; Peripheral blood stem cell transplantation

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National Taiwan University Hospital
Department of Internal Medicine
JL Tang, M Yao, BS Ko, YC Chen
Department of Pediatrics
MY Lu, DT Lin, KH Lin

Correspondence to: Dr JL Tang
Tel: 886 2 23123456 Ext 65420
Fax: 886 2 23921976
E-mail: tangntuh@gmail.com

Allogeneic peripheral blood stem cell transplantation is associated with higher incidence of chronic graft-versus-host disease: National Taiwan University Hospital experience

Between 1993 and July 2008, a total of 354 leukaemic patients received either allo-BMT (n=180) or PBSCT (n=174) from human leukocyte antigen (HLA)–matched sibling donors in National Taiwan University Hospital (NTUH). Patients with prior history of myelodysplastic syndrome (MDS), secondary acute myeloid leukaemia (AML) transformed from MDS or myeloproliferative disorder were excluded. Those who received haematopoietic stem cell transplantation (HSCT) from identical twins or second HSCT were also excluded from analysis. The primary diagnosis included 192 AML, 90 acute lymphoblastic leukaemia, and 70 chronic myeloid leukaemia. The disease status at the time of HSCT included 173 patients with standard risks (SR), 110 with intermediate risks (IR), and 71 with high risks (HR). There were more HR patients receiving PBSCT (P<0.001, Chi squared test). The GVHD prophylaxis consisted of standard-dose cyclosporin A (CsA) and short-course methotrexate (MTX). When comparing with BMT group, patients in the PBSCT group received much higher nucleated cells and CD34+ cells, and had much faster recovery of the neutrophil and platelet counts.

As shown in the Figure, the probability of developing grade I-IV aGVHD was 32%

白血病病人接受親屬間HLA相合異體周邊血幹細胞移植的長期結果

自1993年至2008年7月間，共有354例白血病病人在台大醫院接受同胞捐贈之異體造血幹細胞移植，其中180例為骨髓移植，174例為周邊血幹細胞移植。GVHD預防措施為標準的CsA加上MTX。PBSCT組可以收集到更多有核細胞及CD34陽性細胞，移植後中性球及血小板更快恢復，急性GVHD略微增加，但是慢性GVHD發生率高達70%（48%為瀰漫型），而BMT組只有24%（瀰漫型為10%），P<0.001，慢性GVHD影響長期生活品質及其調整後的存活率。標準危險組的白血病病人接受PBSCT者，慢性GVHD及移植相關死亡率均明顯增加，導致整體存活率比接受BMT者來得差。中國人接受異體周邊血幹細胞移植的慢性GVHD發生率高，在早期白血病人的長期利弊需要再評估。

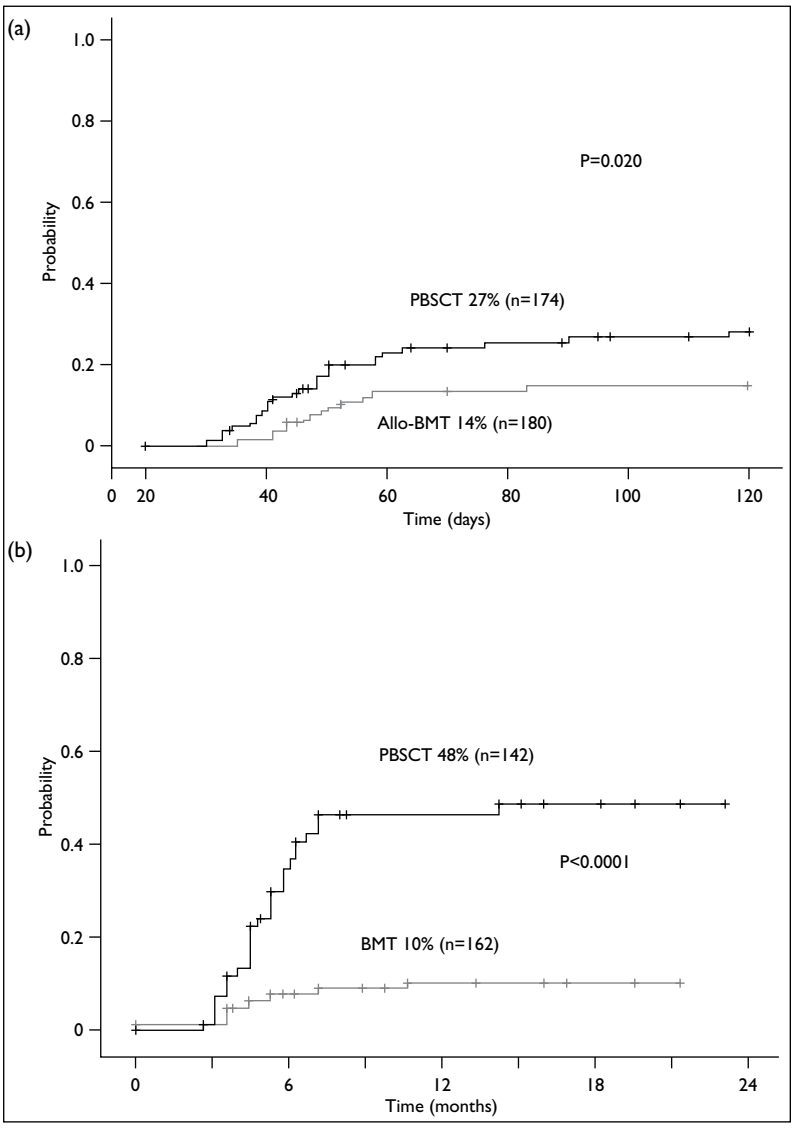

FIG. Kaplan-Meier probability of (a) grade II-IV acute graft-versus-host disease (GVHD) and (b) extensive chronic GVHD after human leukocyte antigen–matched sibling-donor haematopoietic stem cell transplantation in National Taiwan University Hospital, 1993-2008

PBSCT denotes peripheral blood stem cell transplantation, and Allo-BMT allogeneic bone marrow transplantation

in PBSCT group, which was slightly higher than 18% in BMT patients with statistical significance (P=0.016). The probability of grade II-IV aGVHD was 27% (PBSCT) and 14% (BMT) respectively (P=0.020). For 304 patients who survived more than 4 months, cGVHD incidence was much higher in PBSCT (70±5.4%, extensive 48±6.5%) than in BMT (25±4.7%, extensive 10±3.4%; P<0.001). The majority of cGVHD was of de-novo onset and became extensive, involving mouth, liver, skin, and eyes. Patients with cGVHD after PBSCT tended to require longer immunosuppressive treatment than BMT patients. There were also more cGVHD with lung involvement in PBSCT patients.

Chronic graft-versus-host disease after allogeneic peripheral blood stem cell transplantation compared to allogeneic bone marrow transplantation

In 2001, Cutler et al[5] performed a meta-analysis including 16 cohort studies to show that there was a slight increase of the relative risk (RR) for aGVHD (RR=1.16; P=0.006) while the risk was much higher for cGVHD (RR=1.53; P<0.001) after allo-PBSCT when compared with BMT. This might be explained by differences in the T-cell dose delivered. In 2005, an advanced meta-analysis using data from nine randomised trials enrolling 1111 adult patients confirmed that PBSCT was indeed associated with a significant increase in the development of grade III-IV aGVHD (odds ratio=1.39) and extensive cGVHD (odds ratio=1.89; P<0.000001) in haematologic malignancies.[7] In 2001, Zaucha et al[8] reported that higher doses of infused CD34 cells over $8x10^6$ /kg were associated with a significantly increased risk of extensive cGVHD (hazard ratio=2.3, P=0.001), but neither T cell nor monocyte doses were associated with cGVHD. Yamasaki et al[9] suggested that higher incidence of extensive cGVHD was seen in those receiving PBSCT with a lower CD56+16+ to CD34+ cell dose ratio (hazard ratio <0.00001; P=0.0035).

Long-term outcome after allogeneic peripheral blood stem cell transplantation compared to allogeneic bone marrow transplantation

At a median follow-up of 56.0 months for surviving patients in the NTUH series, the actuarial probability of OS was 71% (BMT) versus 60% (PBSCT) at 1 year, 60% versus 49% at 3 years, 58% versus 41% at 5 years, and 52% versus 34% at 10 years (P=0.003). There was significantly more late mortality due to non-relapse causes in PBSCT group. Univariate analysis showed that female sex (P=0.015) and early disease status at HSCT (P<0.001) were another two significant favourable prognostic factors for OS. Multivariate Cox analysis showed that disease status and BMT

were two independent prognostic factors for OS.

For LFS, the probability was 62% (BMT) versus 57% (PBSCT) at 5 years (P=0.344). The LFS was correlated with disease status at HSCT: 72% for SR, 54% for IR and 35% for HR patients (P<0.001). Patients with GVHD were associated with improved 5-year LFS (78% vs 61%; P=0.006). Subgroup analysis showed that the 5-year LFS was not associated with occurrence of aGVHD (P=0.316), but there was a trend for cGVHD (P=0.108). We further stratified LFS analysis according to disease status and the results showed that the beneficial effect of cGVHD was significant only in the HR patients (P=0.011), with a favourable trend in IR patients (P=0.163), and no difference in SR group (P=0.295).

Since the quality of life (QOL) after HSCT may be influenced by the occurrence of cGVHD, we performed a cross-sectional survey using the European Organization for the Research and Treatment of Cancer-QLQ-C30 questionnaire to estimate the QOL function in 120 surviving allogeneic HSCT (allo-HSCT) patients. The quality-adjusted survival was measured by integrating the individual score of global QOL into the survival function with a novel statistical function published previously.[10,11] For BMT patients, functioning status and symptoms generally improved in the first 2 years after transplantation and stabilised thereafter. By contrast, QOL function did not show significant change over time in most functioning and symptom items for PBSCT patients. Patients without cGVHD had better mean QOL scores than patients with cGVHD in all of the functioning domains and symptom item.

Immunomodulatory effect of granulocyte colony-stimulating factor given before and after allogeneic haematopoietic stem cell transplantation

A different graft composition might affect immune reconstitution, GVHD, and graft versus leukaemia (GVL) effect. Although the G-CSF–mobilised stem cell grafts contain approximately 1-log greater T cells than conventional bone marrow harvests, the incidence and severity of aGVHD is not greatly changed. This could be partly explained by the effect of G-CSF–mediated immune regulation to switch T-cell cytokine secretion profile to Th2 responses and to promote differentiation of regulatory T-cell and tolerogenic dendritic cells.[12] In animal models, G-CSF was reported beneficial in preventing or treating experimental GVHD and other immune-mediated disease such as multiple sclerosis and diabetes. However, prophylactic use of G-CSF after allo-HSCT was associated with higher incidence of aGVHD and cGVHD and with an increase in transplant-related mortality. There was laboratory evidence suggesting G-CSF induction of transforming growth factor–beta can exacerbate cGVHD.[13] Joshi et al[14] reported that post-HSCT use of G-CSF might impair functional immune recovery and delayed reconstitution of fungus-specific immunity. A recent review suggested use of G-CSF after allo-HSCT should take into consideration the impact on immune reconstitution, risk of leukaemic progression (in patients with chromosome 7 abnormalities) and the absence of proven benefit in patients receiving marrow or peripheral blood progenitors as the stem cell source.[15]

Prophylaxis of chronic graft-versus-host disease after allogeneic peripheral blood stem cell transplantation

Attempts to prevent cGVHD through prolonged use of immunosuppressive medications or addition of other agents have been unsuccessful.[16] Cyclosporin A, steroid, or thalidomide were ineffective in preventing cGVHD in a few randomised, placebo-controlled clinical trials. Depletion or inhibition of alloreactive T-cell seemed to be a better approach. In a randomised study, the addition of antithymocyte globulin (ATG) to CsA/MTX provides significant protection against extensive cGVHD and chronic lung dysfunction, reduces late transplant mortality, and improves QOL in patients undergoing unrelated donor transplantation.[17] Russell et al[18] had recently shown that use of low-dose ATG at 4.5 mg/kg could reduce the cGVHD and transplant-related mortality in matched siblings as well. The role of ATG in preventing cGVHD after allo-PBSCT and the impact on long-term outcome needs to be confirmed in a large, prospective randomised study.

Conclusions

The risk of cGVHD is significantly higher in Chinese leukaemia patients who received allo-PBSCT compared to those receiving traditional allo-BMT. This effect might be associated with the differences of graft composition such as CD34 cell dose, natural-killer cell to CD34 cell ratio, skewed T-cell cytokine expression, and the use of G-CSF before and after transplant. In HR patients, the use of allo-PBSCT might improve the LFS through GVHD-associated GVL effect. However, BMT may be preferable than PBSCT in SR leukaemia when considering the long-term morbidity and late death associated with cGVHD.

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