

REVIEW

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Epidemiology and treatment of beta thalassemia major in China

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ABSTRACT

Thalassemia, classified as the main types α - and β -thalassemia, is a single gene disorder resulting from globin chain synthesis impairment through the mutation or deletion of globin genes. The incidence of thalassemia is high worldwide, with high associated mortality. Therefore, treatment is important to improve patient outcomes. This paper reviews the current status of β -thalassemia major in China, including its epidemiology and treatment.

KEYWORDS

Thalassemia, Epidemiology, Treatment, China

Introduction

Thalassemia, also referred to as Mediterranean anemia, has a high frequency in Mediterranean countries and Southeast Asia, hence its name.¹ It is an autosomal recessive disease with similar incidences in both males and females. The pathogenesis of thalassemia is mainly associated with ineffective erythropoiesis. It comprises a group of congenital hemolytic diseases, and is one of the most common single gene disorders worldwide. Mutations or deletions in globin genes cause abnormal hemoglobin (Hb) formation, resulting in chronic hemolytic anemia. Its essence is the invalid hematopoiesis of marrow, namely in situ hemolysis. However, acute hemolysis can also occur in severe acute infections. In this paper, we review the general status of thalassemia in China, including its epidemiology and treatment.

Epidemiology

Based on incomplete statistics, there are currently an

estimated 300 000 children with major and intermediate thalassemia in China. Surveys of thalassemia in mainland China were first carried out in the 1980s, and an understanding of the epidemiological characteristics of the disease has provided important information to aid its prevention.

Previous studies indicated a high frequency of thalassemia in southern China, mainly south of the Yangtze River and particularly in the provinces of Yunnan, Guangdong, Guangxi, Fujian, and Sichuan.³ However, in recent decades, the mobility and migration of people to northern China has rapidly increased, and thalassemia non-prevalent areas are now facing the 'new' disorder. During the past two decades, China and Southeast Asian countries have seen rapid economic development, and more families are now emigrating to European and American countries for studying, business, family integration, or seeking better standards of living.⁴

China has great variation in the incidence of thalassemia

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among different provinces, and may face similar challenges with migration of the population from south to north. Southern China has a high prevalence of α - and β -thalassemia that is not seen in northern China.⁵ Epidemiological data have also suggested a possible association between a high incidence of thalassemia and the prevalence of malaria. Nationwide prevalences of α -thalassemia and β -thalassemia are 4%–15% and 1%–6%, respectively,⁶ with over 200 million people thought to be affected. The reported incidence of globin gene deficiency related to thalassemia is 2.5%–20% in various regions of southern China, but is as high as 10% and 20% in the provinces of Guangdong and Guangxi, respectively, with the number of cases of thalassemia in these two provinces accounting for more than 40% of all cases in China.

Children with thalassemia show retarded growth and development. Surveys suggest that parents of children with thalassemia were mainly educated to middle school level or below, with the father having a slightly higher level of education than the mother. The parents' occupations are largely in farming or as migrant workers, with the mother undertaking more family responsibilities. Self-financing remains the main method of paying medical expenses for thalassemia in China. However, it is difficult for patients with thalassemia to receive standardized treatment and a guaranteed quality of life. Furthermore, 90% of affected families have an income less than \$8700, and medical treatment and daily expenses account for their main expenditure; therefore, nearly 80% of thalassemia-affected families are in debt, and there is a high risk of poverty because of illness.

Currently, tests for thalassemia involve prenatal screening and genetic testing. However, only 30% of thalassemia parents interviewed had received premarital examinations and fewer than 10% had received genetic testing, while 95.4% of parents did not know about thalassemia before giving birth.⁷ Fetal ultrasounds during mid-gestation enable the simple diagnosis of α -thalassemia by showing whole body skin, subcutaneous tissue edema, pleuroperitoneal effusion, heart enlargement, pericardial effusion, hepatosplenomegaly, and obvious growth retardation.

An alternative diagnostic method is genetic testing. Fetal DNA can be obtained invasively from villi, amniotic fluid, or umbilical cord blood, although this is associated with risks to the mother and child. Instead, fetal cells can be extracted non-invasively by separating and enriching from maternal peripheral blood, or obtained as blastocyst cells or polar bodies from eggs. Prenatal diagnosis is a current research hotspot, and successful cases have been reported within China and overseas.⁸ However, the technique has not yet entered clinical practice.

Treatment

Thalassemia represents a major health issue in China,

resulting in major economic losses and mental stress. Multiple therapeutic approaches are therefore needed.

Blood shortages are the major obstacle to standardized treatment for thalassemia. Standard transfusion volumes for children with thalassemia in China should be at least 90 g/L, but a lack of blood means this is usually limited to 60 g/L, and only 32.1% of children receive the required transfusion. Local governments therefore continue to explore prophylactic and therapeutic options, with some emerging effective empirical models. The Guangxi model proposes effective prophylaxis at childbirth, with outpatient treatment included in the reimbursement; the Guangdong (Shenzhen) model involves adequate blood transfusion and the costs of therapy included in the child's medical insurance; and the Hainan model includes treatment under major disorder relief and offers one-stop reimbursement of medical expenses. At present, the main social support organizations include mutual assistance organizations for thalassemia parents, volunteer service organizations, some foundations, and professional social organizations.

Transfusion and iron chelation therapy

Transfusion is the main treatment for β -thalassemia major, and the Thalassemia International Federation recommends washing red blood cells to avoid transfusion-related reactions. Small transfusions are only suitable for patients with intermediate thalassemia and are not recommended for β -thalassemia major,⁹ which requires medium or large transfusions at an early stage to maintain Hb levels above 90 g/L thus avoiding effects on child growth and development and reducing the incidence of bone lesions.

The iron load should be assessed dynamically every 3–6 months. Iron chelation should be applied if the number of transfusions is more than 10–20 or if the serum ferritin level is $>1000 \mu\text{g/L}$, while it should be suspended if the serum ferritin level is $<1000 \mu\text{g/L}$.¹⁰ Current commonly used chelators are desferrioxamine, deferiprone, and deferasirox. Subcutaneous or intravenous administration of desferrioxamine 30–50 mg/(kg · d), and oral administration of deferasirox 20–40 mg/(kg · d) can be used for children aged over 2 years, while oral administration of deferiprone 25 mg/kg three times daily is suitable for children over 10 years of age. However, safety data for children of 6–10 years are limited, and data for those under 6 years of age are lacking.

Because of major advances in transfusion and chelation, most Chinese patients with β -thalassemia major are in good health, can have a family, and work full time. However, despite such advances and improvements, compliance with comprehensive transfusion and chelation therapy and its availability remain pivotal factors in determining the survival and quality of life. Long-term transfusion and chelation therapy is highly challenging for

many developing countries where the disease is prevalent, representing a major and unsustainable health burden.¹¹ Nevertheless, long-term survival with current management protocols has increased significantly. Multicentric studies suggest that children born after 1995 have a near normal life,¹² and this is likely to continue with the improvement of social economic situation in the future. Therefore, the current treatment approach in China appears to be acceptable at this time.

Hematopoietic stem cell transplantation (HSCT)

HSCT is the only curative treatment for β -thalassemia major, and offers a better long-term quality of life than other therapies. It can be performed using matched sibling donors, matched unrelated donors, or human leukocyte antigen (HLA)-haploidentical donors, and stem cells can be derived from bone marrow, umbilical cord blood, peripheral blood, or a mixture of these.

Nanfang Hospital was the first and remains the largest unit to carry out HSCT for thalassemia in China. For thalassemia HSCT, it is best to transplant as early as possible, preferably with matched sibling donors. A multicenter study examined 1110 children, adolescents, and young adults with β -thalassemia major who underwent HSCT with grafts from HLA-matched relatives (61%), HLA-mismatched relatives (7%), HLA-matched unrelated donors (23%), and HLA-mismatched unrelated (9%) donors. The 5-year incidence of graft failure was 23% among patients aged 16–25 years compared with 8% and 10% in patients aged ≤ 6 and 7–15 years, respectively. Overall survival (OS) and disease-free survival (DFS) were highest in children aged ≤ 6 years who received grafts from HLA-matched siblings or HLA-matched unrelated donors. Five-year OS rates in patients aged ≤ 6 years, 7–15 years, and 16–25 years were 91%, 83%, and 55%, respectively, and corresponding DFS rates were 87%, 79%, and 55%, respectively.¹³

Although there is a current lack of matched sample sources for bone marrow transplants in China, it is relatively easy to obtain hematopoietic stem cells from peripheral blood. This can be done with the injection of hematopoietic cell growth factor before transplantation to promote the release of bone marrow stem cells into peripheral blood, or by the use of hematopoietic monotherapy technology. Nanfang Hospital, the Guangzhou Women and Children's Medical Center, Shenzhen Children's Hospital, and the Department of Pediatrics, West China Second Hospital, Sichuan University carried out 224 sibling peripheral blood stem cell transplantations with a median follow-up of 4 years. They reported OS, event-free survival (EFS), and graft failure rates of 95.9%, 95.5%, and 2%, respectively.

Unmatched cord blood hematopoietic stem cell transplantation (UCBHSCT) and bone marrow hematopoietic stem cell transplantation (BMHSCT) offer

the advantages of: a lower incidence and severity of graft versus host disease (GVHD); a lower risk of infection and spread of latent viruses such as cytomegalovirus, Epstein-Barr virus, hepatitis B virus, and HIV; faster post-transplantation immune reconstruction of recipients; and no risk of damage to donor hematopoietic stem cells. Moreover, in terms of donor selection and matching, studies have shown that the EFS and OS of UCBHSCT for related and unrelated donors are not significantly different from those of BMHSCT.^{14,15} However, UCBHSCT has the disadvantages of a high risk of rejection and delayed hematopoietic recovery after transplantation.¹⁶ A study conducted by the Pediatric Department of Nanfang Hospital and Shenzhen Children's Hospital analyzed the outcome of fresh cord blood transplantation from matched HLA-identical sibling donors in 35 children with β -thalassemia major from 2010 to 2016. The estimated 5-year OS and thalassemia-free survival rates were 97.1% and 94.2%, respectively.¹⁷ The conditioning protocol included intravenous busulfan, cyclophosphamide, fludarabine, and thiotepa.

Suitable unrelated donors can be identified using stringent criteria for immunogenetic compatibility by the high-resolution molecular typing of class I and class II HLA loci. Nanfang Hospital also achieved good outcomes by adopting unrelated donor peripheral blood stem cell transplantation (UDPBSCT).¹⁸ They used a novel NF-08-TM transplant protocol based on intravenous busulfan, cyclophosphamide, fludarabine, and thiotepa in 82 consecutive patients with β -thalassemia major, including 52 with well-matched HLA UDPBSCT and 30 with matched sibling donor hematopoietic stem cell transplantation (MSDHSCT). The age at transplantation was 0.6–15.0 years, and the male:female ratio was 56:26. The follow-up time was 12–39 months. Estimated 3-year OS and thalassemia-free survival rates were 92.3% and 90.4%, respectively, in the UDPBSCT group, and 90.0% and 83.3%, respectively, in the MSDHSCT group. Cumulative incidences of graft rejection and grade III–IV acute GVHD were 1.9% and 9.6%, respectively, in the UDPBSCT group and 6.9% and 3.6%, respectively, in the MSDHSCT group. The cumulative incidence of transplant-related mortality was 7.7% in the UDPBSCT group and 10.0% in the MSDHSCT group. Therefore, UDPBSCT using the well-tolerated NF-08-TM protocol showed similar results to MSDHSCT. However, the transplant protocol needs to be further validated.

The success rate of BMHSCT is generally more than 80%, but in areas with high kinship only 10%–20% of donors are completely matched. Therefore, most patients with thalassemia are unable to undergo HSCT. As an alternative, the problem of stem cell matching can be solved by haploidentical peripheral blood or bone marrow hematopoietic stem cell and complementary transplantation with unrelated cord blood. Between

2012–2017, eight children (four males and four females, median age 5 years) with thalassemia major received haploidentical HSCT at the Department of Hematology in Zhujiang Hospital. The conditioning regimen was fludarabine, busulphan, cyclophosphamide, and anti-thymocyte globulin, which is usually administered to leukemia patients receiving haploidentical HSCT at this center. All patients survived at a median follow-up of 36 months and had achieved independence from blood transfusion, with OS and thalassemia-free survival rates of 100%.¹⁹ Combined cord blood and granulocyte colony-stimulating factor-primed bone marrow grafting is also considered an effective treatment option for thalassemia major, with a previous study showing that mixed transplantation was associated with less acute and chronic GVHD.²⁰

Drug treatment

Drugs can increase the synthesis of fetal hemoglobin by reducing expression of the α -gene or increasing expression of the γ -gene, thus improving the imbalance between α - and non- α -globin chains and reducing the resulting anemia. Busulfan, isoniazide, hydroxyurea, 5-azacytidine, and cytosine have been used to this end. Thalidomide 50 mg/day has also been shown to improve hemoglobin levels to 25 g/L, but its long-term safety remains to be determined.²¹

Splenectomy

Splenectomy can relieve hemolysis in children with obvious hypersplenism or macrosplenism, notably in patients with β -thalassemia major. If the child has already developed splenomegaly and signs of hypersplenism, then splenectomy is indicated.²² However, a child's immune function remains underdeveloped up to 5 years old, and splenectomy may thus have adverse effects on immunity, with an increased risk of secondary infections. Splenectomy should therefore only be performed in children older than 5 years, and surgical indications should be strictly controlled. However, one review recommended that partial splenectomy reduced the transfusion requirement in children younger than 5 years old, but only as a temporary measure.²³

Gene therapy

Gene therapy can be an effective option for diseases caused by a single gene mutation. Conventional treatment involves introducing normal target gene fragments into receptor cells using expression vectors, and expressing them to restore the function of the defective genes. Thalassemia treatment represents a research hot spot for gene therapy, and this is currently being pursued at some transplant centers in China. Gene therapy can be used to knock out/in specific genes and replace particular DNA fragments, as well as to carry out accurate gene editing.²⁴

Another method is induced pluripotent stem cell (iPSC) transplantation, which is mostly used in the treatment of β -thalassemia major. In this procedure, mutant genes of patients are modified by gene editing technology in the process of dedifferentiating into iPSCs or during the differentiation of iPSCs into hematopoietic stem cells; corrected hematopoietic stem cells are then returned to the patient for treatment.^{25,26} Currently, there are three commonly used gene editing technologies: zinc finger nucleases, transcription activator-like effector nucleases, and clustered regularly interspersed short palindromic repeats (CRISPR) associated nuclease /CRISPR-associated protein 9. This latter system is more accurate, efficient, and simple to operate than other gene editing technologies, and has broad application prospects.

Summary

Among patients with thalassemia, thalassemia major has the worst prognosis, and affected patients often die from serious anemia, heart failure, systemic organ failure, or infection if left untreated. The effective prevention of the birth of children with thalassemia major is the primary task. We should learn from international experience in the prevention of thalassemia and establish a long-term cooperation mechanism for it at home and abroad.

A successful prevention program requires efforts such as government policy, public education, genetic counselling, prenatal screening, and diagnosis.²⁷ Prevention programs for β -thalassemia major in endemic areas have been shown to be successful in regions such as Cyprus and Sardinia.⁴ In 1994, the World Health Organization designated May 8 as International Thalassemia Day to raise government and public awareness of thalassemia. Improved understanding and management of thalassemia will help improve the quality of life and reduce the economic and social burdens related to this disease in China.

CONFLICT OF INTEREST

The authors declare that they have no competing interests.

REFERENCES

1. Hu H, Li C, Xiong Q, Gao H, Li Y, Chang Q, et al. Prenatal diagnosis of β -thalassemia by chip-based capillary electrophoresis. *Prenat Diagn.* 2008;28:222-229.
2. Muncie HL Jr, Campbell J. Alpha and beta thalassemia. *Am Fam Physician.* 2009;80:339-344.
3. Lai K, Huang G, Su L, He Y. The prevalence of thalassemia in mainland china: evidence from epidemiological surveys. *Sci Rep.* 2017;7:920.
4. Li CK. New trend in the epidemiology of thalassaemia. *Best Pract Res Clin Obstet Gynaecol.* 2017;39:16-26.
5. Li B, Zhang XZ, Yin AH, Zhao QG, Wu L, Ma YZ, et al. High prevalence of thalassemia in migrant populations in guangdong province, china. *BMC Public Health.* 2014;14:905.
6. Xu XM, Zhou YQ, Luo GX, Liao C, Zhou M, Chen PY,

- et al. The prevalence and spectrum of and thalassaemia in guangdong province: implications for the future health burden and population screening. *J Clin Pathol.* 2004;57:517-222.
7. Chen C. Blue book of thalassemia in China. 2015. (in Chinese)
 8. Ramezanzadeh M, Salehi M, Farajzadegan Z, Kamali S, Salehi R. Detection of paternally inherited fetal point mutations for β -thalassemia in maternal plasma using simple fetal DNA enrichment protocol with or without whole genome amplification: an accuracy assessment. *J Matern Fetal Neonatal Med.* 2016;29:2645-2649.
 9. Taher AT, Musallam KM, Inati A. The hypercoagulable state in thalassemia intermedia. *Hemoglobin.* 2009;33 suppl 1:S160-169.
 10. Angelucci E, Barosi G, Camaschella C, Cappellini MD, Cazzola M, Galanello R, et al. Italian society of hematology practice guidelines for the management of iron overload in thalassemia major and related disorders. *Haematologica.* 2008;93:741-752.
 11. Mohamed SY. Thalassemia major: Transfusion and chelation or transplantation. *Hematol Oncol Stem Cell Ther.* 2017;10:290-298.
 12. Borgna-Pignatti C. The life of patients with thalassemia major. *Haematologica.* 2010;95:345-348.
 13. Li C, Mathews V, George B. Related and unrelated donor transplantation for β thalassemia major: Results of an international survey. *Blood.* 2018;132:308.
 14. Locatelli F, Kabbara N, Ruggeri A, Ghavamzadeh A, Roberts I, Li CK, et al. Outcome of patients with hemoglobinopathies given either cord blood or bone marrow transplantation from an HLA-identical sibling. *Blood.* 2013;122:1072-1078.
 15. Jaing TH, Hung IJ, Yang CP, Chen SH, Chung HT, Tsay PK, et al. Unrelated cord blood transplantation for thalassaemia: a single-institution experience of 35 patients. *Bone Marrow Transplant.* 2012;47:33-39.
 16. Shahrokhi S, Mena F, Alimoghaddam K, McGuckin C, Ebtekar M. Insights and hopes in umbilical cord blood stem cell transplantations. *J Biomed Biotechnol.* 2012;2012:572821.
 17. Chen L, Wen J, He Y, Ruan Y, Li C, Wu X. Encouraging outcome of using sibling HLA-matched fresh cord blood for children β -thalassemia major transplantation. *Blood.* 2018;132:3459.
 18. Li C, Wu X, Feng X, He Y, Liu H, Pei F, et al. A novel conditioning regimen improves outcomes in β -thalassemia major patients using unrelated donor peripheral blood stem cell transplantation. *Blood.* 2012;120:3875-3881.
 19. Sun Q, Wu B, Lan H, Meng F, Ma X, Chen X, et al. Haploidentical haematopoietic stem cell transplantation for thalassaemia major based on an FBCA conditioning regimen. *Br J Haematol.* 2018;182:554-558.
 20. Wen J, Haque Q, Pei F, Chen L, Ruan Y, Liu X, et al. Transplant outcomes in beta-thalassemia major patients receiving combined granulocyte colony-stimulating factor-primed bone marrow and cord blood graft compared to granulocyte colony-stimulating factor-primed bone marrow alone. *Acta Haematol.* 2018;140:20-29.
 21. Vichinsky E. Non-transfusion-dependent thalassemia and thalassemia intermedia: epidemiology, complications, and management. *Curr Med Res Opin.* 2016;32:191-204.
 22. Choudhry VP. Thalassemia minor and major: current management. *Indian J Pediatr.* 2017;84:607-611.
 23. Al-Salem AH. Splenectomy for children with thalassemia: Total or partial splenectomy, open or laparoscopic splenectomy. *J Pediatr Hematol Oncol.* 2016;38:1-4.
 24. Ma YY, Li JZ, Gao EN, Qian D, Zhong JY, Liu CZ. Progress of gene editing technologies and prospect in traditional Chinese medicine. *China Journal of Chinese Materia Medica.* 2017;42:34-40. (in Chinese)
 25. Liu Y, Yang Y, Kang X, Lin B, Yu Q, Song B, et al. One-step biallelic and scarless correction of a β -thalassemia mutation in patient-specific iPSCs without drug selection. *Mol Ther Nucleic Acids.* 2017;6:57-67.
 26. Xu P, Tong Y, Liu XZ, Wang TT, Cheng L, Wang BY, et al. Both talens and crispr/Cas9 directly target the hbb ivs2-654 (C>T) mutation in β -thalassemia-derived iPSCs. *Sci Rep.* 2015;5:12065.
 27. Cao A. Carrier screening and genetic counselling in beta-thalassemia. *Int J Hematol.* 2002;76 Suppl 2:105-113.

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