ORIGINAL ARTICLE

A synopsis of current care of thalassaemia major patients in Hong Kong

CME

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Objective To provide a synopsis of current thalassaemia major patient care in Hong Kong.

Design Retrospective study.

Setting All haematology units of the Hospital Authority in Hong Kong.

Patients All patients with thalassaemia major with regular transfusion.

Results To date, there were 363 thalassaemia major patients under the care of the Hospital Authority. Prenatal diagnosis has helped to reduce the number of indigenous new cases, but in recent years immigrant cases are appearing. The patients have a mean age of 23 (range, 1-52) years, and 78% of them are adults. In 2009, they received 18 782 units of blood. This accounted for 9.5% of all blood consumption from the Hong Kong Red Cross. In the past, cardiac iron overload was the major cause of death (65%) and few patients survived beyond the age of 45 years. The availability of cardiac iron assessment by magnetic resonance imaging (T2* MRI) to direct the use of oral deferiprone chelation has reduced the prevalence of heart failure and cardiac haemosiderosis, which should reduce mortality and improve life expectancy.

Conclusion The future for thalassaemia care in Hong Kong is bright. With better transfusion and chelation, it should be possible to avoid growth and endocrine deficiencies in younger patients.

New knowledge added by this study

- Systematic data on the population-based prevalence of thalassaemia major in Hong Kong are provided.
- Clinically significant improvements in morbidity and mortality are achievable based on magnetic resonance imaging–directed oral chelation therapy.

Implications for clinical practice or policy

- Transfusion and chelation resources have to be planned for current thalassaemia major cases, with the expectation of near-normal health and life expectancy.
- New cases of thalassaemia major continue to appear in Hong Kong, so some patients did not benefit from the availability of universal prenatal screening.

Introduction

Thalassaemia is common in Southern China. In Hong Kong, 3% of the population carries a β-globin thalassaemia gene mutation.[1] Carriage of two β-thalassaemia mutations results in moderate-to-severe anaemia from infancy. Thalassaemia major (TM) refers to the condition of lifelong transfusion dependence. With improved public education, antenatal care and prenatal diagnosis,[2] the incidence of newborn TM cases in Hong Kong has dropped dramatically. There are currently 363 TM patients (long-term regular transfusion over 6 times per year) under the care of the Hospital Authority. In this article, we review the comprehensive care available to these patients. Patients who have successfully received haematopoietic stem cell transplantation (HSCT) and those with milder thalassaemia and other congenital dyserythropoietic or transfusion-dependent conditions are not included in the current review.

Demography

Both paediatric as well as adult medical units take care of TM cases according to their age. Their age and gender distribution are shown in Figure 1a, and the population-based

香港重型地中海貧血患者的治療現況概覽

目的 提供現時香港重型地中海貧血患者的治療概覽。

設計 回顧研究。

安排 香港醫院管理局轄下醫院的血液學部門。

患者 須定期輸血的重型地中海貧血患者。

結果 迄今共363名重型地中海貧血患者於醫院管理局轄下醫院接受治療。在產前診斷有助減少遺傳性新症的同時，近年開始出現來自內地新移民的病例。這363名患者的平均年齡為23歲（介乎1-52歲），78%為成年人。他們於2009年輸血共18782個單位，佔香港紅十字會全年輸血量9.5%。過往，心臟過量鐵質積聚是導致死亡的主因（65%），只有少數患者的壽命超過45歲。透過磁共振成像（T2*）評估心臟鐵質存量，以指引口服除鐵藥物的螯合作用，有助減低心臟衰竭和心臟血黃素沉積病的發病率，從而減低一定程度的死亡率和延長患者壽命。

結論 地中海貧血治療的發展前景是樂觀的。隨着更佳的滲流和螯合治療，有望改善年青患者的發育和內分泌缺乏問題。

prevalence is illustrated in Figure 1b. They included 178 male and 185 female patients, with a mean age of 23 years (range, 1-52 years). Several factors affect the age distribution. The number of new cases has dropped from a median of 16 per year to around 3 per year, but has recently increased again due to Mainland China migrants and cross-border newbirths.[3] Some paediatric cases leave the cohort due to successful (or regrettably, fatal) outcomes from HSCT. There is a rapid dropoff in patient number beyond the age of 40 years, mainly due to premature cardiac deaths. However, with better iron assessment and chelation, future life expectancy of TM patients is expected to approach that of the background population. Presently, 78% of thalassaemia patients are already adults, while only 22% are below the age of 18 years. Hence, it is hoped that thalassaemia care will gradually shift from paediatric to adult (and later geriatric) medicine.

Transfusion

Safe and free red cell transfusion is available for all patients in Hong Kong. Due to their transfusion habits however, the pre-transfusion haemoglobin level of these patients ranges from 55 to 111 g/L with a median of 92 g/L. A total of 132 (36%) of the patients had undergone splenectomy (age range, 5-56; median, 30 years). In 2009, the total blood consumption was 18 782 units, which accounts for 9.5% of all red cells collected in Hong Kong during that period. Pre-storage filtered, phenotype-matched blood units are pre-arranged for all patients ahead of their scheduled transfusions. The prevalence of allo-antibody carriage in Hong Kong TM cases is low.[4] However, lifelong regular transfusion (and cross-matching beforehand) imposes a huge burden on the social life of these patients.

Iron overload

With free transfusions, iron overload and organ failure (particularly cardiac iron overload and heart

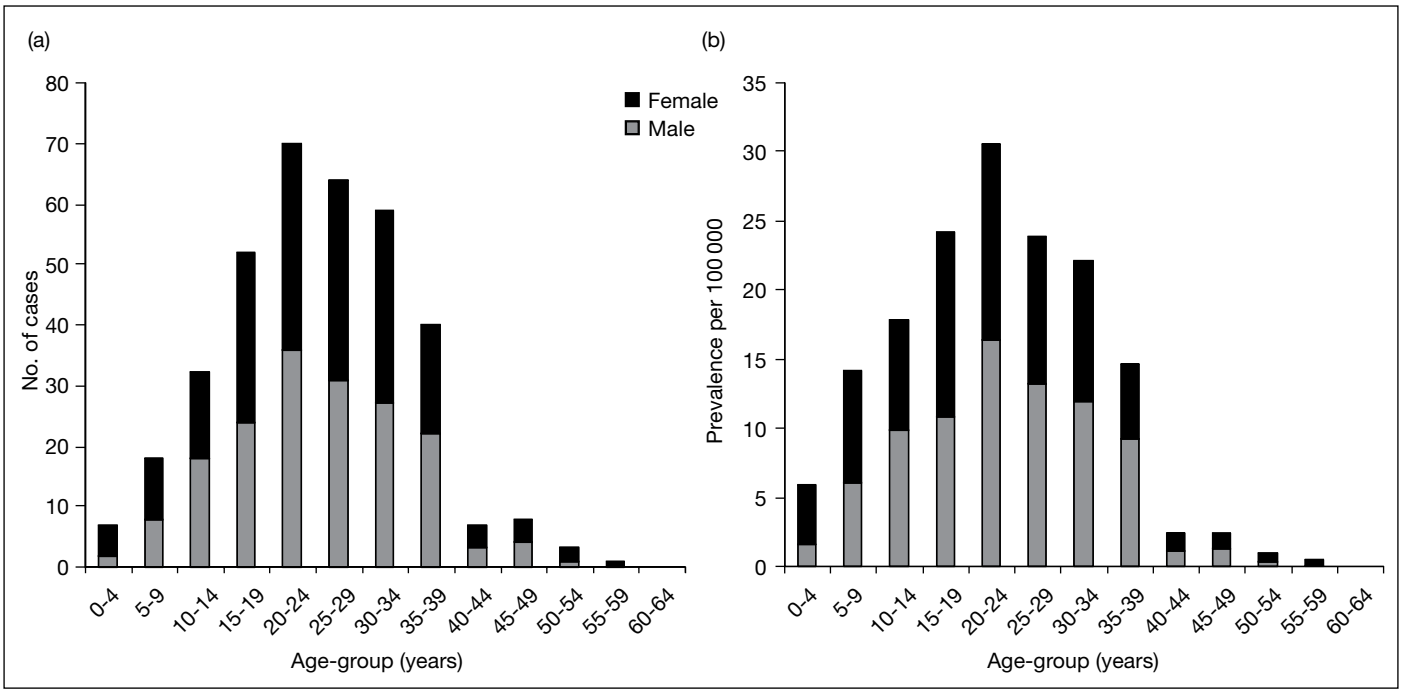

FIG 1. Thalassaemia major: (a) number of cases and (b) population-based prevalence in different age-groups

failure) become the leading cause of death. Parenteral deferoxamine was available in Hong Kong in 1970s and significantly reduced patient mortality.[5] To gauge chelation adequacy and as a surrogate for heart iron, serum ferritin is the cheapest and most convenient means of monitoring. It is checked quarterly in the clinics, and the current median ferritin level among all TM cases in Hong Kong is 3664 (range, 235-51 789; normal range, 52-738) pmol/L. Unfortunately, serum ferritin level fluctuates with inflammation, hepatitis and the time of the day. It also correlates better with liver rather than cardiac iron.[6] In the 1990s, liver iron was commonly adopted as surrogate marker of cardiac iron and chelation adequacy. In Hong Kong, it was only assessed by liver biopsies, which were invasive, and require complex biochemical analysis with limited reproducibility.[7] Liver biopsies are now obsolete in TM cases, except for histological assessments of viral hepatitis.[7] Neither ferritin nor liver iron show significant correlations with cardiac iron as measured by magnetic resonance imaging (MRI).[8] The latter is the only independent predictor of heart failure and cardiac death.[9]

The development of a standardised T2* MRI assessment of cardiac iron was a landmark in thalassaemia management. A lower MRI reading in milliseconds (ms) indicates more cardiac iron (normal, >20 ms; high risk of death, <10 ms).[9] As part of an international effort, the MRI scanner in Prince of Wales Hospital was calibrated against the international standard in 2006.[10] Later, all TM cases in Hong Kong were offered scanning under the auspices of the Children's Thalassemia Foundation (HKCTF). Among 180 adult patients scanned and reported, the median T2* MRI level of the heart was 19.3 (range, 3.3-63.5) ms and that of liver was 3.1 (range, 1.0-31.8; normal, <6.3) ms. Inadequate chelation was therefore common, with only half of patients having a normal cardiac T2*; and 26% and 14% of cases had severely abnormal MRI cardiac T2* (<10 ms) and liver (<1.6 ms) T2* levels, respectively.[11] Considerable iron accumulation was also demonstrated in endocrine organs. Both heart and endocrine haemosiderosis correlated with organ dysfunction.[12,13] Clearly, subcutaneous deferoxamine-based chelation did not completely prevent cardiac haemosiderosis and premature mortality. Nonetheless, in young patients and for historical reasons it was still the first-line chelation therapy.

Oral deferiprone can reduce cardiac iron, leading to prevention and reversal of heart failure.[14] In Hong Kong, the drug was licensed in 2005.[7] The use of oral deferiprone (either as monotherapy or in combination with nocturnal subcutaneous deferoxamine)[15] resulted in a dramatic reduction in cardiac haemosiderosis and ferritin levels. With the advent of combination therapy, 13% of Hong Kong TM cases now have ferritin levels within normal range. Epidemiological experience from Italy, England, and Cyprus suggests that MRI-directed deferiprone therapy could reduce cardiac iron and TM mortality.[16-18] This was supported by our local data.[15] A 3-year reassessment MRI (HKCTF scheme) showed improvement among all 84 of the 90 previously poorly chelated adult patients (2 died of heart failure, 4 refused re-scan). The percentage of very poor T2* MRIs (<10 ms) fell by half. However, agranulocytosis is a life-threatening side-effect of deferiprone, for which reason seven TM patients had to stop treatment. A third chelator, oral deferasirox was introduced in 2008 after extensive safety and efficacy testing.[19,20] Deferasirox monotherapy showed promise in reducing ferritin levels as well as liver and heart iron after prolonged treatment.[21] However, the cost (up to 10 times that of deferiprone or deferoxamine) remains prohibitive, and it is contra-indicated in patients with renal impairment. Survival benefit data are also pending. It is currently used in Hong Kong in very young patients (age <6 years), poorly chelated patients with contra-indication to deferiprone, as well as those who self-finance the treatment or enter clinical trials. At present chelation for TM cases in Hong Kong involves subcutaneous deferoxamine (30%), oral deferiprone (17%), combination deferiprone and deferoxamine therapy (48%), and oral deferasirox (n=5%).

Organ damage

Since iron deposit and organ damage is cumulative, in TM population the prevalence of some organ failures increases with age. Cardiac failure is the most important cause of death in TM. A low cardiac T2* MRI is the only predictor for future heart failure and cardiac deaths.[22] Among the 180 patients surveyed in 2006, the prevalence of low ejection fraction (EF) [<55%] was 19%, while 34% of the cases also had a history of heart failure.[12] Among the 90 patients with abnormal T2*MRIs (<20 ms), the median EF was only 59%. With aggressive chelation, this improved to 68% (P<0.001). Only eight patients still had EFs below 55%, seven of whom showed an improving trend. Two patients died of heart failure (cardiac T2*MRIs being 3.5 ms and 4.3 ms) shortly after their first assessment.

The prevalence of endocrine failure was also high in this population. Diabetes mellitus occurs in up to 25% of adults with TM and is rapidly emerging as the most important cause of morbidity.[11] Such a high prevalence may reflect inadequate chelation at younger ages, since established pancreatic damage is less reversible than cardiac damage, even with aggressive chelation. Hypogonadism is prevalent among older patients and half of all adult male and female patients are on hormone replacements. Younger patients, however, had normal gonadal function, weight and stature, and were physically

indistinguishable from the normal population. Recently, two Hong Kong women with TM successfully gave birth. Other endocrinopathies such as hypothyroidism (20%) and hypoparathyroidism (16%) were less common.[11]

Osteoporosis is highly prevalent in these patients. In a dual-energy X-ray absorptiometry scan screening of 62 adult TM cases, the median vertebral Z score was -1.93 (range, -0.13 to -3.84), while the median hip Z score was -1.79 (range, -0.32 to -3.87).[23] All Z scores fell with age indicating ongoing bone loss. Osteoporosis and osteopenia were diagnosed in 29% and 37% of all Queen Mary Hospital TM cases, respectively; similar findings were also reported from Tuen Mun and Prince of Wales hospitals.[23] Among multiple risk factors, reduced vitamin D levels and hypogonadism are correctable causes of bone loss.[24] Supplements of calcium and vitamin D are recommended. For patients with osteoporosis, additional treatments with standard weekly or monthly bisphosphonates are useful.[25] Strontium has not been used to treat local TM patients.

Infection

With the implementation of nucleic acid testing for viral DNA, the risk of transfusion-related infection for blood products in Hong Kong has been reduced to 1 in 5 million for hepatitis C virus (HCV), 1 in 1 million for human immunodeficiency virus (HIV), and 1 in 11 000 for hepatitis B virus (HBV) [written communication, CK Lee, Hong Kong Red Cross Blood Transfusion Service]. A total of 59 TM patients tested positive for HCV antibody carriage (age range, 13-49 years). It is known that up to 30% of HCV antibody carriers may be non-viraemic,[26] and have had no evidence of hepatitis on biopsy.[27] For non-viraemic TM patients, HCV antiviral treatment is not necessary, but monitoring for HCV recrudescence and liver cancer is advisable.[28] In young Hong Kong TM patients with HCV viraemia and active hepatitis, the response to a combination treatment of ribavirin and pegylated interferon was good.[29] Since 1999, no more transfusion-related HCV has been reported among TM patients in Hong Kong. Only six patients (age range, 22-49 years) were HBV surface antigen

TABLE. Numbers of thalassaemia major patients in Hong Kong succumbing to various causes

Year*	Heart failure	HSCT†	Infection	Renal failure	Cancer	Suicide	Stroke	Total (all causes)
95-97	7	4	1	0	1	0	0	13
98-00	8	2	3	0	0	0	0	13
01-03	7	1	0	1	1	0	0	10
04-06	4	0	1	1	0	0	1	7
07-09	3	0	0	1	0	1	0	5
Total	29 (61%)	7 (15%)	5 (10%)	3 (6%)	2 (4%)	1 (2%)	1 (2%)	48

* Secular years from 1995 to 2009

† HSCT denotes haematopoietic stem cell transplantation

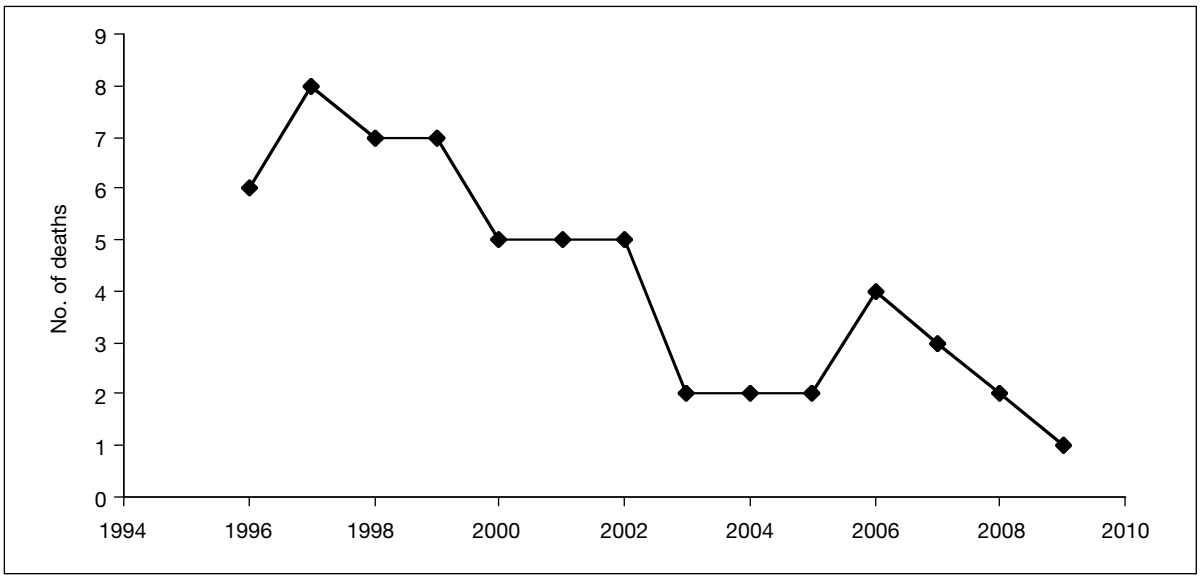

FIG 2. Deaths in thalassaemia major patients in Hong Kong: 1996 to 2009

(HBsAg) carriers. No new TM HBV carriers were reported since the advent of universal vaccination in Hong Kong lifebirths in 1988. The HBsAg carriage rate was 2.7% in TM cases aged older than 22 years. This was consistent with the background prevalence rate, and unlikely to be related to local blood transfusions. There was one reported TM case of transfusion-related HIV. This occurred prior to the era of screening blood products by nucleic acid testing.[30]

There was a considerable frequency of *Klebsiella* sepsis in deferoxamine-treated TM patients in Hong Kong.[31] *Campylobacter* infection has also been reported. Both are ferrophilic organisms and can cause life-threatening infections and abscesses. In TM patients, there is also an increased prevalence of haemolytic anaemia-related gallstones, acute cholecystitis, cholangitis, and even liver abscesses.[32] *Yersinia* infection was commonly reported in Italian and Greek TM cases, but is seldom encountered locally.

Mortality

A survey in 1999 showed that heart failure, HSCT, and sepsis were the three leading causes of mortality in TM patients.[5] An updated survey of mortality from 1996 to 2009 revealed that heart failure (61%), HSCT (15%), and sepsis (10%) remained the main causes of death (Table). The risk-benefit ratio of HSCT in young thalassaemia patients is debatable, and depends on donor availability, age, iron load, organ damage, and HSCT expertise.[33] Encouragingly, in TM patients there has been a steady decline in the crude incidence of death (Fig 2). There is also suggestion that better chelation, HSCT, and infection control has reduced the traditional causes of death. With increasing age, other causes of mortality (eg renal failure secondary to diabetes mellitus) may begin to emerge.

Social challenges and conclusions

Reduced life expectancy, the need for regular blood-taking follow-ups, and daily medications (including injections), as well as retardation in growth and sexual developments (particularly in earlier cohorts) impose huge personal challenges to TM patients and their families. With improved treatment, the external appearance of younger TM cases can be indistinguishable from normal children and adults. Historically, disruption to schooling and employment could be prohibitive. Such difficulties can be alleviated by increasing weekend and evening cross-matching and transfusions. Today, many TM patients in Hong Kong are able to enjoy a full education, career, marriage and family life. This is a tribute to the 0.2 million annual blood donors in Hong Kong, our safe blood supply, the efficiency of our public hospital care system, and the dedication of the numerous medical and nursing colleagues who provide lifelong care for affected patients. With increasing age, more TM patients are transferred to adult units. A redistribution of resources, plus a readjustment of patient and parent expectations, has to follow. Novel approaches such as the establishment of special transfusion centres need to be explored. Medical professionals will continue to work closely with the patient and parent groups to achieve a continuously improving quality of life for these individuals.

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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. Leung KY, Lee CP, Tang MH, et al. Cost-effectiveness of prenatal screening for thalassaemia in Hong Kong. Prenat Diagn 2004;24:899-907.
3. Lee AC, Wong KW, So KT, Cheng MY. Why are thalassaemia patients born when prenatal screening is available? Hong Kong Med J 1998;4:121-4.
4. Ho HK, Ha SY, Lam CK, et al. Alloimmunization in Hong Kong southern Chinese transfusion-dependent thalassemia patients. Blood 2001;97:3999-4000.
5. Li CK, Luk CW, Ling SC, et al. Morbidity and mortality patterns of thalassaemia major patients in Hong Kong: retrospective study. Hong Kong Med J 2002;8:255-60.
6. Cohen AR. New advances in iron chelation therapy. Hematology Am Soc Hematol Educ Program 2006:42-7.
7. Ha SY, Chik KW, Ling SC, et al. A randomized controlled study evaluating the safety and efficacy of deferiprone treatment in thalassemia major patients from Hong Kong. Hemoglobin 2006;30:263-74.
8. Anderson LJ, Holden S, Davis B, et al. Cardiovascular T2-star (T2*) magnetic resonance for the early diagnosis of myocardial iron overload. Eur Heart J 2001;22:2171-9.
9. Pennell DJ. T2* magnetic resonance and myocardial iron in thalassemia. Ann N Y Acad Sci 2005;1054:373-8.
10. He T, Kirk P, Firmin DN, et al. Multi-center transferability of a breath-hold T2 technique for myocardial iron assessment. J Cardiovasc Magn Reson 2008;10:11.

11. Au WY, Lam WW, Chu W, et al. A T2* magnetic resonance imaging study of pancreatic iron overload in thalassemia major. Haematologica 2008;93:116-9.
12. Au WY, Lam WW, Chu WW, et al. A cross-sectional magnetic resonance imaging assessment of organ specific hemosiderosis in 180 thalassemia major patients in Hong Kong. Haematologica 2008;93:784-6.
13. Lam WW, Au WY, Chu WC, Tam S, Ha SY, Pennell D. One-stop measurement of iron deposition in the anterior pituitary, liver and heart in thalassemia patients. J Magn Reson Imaging 2008;28:29-33.
14. Pennell DJ, Berdoukas V, Karagiorga M, et al. Randomized controlled trial of deferiprone or deferoxamine in beta-thalassemia major patients with asymptomatic myocardial siderosis. Blood 2006;107:3738-44.
15. Ha SY, Mok AS, Chu WC, et al. A practical chelation protocol based on stratification of thalassemic patients by serum ferritin and magnetic resonance imaging cardiac T2*. Hemoglobin 2009;33:323-31.
16. Borgna-Pignatti C, Cappellini MD, De Stefano P, et al. Cardiac morbidity and mortality in deferoxamine- or deferiprone-treated patients with thalassemia major. Blood 2006;107:3733-7.
17. Telfer P, Coen PG, Christou S, et al. Survival of medically treated thalassemia patients in Cyprus. Trends and risk factors over the period 1980-2004. Haematologica 2006;91:1187-92.
18. Modell B, Khan M, Darlison M, Westwood MA, Ingram D, Pennell DJ. Improved survival of thalassaemia major in the UK and relation to T2* cardiovascular magnetic resonance. J Cardiovasc Magn Reson 2008;10:42.
19. Cappellini MD, Cohen A, Piga A, et al. A phase 3 study of deferasirox (ICL670), a once-daily oral iron chelator, in patients with beta-thalassemia. Blood 2006;107:3455-62.
20. Cappellini MD, Porter J, El-Beshlawy A, et al. Tailoring iron chelation by iron intake and serum ferritin: the prospective EPIC study of deferasirox in 1744 patients with transfusion-dependent anemias. Haematologica 2009;95:557-66.
21. Pennell DJ, Porter JB, Cappellini MD, et al. Efficacy of deferasirox in reducing and preventing cardiac iron overload in beta-thalassemia. Blood 2010;115:2364-71.
22. Kirk P, Roughton M, Porter JB, et al. Cardiac T2* magnetic resonance for prediction of cardiac complications in thalassemia major. Circulation 2009;120:1961-8.
23. Au WY, Kung AWC, Chan GC, Ha SY, Tam S, Liang R. High prevalence of osteoporosis / osteopenia and favorable one-year treatment response to oral alendronate, calcium and vitamin D supplements: a prospective study of 122 Chinese patients with beta thalassemia and hemoglobin H disease [abstract]. Blood 2002;100:235a.
24. Voskaridou E, Terpos E. Pathogenesis and management of osteoporosis in thalassemia. Pediatr Endocrinol Rev 2008;6 Suppl 1:86S-93S.
25. Leung TF, Chu Y, Lee V, et al. Long-term effects of pamidronate in thalassemic patients with severe bone mineral density deficits. Hemoglobin 2009;33:361-9.
26. Sookoian S, Castaño G. Evaluation of a third generation anti-HCV assay in predicting viremia in patients with positive HCV antibodies. Ann Hepatol 2002;1:179-82.
27. Gamberini MR, Francesconi R, Fortini M, et al. HCV and HGV infection, iron overload and liver disease in multitransfused patients with thalassaemia and persistently normal or abnormal transaminase levels. Pediatr Endocrinol Rev 2004;2 Suppl 2:259S-266S.
28. Puoti C. HCV carriers with persistently normal ALT Levels: not too much healthy, not true patients. Rom J Gastroenterol 2004;13:329-32.
29. Li CK, Chan PK, Ling SC, Ha SY. Interferon and ribavirin as frontline treatment for chronic hepatitis C infection in thalassaemia major. Br J Haematol 2002;117:755-8.
30. HIV – From epidemiology to diagnosis. HKSAR Government website: http://www.info.gov.hk/aids/pdf/g104htm/1.1.htm. Accessed Dec 2010.
31. Chung BH, Ha SY, Chan GC, et al. *Klebsiella* infection in patients with thalassemia. Clin Infect Dis 2003;36:575-9.
32. Au WY, Cheung WC, Chan GC, Ha SY, Khong PL, Ma ES. Risk factors for hyperbilirubinemia and gallstones in Chinese patients with b thalassemia syndrome. Haematologica 2003;88:220-2.
33. Li CK, Lee V, Shing MM, Leung TF. Haematopoietic stem cell transplantation for thalassaemia in Chinese patients. Hong Kong Med J 2009;15(3 Suppl 3):39S-41S.