

Haematopoietic stem cell transplantation for thalassaemia in Chinese patients

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Beta thalassaemia major is a common hereditary haematological disease in southern Chinese. Advances in transfusion and iron chelation improve survival but haematopoietic stem cell transplantation (HSCT) is still the only curative treatment. Due to repeated blood transfusion and iron overload, thalassaemia patients undergoing HSCT are at a higher risk of graft rejection and transplant-related mortality. The prognostic factors identified to be affecting transplant outcome include hepatomegaly, hepatic fibrosis, and compliance to chelation therapy. Patients can be classified into three classes and conditioning regimens are modified according to the risk. Early stage patients have 85 to 90% chance of disease-free survival, whereas advanced stage only has 60% disease-free survival. Mixed chimerism is common after HSCT but majority have satisfactory erythropoiesis without need for further transfusion. Sibling cord blood and bone marrow transplantation has similar outcome. Recently alternative donor transplant has been performed in patients without human leukocyte antigen (HLA)-identical siblings. The result of unrelated-donor bone marrow transplantation is in general inferior but extended HLA matching may improve outcome. The use of unrelated cord blood transplant from a single-centre study showed promising result. The survivors require iron depletion to remove excessive iron store and some may require hormonal replacement therapy. Most of the patients have good quality of life after successful HSCT.

Introduction

Beta thalassaemia carrier is common in South China and the carrier rate is about 3 to 4%.¹ There is significant morbidity and mortality in the transfusion-dependent thalassaemia major (TM) mainly due to infection and iron overload.² With advances in transfusion and iron chelation therapy, beta-TM (b-TM) patients can now survive beyond 40 years of age but haematopoietic stem cell transplantation (HSCT) is still the only curative treatment. Pesaro centre in Italy performed the largest series of HSCT for TM and identified important prognostic factors for HSCT.³ In recent years, there are more reports of HSCT for Chinese TM.⁴⁻⁶ Graft rejection and treatment-related mortality are the common causes of treatment failure. With improvement in preparative regimen and supportive care, there is better disease-free outcome and HSCT is now extended to the more advanced disease patients. Sibling donor is the preferred option but is only available in less than 30%, the recent alternative donor transplant, including unrelated bone marrow and umbilical cord blood transplant, shows encouraging results.

Prognostic factors and conditioning

Immunosuppression and myeloablation is important for successful HSCT. However stable mixed chimerism in long-term disease-free survivors of TM suggested myeloablation may not be required for this condition.⁷ However sufficient immunosuppression to allow stable engraftment is essential. Total body irradiation (TBI) is effective in marrow ablation and immunosuppression but is associated with significant long-term side-effects especially in children. Most centres avoid TBI in the conditioning for TM. The combination of busulphan and cyclophosphamide is the most commonly adopted conditioning regimen for b-TM. The Pesaro group identified three independent prognostic factors: presence of hepatomegaly, presence of liver fibrosis, and the poor compliance to iron chelation.³ Patients can be categorised into three classes: class 1 does not have any of the three factors, class 3 has all three factors, and class 2 has only one or two of these factors. Patients with class 3 received a lower dose of cyclophosphamide to reduce the treatment-related mortality. Class 1 and 2 patients have 80 to 90% chance of long-term disease-free survival (DFS), while class 3 patients only have around 60% DFS. Antithymocyte globulin (ATG) is effective to deplete T-lymphocytes of the recipients which may be responsible for rejection of donor's graft. The value of including ATG in the conditioning regimen for b-TM is controversial. Pesaro group had included ATG in the high-risk patients in the earlier studies but ATG was abandoned later as it appeared to have no additional benefit. However, this has never been tested in

Key words

China; stem cell transplantation;
Thalassaemia

Hong Kong Med J 2009;15 (Suppl 3):39-41

Declaration

The authors did not receive grants or outside funding in support of their research for or preparation of this manuscript. They did not receive payments or other benefits, or a commitment or agreement to provide such benefits from a commercial entity.

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造血幹細胞移植 (HSCT) 治療重型地中海貧血

重型地中海貧血在華南、台灣及東南亞華人頗為普遍，隨著輸血及除鐵治療進步，病者可活至40歲以上，但HSCT仍是唯一能根治這遺傳性紅血球病症。地貧病人因長期輸血及鐵沉積，移植面對兩大問題：植入失敗及移植相關死亡。影響成功移植因素包括肝腫大，肝纖維化及除鐵依從性。病者按預後因素可分3級，預處理化療方案需調整以減低死亡率。低危病人移植後無病存活率達80至90%，高危組只有別60%。植入後不少病者出現混合嵌合情況，但大部份均可造血正常，血紅蛋白保持正常不需輸血。同胞骨髓與同伴臍血移植的結果沒有分別。近期有報導對沒有同胞相合者作非血緣移植，一般移植效果較同胞移植差，但較佳的HLA配型或可改善結果。最近一中心採用非血緣臍血移植，初步成效不錯。成功移植者需作除鐵治療以清除鐵沉積，一些病者或需接受荷爾蒙替代治療，大部分存活者有較佳生活品質。

a randomised study. Centres outside Italy are more in favour of including ATG in the conditioning. Hong Kong has routinely included ATG in the conditioning and the rejection rate is low.⁶ The commonly used conditioning regimens and outcomes are shown in the Table. More recently, a modified protocol including hydroxyurea, azathioprine and fludarabine in addition to busulphan and cyclophosphamide improved the DFS and reduced treatment-related mortality in high-risk patients.⁸

Treatment failures

Failures after HSCT in the first 3 months include primary rejection of donor's graft (non-engraftment), treatment-related deaths such as infection, organ failure and graft-versus-host disease (GVHD). Late complications include secondary rejection of donor's graft and infectious death due to chronic GVHD; second malignancy is uncommon. Graft rejection

is more common in TM as compared with other hereditary diseases. The rejection rate ranged from 7 to 32% depending on the patient's pre-transplant condition and the conditioning intensity.³⁻⁶ The high rejection rate may be related to allo-immunisation of minor human leukocyte antigens (HLAs) due to repeated blood transfusion before HSCT. Most patients have autologous regeneration of bone marrow and become transfusion-dependent again. However a small percentage of patients may reject the donor's bone marrow without autologous recovery and has marrow aplasia. These patients have high mortality due to failed engraftment after second transplant.⁹ Another major cause of failure is treatment-related mortality. Of the 145 deaths analysed at Pesaro, infection is the commonest cause of death (37%) and usually occurs during the marrow aplasia period. Graft-versus-host disease has been contributed to 23% of deaths. Transfusion-induced haemosiderosis predisposes patients to severe organ toxicity after the conditioning regimen.⁶ Hepatic fibrosis has been demonstrated in over 50% of patients receiving HSCT and busulphan is hepatotoxic. High busulphan level may be associated with severe veno-occlusive disease of liver and pharmacokinetic study of busulphan with dose adjustment may reduce the complication.¹⁰

Long-term outcome

Thalassaemia major patients with sustained engraftment of more than 2 years rarely have late rejection and these patients are free from further transfusion and also transfusion-related complications. However these survivors, or called ex-thalassaemias, still have excessive body iron due to previous transfusion and require iron depletion therapy. Desferrioxamine or phlebotomy are both

TABLE. Conditioning protocols and outcome

Groups	No. of patient	Conditioning protocol*	Death	Disease-free survival	
Pesaro, Italy ³					
Class I	111	Bu14-CY200	4%	90%	
Class II	294	Bu14-CY200	14%	81%	
Class III	55	Bu14-CY200	42%	55%	
Class III	110	Bu14/16, Cy120/160	21%	57%	
Adults	6	Bu14-CY200	100%	0	
Adults	86	Bu14/16 CY120/200	31%	67%	
Total	697		141 (20%)	502 (72%)	
UK ²⁰	All patients	50	Bu14-16—CY (30%) Bu-Cy+ALG/campath (70%)	10%	76%
Malaysia ⁴	All patients	28	Bu14-18—CY200+ATG	14%	75%
Taiwan ¹⁹	All patients	30	Bu-Cy-ATG	13%	82%
Hong Kong ^{6†}	All patients	50	Bu16-CY150-200+ATG	10%	86%

* Bu14-18 denotes busulphan 14 to 18 mg/kg, CY200 cyclophosphamide 200 mg/kg, ALG anti-lymphocyte globulin, ATG antithymocyte globulin, and campath monoclonal antibody

† Updated results from earlier report

effective to remove the body iron.¹¹ It has been demonstrated that reversibility of hepatic cirrhosis is possible after successful HSCT.¹² Growth and endocrine complications may be caused by iron-induced damage on hypothalamic-pituitary-gonadal axis before HSCT. Growth hormone and sex hormone replacement is required in some patients.¹³ The quality of life in HSCT survivors is better than that of transfusion-dependent TM.¹⁴

Alternative stem cell source for transplantation

Human leukocyte antigen-identical sibling is only available in 20 to 30% of patients. The experience of alternative donor HSCT in thalassaemia is still limited. In a multi-centre report from Italy, 68 patients received unrelated-donor bone marrow transplantation (BMT) and 13% had primary or secondary graft failure and 20% died from treatment-related causes. The DFS was only 65.8%, and the class 1/2 had better DFS than class 3 patients (80% vs 54.5%).¹⁵ With extended HLA typing, better matching may reduce graft rejection. The result of mismatched family donor BMT is disappointing with high rejection rate. Issaragrisil et al¹⁶ reported the first successful case of umbilical cord blood transplant (UCBT)

in thalassaemia. A recent multi-centre analysis comparing sibling cord blood and sibling BMT found that there is no difference in the rejection rate and DFS.¹⁷ Adding fludarabine or thiotepa to the standard busulphan-cyclophosphamide conditioning in UCBT appeared to improve the engraftment. Mismatched sibling or unrelated cord blood transplant was reported to have high engraftment failure and low DFS.¹⁸ Recently a single centre report from Taiwan showed encouraging result of unrelated cord blood transplantation.¹⁹ Grade III/IV acute GVHD occurred in 40%, and extensive chronic GVHD occurred in only 4% of the patients. Transplant-related mortality was 13% and overall survival and DFS at 3 years were 82% and 78%, respectively. Of the 30 transplants, nine received double cord blood units.

Conclusion

There is steady improvement in transplant outcome of TM but HSCT still carries significant morbidity and mortality especially in advanced TM. Alternative donor transplant is associated with higher graft rejection and treatment-related mortality rates. Further research is necessary to reduce transplant-related mortality and improve outcome of unrelated donor transplant that will benefit majority of patients.

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