*CK Li 李志光
CW Luk 陸頌榮
SC Ling 凌紹祥
KW Chik 戚其威
HL Yuen 袁煦樑
CK Li 李志強
MMK Shing 成明光
KO Chang 鄭啟安
PMP Yuen 阮文賓

Morbidity and mortality patterns of thalassaemia major patients in Hong Kong: retrospective study

香港的重型地中海貧血病患者的發病率及死亡率模式：回顧性研究

Objectives. To study the morbidity and mortality patterns of transfusion-dependent thalassaemia major patients in Hong Kong, and compare the outcomes of these patients according to different periods of birth.
Design. Retrospective study.
Setting. Paediatric departments of three regional hospitals, Hong Kong.
Subjects and methods. Medical records of thalassaemia major patients were reviewed. Data gathered included demographic and survival data, complications of iron overload, repeated transfusion, and bone marrow transplantation; the probability of survival of three cohorts was also estimated.
Results. Two hundred and thirty-two patients were studied at a median age of 15.5 years (range, 1.4-30.3 years). There were 60 patients born before 1980 (cohort 1), 117 patients born between 1980 and 1989 (cohort 2), and 55 patients born after 1989 (cohort 3). The median age of starting desferrioxamine was 8 years, 4 years, and 3 years for cohorts 1, 2, and 3, respectively. Cardiomyopathy, diabetes mellitus, and hypothyroidism occurred in 15.1%, 8.6%, and 6.9% of patients with thalassaemia major, respectively. The above complications developed in 5% to 12% of cohort 2 patients. Delayed puberty was present in 38.4% and hormonal replacement for gonadal failure was required in 29.7% of evaluable patients. Short stature was common and the median height standard deviation score was -1.63. Twenty patients had died, and cardiomyopathy was the leading cause of death, followed by complications of bone marrow transplantation. The probability of survival beyond the age of 20 years was 87.6%.
Conclusion. Despite the use of iron chelation in the past two decades, severe complications of iron overload still occurred even in those who started chelation therapy early. Cardiomyopathy was the leading cause of death, while endocrinopathies and short stature were common complications especially in teenagers and adults.

目的：研究在香港長期輸血的重型地中海貧血病患者的發病率及死亡率模式，並根據不同出生時間比較其結果。
設計：回顧性研究。
安排：香港三所地區醫院的兒科。
患者與方法：總結重型地中海貧血病患者的醫療紀錄。收集的資料包括人口統計學、存活數據、鐵過量的併發症、重複輸血及骨髓移植等數據；還評估了三組患者的存活率。
結果：研究的患者共232名，中值年齡為15.5歲(範圍，1.4-30.3歲)。60名患者於1980年前出生(組1)，117名患者在1980年至1989年之間出生(組2)，55名患者於1989年後出生(組3)。組1、2、3的患者開始服用除鐵靈的中值年齡分別是8歲、4歲和3歲。心肌病、糖尿病和甲狀腺機能減退的發病率分別是15.1%，8.6%和6.9%。上述併發症在組2患者中的發病率為5%至12%。在所評估的患者中，38.4%出現青春期延時，29.7%需要為生殖腺障礙作補充激素。個子矮小是患者的共通點，中值高度標準偏差值為-1.63。20名患者已死亡，心肌病是死亡的主要原因，其次是骨髓移植併發症。患者達至20歲後的存活率是87.6%。
結論：儘管在過往20年使用鐵螯合劑，嚴重的鐵過量併發症仍然發生。這種情況甚至在一些早期已開始除鐵治療的患者中出現。心肌病是死亡的主要原因，內分泌病及個子矮小是常見的併發症，尤其在青少年和成人患者中。

Key words:
Beta-thalassemia;
Morbidity;
Mortality

關鍵詞：
B一重型地中海貧血病；
發病率；
死亡率

Hong Kong Med J 2002;8:255-60

Department of Paediatrics, The Chinese University of Hong Kong, Prince of Wales Hospital, Shatin, Hong Kong
*CK Li, FRCPCH, FHKAM (Paediatrics)
KW Chik, MRCP, FHKAM (Paediatrics)
MMK Shing, FRCP, FHKAM (Paediatrics)
PMP Yuen, FRCPC, FHKAM (Paediatrics)
Department of Paediatrics, Queen Elizabeth Hospital, 30 Gascoigne Road, Hong Kong
CW Luk, MRCP, FHKAM (Paediatrics)
HL Yuen, FRCP, FHKAM (Paediatrics)
KO Chang, MRCP, FHKAM (Paediatrics)
Department of Paediatrics, Princess Margaret Hospital, 2-10 Princess Margaret Hospital Road, Hong Kong
SC Ling, MRCP, FHKAM (Paediatrics)
CK Li, FRCPCH, FHKAM (Paediatrics)

Correspondence to: Dr CK Li*

Introduction

Thalassaemia major (TM) is the most common transfusion-dependent anaemia in Hong Kong. The carrier rates of α- and β-thalassaemia are 5% and 3.4%, respectively.[1] β-Thalassaemia is inherited in an autosomal recessive pattern and is the most common type of TM. α-Thalassaemia major, haemoglobin Bart's Disease, previously an invariably fatal disease, is now occasionally salvageable.[2] With the introduction of prenatal diagnosis, the number of newly diagnosed TM cases has decreased significantly. The natural course of TM is modified by the use of the iron chelator desferrioxamine. Without iron chelation, most TM patients cannot survive beyond the second decade of life, and mostly die from cardiomyopathy.[3] Complications such as diabetes mellitus (DM) and hypothyroidism are also common. Since the early 1980s, the Hong Kong Government has provided a free supply of desferrioxamine to all TM patients. Patients receive daily subcutaneous infusion of desferrioxamine at home. We, however, still encounter patients with complications of severe iron overload as a result of poor compliance to desferrioxamine. In the early 1990s, bone marrow transplantation (BMT) was introduced in Hong Kong as a curative treatment for TM patients. With introduction of these new treatment modalities in the past two decades, it is anticipated that clinical outcomes will improve. This study aimed to assess the impact of new treatment on morbidity and mortality patterns of TM patients born during different periods.

Methods

A retrospective analysis of TM patients treated by paediatric departments of three regional hospitals was performed. Medical records of all surviving and deceased patients with retrievable records were reviewed. The patient demographic data and information regarding treatment and complications were collected. Survival and complication rates were compared among three different cohorts: cohort 1 for those born before 1980, cohort 2 for those born between 1980 and 1989, and cohort 3 for those born after 1989. The data were complete for one hospital, while the other two hospitals did not have complete data on those patients who had died before 1990. Therefore, mortality rates of TM patients were underestimated for those born before 1990.

Iron chelation therapy among the three hospitals was uniform. Patients were started on desferrioxamine after they had received regular blood transfusion for 1 to 2 years, ie usually at the age of 3 to 4 years. Desferrioxamine was given as a continuous subcutaneous infusion over 10 hours on 5 to 6 days per week. Morbidity studied included cardiomyopathy, DM, hypothyroidism, and hypoparathyroidism. Patients were screened annually for echocardiographic and biochemical abnormalities related to the above complications. Cardiomyopathy was defined as the presence of congestive heart failure without evidence of myocarditis. Growth was analysed by height percentiles according to local growth charts, and a height standard deviation score (SDS) was calculated for each patient. Puberty was assessed for all teenagers according to the local pubertal staging scale, and the absence of signs of puberty by the age of 16 years was considered as delayed puberty. Girls were also checked for primary and secondary amenorrhoea. Severe infection was recorded and types of infection were reported. Survival and complication data were analysed on 1 January 2001 or at time of death.

Bone marrow transplantation was performed centrally at one hospital. If a patient had a human leukocyte antigen (HLA)–identical sibling, and was without cardiomyopathy or cirrhosis of the liver, the patient would be offered BMT. The patients were prepared for BMT with standard chemotherapy conditioning.[4] Complication and survival rates of BMT patients were compared with non-BMT patients. The outcomes of the three different cohorts were also compared.

The values were expressed as a median and range for continuous variables. Complication and mortality rates of different cohorts were compared by Chi squared or Fisher's exact test as appropriate. The serum ferritin, liver iron content, and height SDS were compared by analysis of variance (ANOVA). The probabilities of survival and survival without complications were predicted by the Kaplan Meier test, and the difference among the three cohorts was tested by the log rank test. P values less than 0.05 were regarded as significant.

Results

A total of 232 patients were included in the study. The male to female ratio was equal; there were 118 males and 114 females. There were 60 patients in cohort 1, and they were all over the age of 20 years. The 117 cohort 2 patients were aged between 11 and 20 years. The 55 cohort 3 patients were under the age of 11 years. The number of deaths in cohort 1 was underestimated because records of some patients who died before 1990 were not retrievable. Assuming the birth rates in periods of cohorts 1 and 2 were similar, it would be expected that about 60 patients in cohort 1 would be missed in this study. The median age of the whole group at analysis was 15.5 years (range, 1.4-30.3 years). Most of the patients presented before the age of 1 year. Occasional patients were diagnosed with TM quite late because they initially presented as thalassaemia intermedia. Desferrioxamine was started in 221 patients. The median age of starting desferrioxamine was 4 years for the whole group (range, 1.1-18.0 years). Desferrioxamine was started at the median age of 8 years in cohort 1 when the drug was newly introduced in Hong Kong, whereas cohorts 2 and 3 were started at 4 and 3 years, respectively. The serum ferritin at time of analysis was 5140 pmol/L for the whole group (range, 468-48490 pmol/L). The mean serum ferritin levels were 8810 pmol/L, 6579 pmol/L, and 4525 pmol/L for cohorts 1, 2, and 3, respectively, and there was a significant difference among the three groups (P=0.002). Splenectomy

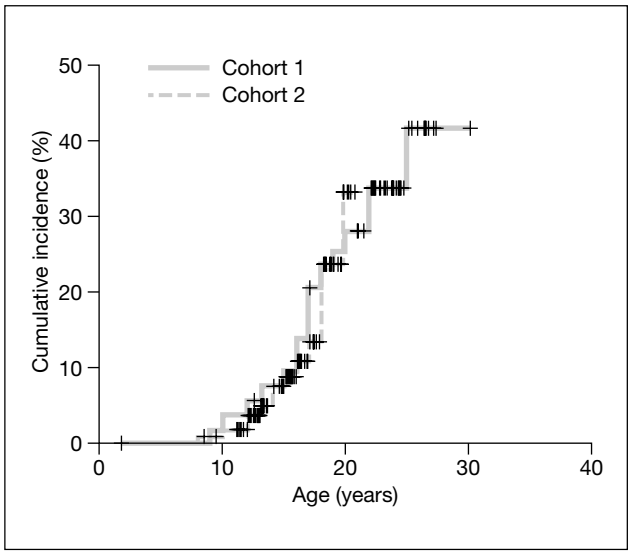

Fig 1. Cardiomyopathy according to birth cohort

was performed in 88 (37%) patients at a median age of 9 years, ranging from 1 to 23 years.

Cardiomyopathy was present in 35 (15.1%) patients with the median age of onset at 16 years. It was more common in older patients, 33% versus 12% versus 1.8% for cohorts 1, 2, and 3, respectively. The probability of survival without cardiac disease at 15 years was 91% for both cohorts 1 and 2 (P=0.96). Despite iron chelation therapy being introduced at rather a young age in cohort 2, the hazard of developing cardiac disease in the second decade as compared with cohort 1 was very similar (Fig 1). Diabetes, hypothyroidism, and hypoparathyroidism were present in 8.6%, 6.9%, and 3.4% of the patients, respectively. None of the patients in cohort 3 had developed these endocrine complications. The median age of developing these endocrine complications was around 16 years, and they were more common in cohort 1 (Table 1). The probability of survival without DM or hypothyroidism between cohorts 1 and 2 did not differ significantly. Of the 46 patients treated with BMT, only one developed DM, and none had cardiomyopathy or endocrine complications during a median follow-up of 5 years. The median age of BMT patients at time of analysis was 15 years (range, 6-26 years).

Of 138 patients evaluable for puberty, delayed puberty was observed in 53 (38.4%). Among 48 females over the age of 16 years, 13 (27.1%) did not have menarche, and three girls had menarche but subsequently developed secondary amenorrhoea. Hormonal replacement, either testosterone for males or oestrogen for females, was required in 41 (29.7%) patients. The median height percentile was 10% and the median height SDS was -1.63. In patients below the age of 10 years, the height SDS in cohort 3 was significantly lower as compared with cohorts 1 or 2 (P<0.001) [Table 2]. Short stature was defined as a height SDS less than -2. There were a total of 69 (29.7%) patients with short stature, and it was more common in cohort 1 (31.7%) and cohort 2 (40.2%) as compared with cohort 3 (5.5%; P=0.003). Some patients were very short, and about 20 to 30 cm below the third percentile, or SDS -5 to -6. Growth hormone deficiency was suspected if the growth velocity deviated from the normal curve, and was confirmed by the growth hormone profile after two stimulation tests. Only one patient was found to have growth hormone deficiency. The bony abnormality was not systematically studied for the whole group. Genu valgum was present in five and platyspondyly in 10 patients with short stature. Bone infarcts and dysplasia of metaphyseal and epiphyseal regions have been observed on careful evaluation of X-ray films or magnetic resonance imaging (MRI).[5,6]

Severe infection occurred in 19 patients. Three patients died from infection and Klebsiella meningitis accounted for two cases. Klebsiella brain abscess and sinusitis developed in another three patients. The types of infection are listed in Table 3. Severe infection occurred more commonly in cohort 1. Anti-hepatitis C antibody was present in 32 (13.8%) patients. Elevated liver enzymes were present in 18% of patients, and the anti-hepatitis C virus–positive patients all had persistent elevation of liver enzymes. Hepatitis B surface antigen was uncommon and was present in only six (2.6%) patients. Liver biopsy was performed in 83

Table 1. Complications of thalassaemia major in Hong Kong

	Cardiomyopathy	Diabetes mellitus	Hypothyroidism	Hypoparathyroidism
No. (%)	35 (15.1)	20 (8.6)	16 (6.9)	8 (3.4)
Year of birth				
Cohort 1 (%), n=60	20 (33.3)	13 (21.7)	10 (16.7)	5 (8.3)
Median (range) age of onset (years)	17 (9-25)	16.5 (12-21)	19 (10-25)	17 (10-21)
Cohort 2 (%), n=117	14 (12.0)	7 (6.0)	6 (5.1)	3 (2.6)
Median (range) age of onset (years)	14 (8.0-18.0)	14 (13.0-16.0)	14.5 (10.0-16.8)	15 (13.0-17.0)
Cohort 3 (%), n=55	1 (1.8)	0	0	0
Male/female	20/15	10/10	6/10	4/4
Surviving	20	10	11	4
Bone marrow transplantation patients	0	1	0	0

Table 2. Height standard deviation score in thalassaemia major patients

	Mean (SD)	95% CI	P value
Cohort 1 (>20 years)	-1.58 (1.45)	-1.97 to -1.19	Cohort 1 vs 2, P=0.43
Cohort 2 (11-20 years)	-1.75 (1.27)	-1.99 to -1.52	Cohort 2 vs 3, P<0.004
Cohort 3 (≤10 years)	-0.51 (1.0)	-0.78 to -1.23	Cohort 3 vs 1, P<0.001

Table 3. Types of infection in thalassaemia major patients

Type of infection	No.	Cohort 1	Cohort 2	Cohort 3
Central nervous system				
Klebsiella meningitis	3	1	1	1
Klebsiella abscess	1	-	1	-
Other brain abscess	1	1	-	-
Yersinia infection				
Peritonitis	2	1	1	-
Septicaemia	1	1	-	-
Peritonitis of unknown organism	1	1	-	-
Septicaemia				
Staphylococcus	1	1	-	-
Pseudomonas	1	1	-	-
Other organism	1	1	-	-
Klebsiella sinusitis	2	1	1	-
Liver abscess	1	1	-	-
Tuberculosis	2	-	2	-
Skin abscess	2	1	1	-
Herpes zoster	1	-	1	-

patients. The liver iron content was measured in 33 patients; the median liver iron was 8.7 mg/g dry weight (range, 2.0-41.8 mg/g). Only one patient in cohort 1 had liver iron content measured, at 13.1 mg/g. Of 24 patients in cohort 2 with liver iron content measured, the median content was 5.1 mg/g. The median liver iron content of eight patients in cohort 3 was 9 mg/g. There was no significant difference in the liver iron content between cohorts 2 and 3 (P=0.22). Liver iron was also graded histologically according to standard criteria.[7] Moderate-to-severe haemosiderosis, grades 3 and 4, was present in 35% of the whole group, and was 57%, 30%, and 31.6% in cohorts 1, 2, and 3, respectively. There was no significant difference in grades 3 and 4 haemosiderosis among the three cohorts (P=0.16). Hepatic fibrosis was present in 19% of the whole group, and was 28%, 22%, and 5% in cohorts 1, 2, and 3, respectively. There was no significant difference in the incidence of hepatic fibrosis among the three cohorts (P=0.18). None of the patients had cirrhosis of the liver on liver biopsy.

A total of 20 patients died during the study period. The probability of survival for the non-BMT group up to 10 years, 20 years, and 25 years was 100%, 87.6%, and 79.5%, respectively. The probability of survival for the non-BMT and BMT groups of the three cohorts is shown in Table 4. The survival curves for the three cohorts are shown in Fig 2. The 3-year disease-free survival of BMT patients was 86%. Bone marrow transplantation patients had similar survival rates to non-BMT patients. The median age of death was 16.4 years (range, 6.8-27.4 years). Cardiomyopathy accounted for 65% of all deaths, followed by BMT complications (25.0%). Veno-occlusive disease of the liver and idiopathic interstitial pneumonitis were the leading causes of death in BMT patients.

Discussion

Iron chelation therapy has altered the natural course of TM remarkably. Without desferrioxamine treatment, only 40% of patients would survive up to the age of 25 years.[3] With the introduction of iron chelation therapy in Hong Kong since the 1980s, more and more TM patients are now surviving into adulthood. The median age of this TM cohort is now 16 years. Iron chelation treatment, however, is an extremely demanding treatment. It requires daily subcutaneous infusion of desferrioxamine over 10 hours. The short half-life of desferroxamine makes continuous infusion the only effective mode of administration. Poor compliance in some patients, especially adolescents, is not uncommon. Morbidity and mortality due to poor compliance with chelation therapy have been reported in various studies.[8-10]

This study has attempted to analyse all TM patients treated in these three regional hospitals. At present, there are about 300 TM patients treated by paediatric departments in public hospitals in Hong Kong.[11] These patients represent about 60% of all TM patients in Hong Kong. Since treatment of TM is uniform among hospitals in Hong Kong, the data presented in this report are likely to be

Table 4. Likelihood of survival for thalassaemia major patients in relation to age

Non-BMT*	10 years	15 years	20 years	25 years	
All, n=186	100.0%	94.3%	87.6%	79.5%	
Cohort 1, n=53	100.0%	92.3%	86.4%	79.6%	
Cohort 2, n=91	100.0%	95.7%	89.2%	-	
Cohort 3, n=42	100.0%	-	-	-	
BMT					P value (non-BMT vs BMT)
All, n=46	97.7%	91.6%	75.4%	75.4%	0.24
Cohort 1, n=7	100.0%	100.0%	85.7%	85.7%	0.67
Cohort 2, n=26	100.0%	91.6%	71.3%	-	0.132
Cohort 3, n=13	91.0%	-	-	-	0.148

* BMT bone marrow transplantation

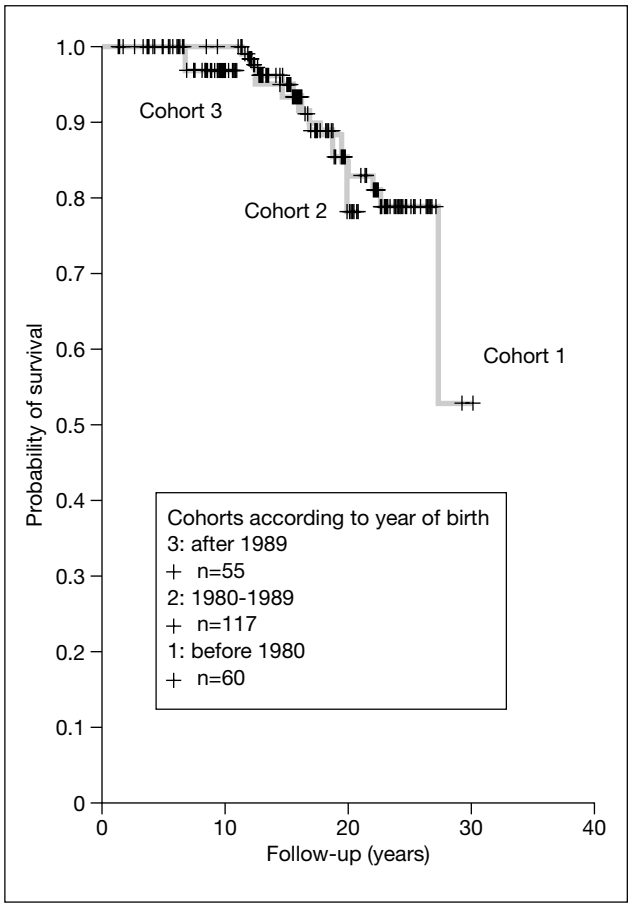

Fig 2. Survival according to birth cohort

representative of the Hong Kong TM population. Cardiomyopathy is still the leading cause of death. It has been reported that of patients who started chelation therapy late, at around the age of 15 years, only 55% survived without cardiac disease after 15 years of chelation therapy.[8] More frequent use of desferrioxamine has been shown to protect TM patients from cardiac disease and also to reduce cardiac death. In cohort 1, patients were started on desferrioxamine at the median age of 8 years, and the rate of survival without cardiac disease at 15 years after starting chelation treatment was 71%. This, however, must be an overestimation because the number of patients in this cohort probably only represented 50% of the original number of patients born during that period. The other 50% of patients missed in cohort 1 probably died from complications of treatment, but unfortunately the records were not retrievable. We believe that the actual survival of cohort 1 would be much lower than what we reported here. Cohort 2, with complete data and desferrioxamine started at the age of 4 years, was anticipated to have fewer complications. However, the probability of developing cardiomyopathy was very similar to that of cohort 1. The median age of onset of cardiomyopathy for cohorts 1 and 2 were 17 and 14 years, respectively. This poor outcome is related to the poor compliance with medical treatment, especially in the adolescent age-group. Whether the new oral chelators may improve compliance and reduce mortality is still unknown.[12]

Endocrinopathies are common in the older age-group as well. As expected, cohort 1 had a higher prevalence of DM, hypothyroidism, and hypoparathyroidism. Diabetes mellitus and hypothyroidism were common in the patients in this study: 21.7% and 16.7% in cohort 1, compared with 10% and 8%, respectively, in an Italian study in patients of similar age.[13] Whether this discrepancy is due to poorer control of iron overload or genetic predisposition in these patients requires further study. The younger patients are still at risk of developing cardiomyopathy and endocrinopathies as they grow older. To prevent these complications, there must be constant control of iron balance for life.

Delayed puberty was common in the adolescent age-group, and failure of puberty was observed in 38.4% of patients reaching pubertal age. Hormonal replacement for gonadal failure was required in 29.7% of patients. Gonadal failure is related to the age of starting iron chelation. Patients who started desferrioxamine late and with a high serum ferritin more commonly experienced gonadal failure.[14] Short stature appeared to be the norm for TM patients; the median height percentile in this study was only 10% and the median height SDS was -1.63. Only 9.5% of patients were above the 50% height percentile, and these were mostly below the age of 10 years. Chronic anaemia was not the cause for short stature, as these patients were all regularly transfused with pretransfusion haemoglobin above 95 g/L. Endocrine causes were not primarily responsible for short stature, as there was only one patient with growth hormone deficiency. Patients with hypothyroidism all received thyroxin replacement. Skeletal abnormalities were common in TM patients receiving desferrioxamine. Early start of desferrioxamine before 2 years has been shown to produce rickets-like dysplasia and growth failure.[15,16] The patients in this study were started on desferrioxamine, at a median age of 3 to 4 years, but they may have been more intensively chelated leading to more bony damage. We observed a high percentage of bony dysplasia when radiographs were carefully studied.[5] When MRI was included in the investigations, desferrioxamine-induced bony dysplasia was more commonly identified.[6] Bony dysplasia was not studied systemically in this study, but clinical manifestations of genu valgum and short trunk due to platyspondyly were observed in some patients. Disproportionate trunkal shortening has been demonstrated to be the cause of short stature.[17,18] These patients were usually better chelated with lower serum ferritin levels, and thus the dose effect of desferrioxamine accounted for the bony damage. Lowering the desferrioxamine dosage may reverse some of the bony abnormalities, but this may lead to more severe iron overload. The balance between growth needs and iron overload needs fine-tuning.

We observed severe infection in some patients and this led to death in a few of them.[19] In non-BMT patients, infection was the second leading cause of death. The immune system of TM patients is impaired as a result of repeated blood transfusion or iron overload.[20] Transfusion-transmitted

infection is difficult to avoid completely. Hepatitis C infection occurred in 14% of all patients. Because of this, and haemosiderosis of the liver, TM patients may progress to cirrhosis earlier than non-TM patients. Antiviral treatment should be considered in this group of patients since they are at higher risk of progression. The only way to eliminate all the above complications, however, is to cure the underlying haematological disease. Bone marrow transplantation has been shown to be effective in curing the disease, especially if this is performed early.[21] Patients with successful transplants are free from transfusion-related complications and have a much better quality of life. Unfortunately only about one third of patients have HLA-identical siblings available as donors for BMT, and the outcome of unrelated donor or mismatched donor transplant for TM is poor.[22] Gene therapy provides hope for treatment of hereditary diseases, such as TM, but may take many years to reach clinical use.

Conclusion

Despite the use of iron chelation therapy in the past two decades in Hong Kong, severe complications leading to death or significant morbidities in TM patients remain evident. Compliance should be reinforced to reduce complications. Short stature and endocrine dysfunction are still common in older patients.

References

1. Lau YL, Chan LC, Chan YY, et al. Prevalence and genotypes of alpha- and beta-thalassemia carriers in Hong Kong – implications for population screening. N Engl J Med 1997;336:1298-301.
2. Chik KW, Shing MM, Li CK, et al. Treatment of hemoglobin Bart's hydrops with bone marrow transplantation. J Pediatr 1998;132: 1039-42.
3. Modell B, Letsky EA, Flynn DM, Peto R, Weatherall DJ. Survival and desferrioxamine in thalassaemia major. Br Med J (Clin Res Ed) 1982; 284:1081-4.
4. Li CK, Yuen PM, Shing MK, et al. Stem cell transplant for thalassaemia patients in Hong Kong. Bone Marrow Transplant 1997;19(Suppl 2):62S-4S.
5. Chan YL, Li CK, Pang LM, Chik KW. Desferrioxamine-induced long bone changes in thalassaemic patients – radiographic features, prevalence and relations with growth. Clin Radiol 2000;55:610-4.
6. Chan Y, Li C, Chu WC, Pang L, Cheng JC, Chik KW. Deferoxamine-induced bone dysplasia in the distal femur and patella of pediatric patients and young adults: MR imaging appearance. AJR Am J Roentgenol 2000;175:1561-6.
7. Searle JW, Kerr JF, Halliday JW, Powell LW. Iron storage disease. In: MacSween RN, Anthony PP, Scheuer PJ, editors. Pathology of the liver. 2nd ed. Edinburgh: Churchill Livingstone; 1987:185-6.
8. Olivieri NF, Nathan DG, MacMillan JH, et al. Survival in medically treated patients with homozygous beta-thalassemia. N Engl J Med 1994;331:574-8.
9. Zurlo MG, De Stefano P, Borgna-Pignatti C, et al. Survival and causes of death in thalassaemia major. Lancet 1989;2:27-30.
10. Modell B, Khan M, Darlison M. Survival in beta-thalassaemia major in the UK: data from the UK Thalassaemia Register. Lancet 2000; 355:2051-2.
11. Li CK. Current status of thalassaemia major in Hong Kong: 2000. The 20th Anniversary Special Issue of the Thalassaemia Association of Hong Kong; 2001:23-4.
12. Cohen AR, Galanello R, Piga A, Dipalma A, Vullo C, Tricta F. Safety profile of the oral iron chelator deferiprone: a multicentre study. Br J Haematol 2000;108:305-12.
13. Italian Working Group on Endocrine Complications in Non-endocrine Diseases. Multicentre study on prevalence of endocrine complications in thalassaemia major. Clin Endocrinol (Oxf) 1995;42:581-6.
14. Bronspiegel-Weintrob N, Olivieri NF, Tyler B, Andrews DF, Freedman MH, Holland FJ. Effect of age at the start of iron chelation therapy on gonadal function in beta-thalassemia major. N Engl J Med 1990; 323:713-9.
15. De Virgiliis S, Congia M, Frau F, et al. Deferoxamine-induced growth retardation in patients with thalassemia major. J Pediatr 1988;113: 661-9.
16. Olivieri NF, Koren G, Harris J, et al. Growth failure and bony changes induced by deferoxamine. Am J Pediatr Hematol Oncol 1992;14:48-56.
17. Rodda CP, Reid ED, Johnson S, Doery J, Matthews R, Bowden DK. Short stature in homozygous beta-thalassaemia is due to disproportionate truncal shortening. Clin Endocrinol (Oxf) 1995;42:587-92.
18. Filosa A, Di Maio S, Baron I, Esposito G, Galati MG. Final height and body disproportion in thalassaemic boys and girls with spontaneous or induced puberty. Acta Paediatr 2000;89:1295-301.
19. Li CK, Shing MM, Chik KW, Lee V, Yuen PM. Klebsiella pneumoniae meningitis in thalassemia major patients. Pediatr Hematol Oncol 2001; 18:229-32.
20. Li K, Li CK, Wong RP, et al. Transfusion-related immunomodulation in Chinese children with thalassaemia. Vox Sang 1997;73:167-73.
21. Lucarelli G, Galimberti M, Polchi P, et al. Bone marrow transplantation in patients with thalassemia. N Engl J Med 1990;322:417-21.
22. Gaziev D, Galimberti M, Lucarelli G, et al. Bone marrow transplantation from alternative donors for thalassemia: HLA-phenotypically identical relative and HLA-nonidentical sibling or parent transplants. Bone Marrow Transplant 2000;25:815-21.