Management and clinical outcomes of transfusion-dependent thalassaemia major in an Australian tertiary referral clinic

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ABSTRACT

Objective: To evaluate the management, clinical outcomes and adherence to chelation therapy in adult transfusion-dependent patients with thalassaemia major.

Design, setting and participants: We reviewed all transfusion-dependent adults with thalassaemia major ($n = 44$) attending the Haematology Department at the Prince of Wales Hospital, Sydney, in 2005. Data were collected retrospectively (2000–2005) and prospectively (2005) for cross-sectional clinical audit from clinical reviews, patient questionnaires, pharmacy dispensing records and routine laboratory investigations.

Main outcome measures: Iron overload and its complications; complications of transfusion; adherence to subcutaneous and oral chelation therapy (expressed as a percentage based on the ratio of the amount dispensed to the prescribed dose).

Results: The prevalence of diabetes mellitus was 18%; hypothyroidism, 16%; hypogonadism, 32%; cardiomyopathy, 9%; and osteopenia/osteoporosis, 83%. Serological evidence of exposure to hepatitis C and hepatitis B was present in 41% and 14% of patients, respectively, and 23% of patients had active hepatitis C infection. Predictors of complications included increasing number of years of transfusion, increasing age, coprescription of desferrioxamine and deferiprone, and poor adherence to desferrioxamine treatment. There was a wide range of adherence to therapy with desferrioxamine (0–100% of prescribed dose; mean, 46%; median, 49%) and deferiprone (29%–214% of prescribed dose; mean, 117%; median 112.5%).

Conclusion: The health outcomes in our patients were similar to or better than those of patients in other cohorts, but, despite the availability of effective chelating agents, our patients had marked iron overload and a high incidence of complications.

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Thalassaemia major is characterised by inadequate globin chain synthesis, leading to ineffective erythropoiesis, severe anaemia and chronic disease in adulthood. Red cell transfusions are administered every 3–5 weeks from childhood in order to prolong survival and reduce extramedullary haematopoiesis. Unfortunately, transfusion leads to iron overload, transfusion-transmitted infections and red-cell antibody production. Progressive iron deposition can result in diabetes mellitus, hypothyroidism, hypogonadism, hepatic cirrhosis and cardiac complications, including arrhythmias and congestive cardiac failure. In one contemporary study of an Italian cohort of patients offered optimal iron chelation therapy, 68% lived to the age of 35 years.[1]

Iron chelators in current clinical use include subcutaneous or intravenous desferrioxamine, oral deferiprone and oral deferasirox. In a substantial proportion of patients in routine clinical practice, adequate control of tissue iron levels is not achieved, despite clinical trials demonstrating this to be possible.

Desferrioxamine is most commonly self-administered as a subcutaneous infusion over 8–10 hours, 3–7 nights weekly, while oral deferiprone is approved for use in Australia for patients in whom chelation with desferrioxamine has been inadequate or intolerable. A small risk of agranulocytosis associated with deferiprone therapy necessitates weekly neutrophil counts at the initiation of therapy.

The Haematology Department at the Prince of Wales Hospital (a tertiary referral hospital) in Sydney manages a cohort of 44 adult patients with thalassaemia. We present here the results of an audit undertaken to quantify their health outcomes and examine adherence to chelation therapy.

METHODS

Patients

Forty-four adult patients (≥ 18 years of age) who were receiving regular blood transfusions for thalassaemia or a related haemoglobinopathy in 2005 were included in our study, which was undertaken before the availability of oral deferasirox.

Pharmacy dispensing records

Pharmacy dispensing records for desferrioxamine and deferiprone for 12 consecutive months (October 2004 to October 2005) were reviewed. The hospital pharmacy is the only source of these medications. The "percentage dispensed", a measure of adherence, is calculated from the ratio of the amount dispensed to the prescribed dose over the 12-month period. Appropriate adjustments were made for prescribed dose modifications (eg, during pregnancy).

Patient questionnaire

A written questionnaire seeking information on patient-reported compliance with chelation therapy, reasons for non-compliance, side effects and general life activities was completed by all patients in October 2005. Patients were assured that their prescribing clinician would not have access to their individual responses.

Clinical parameters

The records of all 44 patients were examined to obtain the following information from January 2000 to December 2005: quarterly serum ferritin levels; results of gated heart pool scan with dobutamine stress; bone mineral densitometry measurements; hepatitis B and C and HIV serology and viral loads; the results of tests for autoantibodies and alloantibodies; comorbid conditions; and prescribed doses of chelators.

Statistical methods

Exploratory statistical modelling with linear regression, univariate logistic regression and χ^2 tests was used to determine the likelihood of a statistically significant relationship between outcomes and predictors. Patients were stratified into quartiles according to the percentage of desferrioxamine dispensed.

1 Reasons for non-compliance with desferrioxamine treatment*

Reason	Proportion of patients
Too busy	35%
Local reaction	26%
Painful injection	19%
Too tired	12%
Forgetfulness	12%
Social reasons	12%
Inadequate supply	12%

* Some patients gave more than one reason. ◆

2 Transfusion-associated complications

	Patients aged 20–29 years ($n = 21$)	Patients aged 30–54 years ($n = 23$)	P
Diabetes mellitus	1	7	0.02
Hypothyroidism	2	5	0.27
Hypogonadism	4	10	0.05
Cardiac disease	2	2	0.92
Cardiac and/or endocrine complications	5	15	0.02
Hepatitis B	3	3	0.90
Hepatitis C	3	15	< 0.001
Alloantibodies	5	6	0.86
Autoantibodies	2	6	0.05

Ethics approval

Approval was obtained from the hospital's Human Research Ethics Committee before the questionnaire was distributed.

RESULTS

Demographics

All of the current transfusion-dependent thalassaemia patients (20 men and 24 women) completed the questionnaire. Thirty-nine patients (88%) had a diagnosis of β-thalassaemia major and had been transfused for a mean of 30 years (SD, 13 years; range, 19–46 years). Other subjects included patients who had been commenced on a regular transfusion regimen because of sickle cell disease (two patients; mean, 13.5 years of regular transfusion); sickle cell β-thalassaemia compound heterozygosity (one patient; 29 years of transfusion); and thalassaemia intermedia (two patients; mean, 8 years of transfusion).

The mean age at the time of the audit was 31 years (range, 20–54 years). The majority of patients (31 [71%]) were of Greek or Cypriot ethnicity, and the remainder were Italian (7), Vietnamese (2), Lebanese (1), Indian (1), Indonesian (1) and Australian Aboriginal (1).

Fifteen patients had offspring. Seven of 20 men (35%) had fathered children, and eight of 24 women (33%) had had successful pregnancies. Three women required assisted reproductive services because of hypogonadism.

The majority of patients (38 [86%]) were gainfully employed. Twenty-four (55%) were in full-time paid employment, eight (18%) were employed part-time, four (9%) had full-time responsibility for the care of children, and one (2%) was a full-time university student.

Use of chelating agents

Subcutaneous desferrioxamine infusion was prescribed for 43 patients, but the percentage dispensed was highly variable (mean, 46%; median, 49%; range, 0–100%). Only five patients (12%) collected at least 90% of their prescribed dose, and six patients (14%) did not collect any desferrioxamine during the 12-month period. Reasons given for missing doses are summarised in Box 1.

Oral deferiprone was prescribed for 18 patients, with desferrioxamine coprescription in 17. The mean percentage of deferiprone dispensed was 117% (range, 29%–214%). Ten patients were collecting more than their actual prescribed dose by filling prescriptions more often than intended and then obtaining renewal prescriptions (range, 110%–214%). Those whose deferiprone dispensing was over 110% had low desferrioxamine dispensing. The most common reason cited for non-compliance with deferiprone therapy was forgetfulness (50%).

No patients suffered from neutropenia (neutrophils $< 1.5 \times 10^9$/L), agranulocytosis (neutrophils $< 0.5 \times 10^9$/L) or clinically significant arthropathy.

Complications

Transfusion-related complications in younger and older age groups are summarised in Box 2. The prevalence of diabetes mellitus was 18%; hypothyroidism, 16%; and hypogonadism, 32%. Four patients (9%) had significant cardiac disease, including poor ejection fraction, dilated cardiomyopathy and arrhythmias. Osteopenia or osteoporosis was present in 33/40 patients (83%) (four patients did not attend for their bone mineral density test).

Increasing age was predictive of diabetes mellitus ($P = 0.02$) and hypogonadism ($P = 0.05$). The cumulative presence of endocrine and cardiac complications was associated with increase in the number of years of transfusion (odds ratio [OR] [≥ 30 years v 0–29 years], 1.3 [95% CI, 1.1, 1.6]; $P = 0.002$) and increasing age (OR [≥ 30 years v 18–29 years], 1.1 [95% CI, 1.0, 1.3]; $P = 0.02$). There was an inverse association between endocrine and cardiac complications and adherence to chelation therapy (P for trend = 0.02) and between endocrine and cardiac complications and prescription of desferrioxamine alone (OR, 0.2 [95% CI, 0.1, 0.9]; $P = 0.03$).

Serological evidence of exposure to hepatitis C was identified in 18 patients (41%). The presence of hepatitis C infection was related to increasing number of years of transfusion (OR, 1.1 [95% CI, 1.0, 1.2]; $P = 0.03$) and increasing age (OR, 1.2 [95% CI, 1.1, 1.4]; $P = 0.005$). Eight of 18 patients had cleared the hepatitis C virus spontaneously or with treatment. Hepatitis B infection had affected 6 patients (14%).

Twenty-one patients (48%) had mean serum ferritin concentrations of < 2000 μg/L over a 6-year period, and 23 (52%) had values > 2000 μg/L, including six with values > 4000 μg/L. There was no direct correlation between higher ferritin levels and the presence of iron overload complications.

Significant levels of red cell alloantibodies were present in 11 patients (25%), and eight (18%) had red cell autoantibodies.

Dispensing

There was an inverse relationship between desferrioxamine dispensing and mean ferritin levels in 2005 (linear regression coefficient [LRC], –27 [95% CI, –41.2, –13.4]; $P < 0.001$) (ie, for every 1% increase in desferrioxamine dispensing, there was a 27-unit reduction in serum ferritin value) and

3 Factors associated with desferrioxamine dispensing*

	Percentage desferrioxamine dispensed				
	0–24% (*n* = 14)	25%–49% (*n* = 8)	50%–74% (*n* = 12)	75%–100% (*n* = 9)	*P* (trend)
Mean serum ferritin level (in 2005)					< 0.001
0–2000 µg/L	3	5	6	7	
2001–4000 µg/L	7	3	6	2	
> 4000 µg/L	4	0	0	0	
Deferiprone prescription					< 0.001
Yes	9	5	3	0	
No	5	3	9	9	
Clinic attendance in previous 6 months					0.001
Yes	4	7	10	8	
No	10	1	2	1	
Discrepancy between self-reported use of medication and pharmacy records					< 0.001
< 10% discrepancy	3	2	8	5	
10%–50% discrepancy	2	2	4	4	
> 50% discrepancy	9	4	0	0	

* Figures represent number of patients. Data on the one patient not receiving desferrioxamine therapy are not included here. ◆

over a 6-year period (LRC, –22 [95% CI, –36.9, –7.2]; $P = 0.005$). Lower dispensing of desferrioxamine was associated with deferiprone coprescription (LRC, 34.9 [95% CI, 16.7, 53.1]; $P < 0.001$), with poor clinic attendance (LRC, 34.0 [95% CI, 14.5, 53.4]; $P = 0.001$) and with less accurate reporting on the questionnaire (LRC, 16.1 [95% CI, 22.1, 10.2]; $P < 0.001$) (Box 3).

DISCUSSION

Our results reflect routine clinical practice in a developed country and are valuable to define the current outcomes for local patients. To our knowledge, this is the first assessment of the relationship between adherence to desferrioxamine and deferiprone therapies in combination, and suggests that patients overuse deferiprone to reduce the need for desferrioxamine infusions. The major clinical issues relate to assessing and minimising iron overload complications.

The rate of symptomatic heart disease in our study (9%) was similar to rates reported in comparable age groups in Italy (6.8%)[1] and the United States (10%),[2] based on recent registry data. Our cohort also had a similar or lower incidence of specific endocrinopathies. The presence of diabetes, in particular, is a further physical and psychological burden, as it involves invasive daily monitoring and treatment, patient-controlled management and significant long-term sequelae. Compared with the US cohort, we had a greater number of patients who had mothered (33% v 8%) and fathered (35% v 13%) children.[2] This trend may reflect changing expectations of longevity and the availability of in-vitro fertilisation treatment.

The cumulative burden of transfusion contributes to iron-overload complications, as indicated by the correlation of increasing number of years of transfusion with age. It is interesting that assessment of only 1 year's compliance with therapy also correlated with complications. A longitudinal study from childhood is required to explore these relationships further, in particular whether certain periods are critical. Such a study could also document age of onset of complications and survival rates.

Transfusion-transmitted infections are another serious consequence of blood transfusions,[2] with implications for patients, their families and health care workers. Since rigorous testing was implemented in Australia in 1991, the risk of contracting hepatitis C, hepatitis B or HIV via blood products has been extremely low.[3] Ongoing hepatitis C infection was a clinically significant concern for 10 of our patients. Other risks associated with the blood supply continue to exist, such as transfusion reactions and antibody production. Ethnic minorities have varied red cell antigen phenotypes, and ideally the donor pool would match these phenotypes. This is an ongoing consideration as the ethnicity of thalassaemia patients in Australia shifts towards people of Asian and African descent.

Traditionally, iron overload has been assessed by serial serum ferritin measurements and liver biopsies. Ferritin level is a convenient measure, but correlates poorly with total body iron stores and cardiac iron overload.[4] Acknowledging the small size of our sample, the data confirmed that ferritin level did not predict complications. Magnetic resonance imaging (MRI) of liver and cardiac iron deposits appears to be the optimal modality to assess iron loading.[5] As cardiac disease is the leading cause of death in patients with thalassaemia,[1] measuring cardiac iron loading is important. The cost of MRI and difficulty of obtaining regular access to it are significant restrictions on iron load monitoring.

Our study demonstrated that adherence to chelation therapy was a major issue. Compliance rates among our patients were similar to those of other cohorts with thalassaemia[6,7] and chronic disease.[8] It was disappointing that few patients maintained over 90% adherence and the majority showed less than 50% adherence. The fact that failure to achieve adequate chelation is the principal determinant of survival[9] should provide the incentive for compliance.

In some countries, difficulty of access to iron chelating medications is a significant reason for non-compliance,[10] but in Australia this is not an issue. Our patients missed doses of desferrioxamine because of the duration and discomfort of the infusion. Higher adherence rates were identified for oral deferiprone, especially in patients with poor desferrioxamine adherence, suggesting that the mode of administration plays a major role.

Wider availability of oral medications is likely to improve adherence and subsequent health outcomes. The higher cost of newer oral agents may be offset by the reduced cost of complications resulting from poor adherence to desferrioxamine therapy.

Given the small size of our patient cohort, our results should not be generalised without caution. On the other hand, a strength of our study was the elimination of selection bias by including all patients treated at a single unit with uniform management policies.

Our "percentage dispensed" value provided an objective, quantitative measure of adherence. However, the assumption that all

the collected medication was administered may have led to an overestimation of adherence. Patients with a poor pharmacy dispensing record answered the questionnaire less accurately, overstating their medication use, and thus demonstrating the inaccuracy and bias of self-reporting.

CONCLUSION

Our data show that the health and life outcomes of Australian patients with thalassaemia major compare favourably with those of patients internationally. Improving adherence to treatment is likely to be the most important strategy for improving the lives of patients. In the future, oral therapy may play a more significant role.

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COMPETING INTERESTS

In 2006, Novartis Pharmaceuticals Australia provided a grant for Robert Lindeman to attend a meeting at which deferasirox and its role in the management of thalassaemia were discussed. In 2007, Orphan Australia sponsored his attendance at a similar meeting relating to the use of deferiprone.

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