

The clinical profile and outcome of children with transfusion-dependent thalassaemia in KwaZulu-Natal Province, South Africa: A 16-year retrospective review

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Background. The clinical presentation and the outcome of patients with transfusion-dependent thalassaemia (TDT) in the province of KwaZulu-Natal, South Africa, have not been previously reported.

Objectives. To document the clinical characteristics, treatment strategies, outcomes and complications from a case series of children with TDT.

Method. A retrospective chart review of the clinical hospital records, laboratory, and blood transfusion data of patients with beta thalassaemia was performed. Data on serum ferritin (SF) levels, magnetic resonance imaging (MRI) R2 and/or T2* radiological tests to assess the presence of iron overload were collated and analysed. Iron chelator medications and haematopoietic stem cell transplantation (HSCT) outcomes were reported.

Results. All the 12 children enrolled with TDT were of Indian descent. All patients had regular blood transfusion and iron chelation therapy (ICT). Four patients had iron overload diagnosed on SF, liver and cardiac MRI scanning. Most of the children in this study were either initiated or changed to oral deferasirox (DFX) during treatment follow-up. One child on parenteral iron chelation deferoxamine, with high SF levels, died. Four patients successfully underwent HSCT without complications and are in remission.

Conclusion. The study confirms that haemoglobin-level-driven blood transfusions with adequate chelation are possible in the public health service in South Africa. Close monitoring for iron overload is required, using a combination of SF and MRI scanning. Oral ICTs are the preferred agents for reducing iron overload. HSCT remains the treatment of choice for TDT when feasible.

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Beta thalassaemias are inherited genetic disorders characterised by reduced (beta⁺) or absent (beta⁰) beta globin chains expression resulting in decreased haemoglobin (Hb) synthesis and reduced production of red blood cells, leading to anaemia. Thalassaemia is an inherited genetic disorder.^[1] Thalassaemia is prevalent in previously malaria-prone parts of the world including Africa, Mediterranean countries, the Middle East, the Indian subcontinent and Southeast Asia. The total annual global incidence of symptomatic individuals with beta thalassaemia is estimated at 1 in 100 000 and that of carriers of the thalassaemia gene is about 1.5% of the global population (80 to 90 million people).^[2] Krause *et al.*^[3] reported that families with beta thalassaemia in Johannesburg, South Africa (SA), were mostly of Indian (Muslim and Hindu subgroup) and Mediterranean descent. In 2011, Winship and Beighton documented 12 patients under 13 years of age with homozygous beta thalassaemia major and 1 with heterozygous HbE/beta thalassaemia.^[4]

The clinical findings in infants with beta thalassaemia major are varied but may include failure to thrive, pallor, feeding problems, diarrhoea, cardiac failure, irritability and recurrent bouts of fever, progressive abdominal distension secondary to spleen and liver enlargement and skeletal changes. Children become symptomatic between 6 and 9 months of age when the haemoglobin switch from fetal haemoglobin (HbF) to adult haemoglobin (HbA) occurs.^[5] Thalassaemia major is suspected in infants younger than 2 years with severe microcytic anaemia, mild jaundice and hepatosplenomegaly. Thalassaemia intermedia presents at later age (>2 - 6 years) with similar but usually milder clinical findings.^[1,5]

Regular blood transfusion, optimal iron chelation, haematopoietic stem cell transplantation (HSCT) and monitoring for associated complications are essential principles in the treatment of thalassaemia major. According to the Thalassaemia International Federation (TIF) guidelines, the initiation of chronic transfusion for the management of transfusion-dependent thalassaemia is recommended when Hb is <7 g/dL on 2 occasions for >2 weeks apart after excluding all other contributory causes or if the following are present, irrespective of haemoglobin level, namely facial changes, poor growth, fractures or extra-medullary haematopoiesis.^[5] A transfusion regimen that maintains the pre-transfusion Hb level between 9 and 10.5 g/dL, reportedly promotes normal growth, allows normal physical activities and adequately suppresses bone marrow activity in most patients.^[6] Regular transfusion therapy leads to iron overload, necessitating iron chelation therapy (ICT), which is usually commenced after 10 - 12 red cell transfusions or when the serum ferritin (SF) level is >1 000 µg/L.^[5-7] In the absence of ICT, iron overload-related complications such as endocrine disorders, cardiac abnormalities and liver damage ensue.^[8,9] In a study of 382 patients with beta thalassaemia major treated at the Dubai Thalassaemia Centre, the frequency of complications from iron overload was between 1.8% and 52%.^[8] Iron status of chronically transfused patients can be assessed by invasive and non-invasive techniques. Serial measurements of SF remain a reliable and the easiest available method to evaluate iron overload and the efficacy of chelation therapy.^[6] Magnetic resonance (MR) techniques exist as non-invasive methods for assessing iron overload of liver MRI R2 (FerriScan) and cardiac MRI T2*.^[9]

Deferoxamine (DFO) is available for chronic iron overload. Owing to the challenges of parenteral administration, a proportion of patients are non-compliant, thus limiting its usefulness. Deferasirox (DFX) is a recently developed oral iron chelator for chronic iron overload.^[10] The compliance with DFX in the Evaluation of Patients' Iron Chelation (EPIC) study was reported to be >80%.^[11] In a phase II study involving 197 TDT patients with myocardial siderosis, iron chelation with oral DFX was non-inferior to intravenous DFO for removal of myocardial iron.^[12] HSCT is the only currently available curative option for patients with thalassaemia.^[13,14] Recent medical and surgical advances have improved the outcomes for bone marrow transplantation.^[15] Access to HSCT is a challenge to the population that needs the therapy the most.^[16]

The present study describes the clinical characteristics, treatment strategies, outcomes and complications of a case series of paediatric patients with TDT who presented to a quaternary hospital in Durban, SA.

Methods

We performed a retrospective chart review of children referred to Inkosi Albert Luthuli Central Hospital (IALCH), Durban, SA, with transfusion-dependent beta thalassaemia major or thalassaemia intermedia. This institution, a quaternary centre with electronic data keeping, accepts referrals from all private and public health centres for the province of KwaZulu-Natal (KZN). The study period reviewed was the 16 years from January 2003 to December 2018. All but one patient (case 1) was diagnosed within the study period (2003 - 2018).

We evaluated the electronic medical records of patients ≤ 12 years old with TDT. We excluded cases with significantly incomplete or unavailable data owing to lack of follow-up. We collected baseline data including ethnicity, gender, age, clinical features and mean haemoglobin at diagnosis. Results of routine monthly haemoglobin, urea, creatinine and serum alanine aminotransferase (ALT) levels from the National Health Laboratory Services data base that were performed at each presentation were collated to determine the trigger for transfusion, and presence or absence of renal and liver dysfunction. We obtained data on the frequency of blood transfusions for all enrolled patients from the South African National Blood Service.

We analysed data on SF levels taken quarterly, as well as magnetic resonance imaging (MRI) R2 and/or T2* radiological tests performed to assess the presence of iron overload. MRI testing for iron load was only available at the study centre during the latter part of the study period while the software interpretation of results was possible through private sponsorship. MRI radiological testing is not readily available in the public health sector currently.

We collated data on iron chelator medications that were routinely administered. DFO has been readily available within the SA public health sector but was associated with challenges relating to availability of the infusion pumps, as these were not provided by the Department of Health. For patients who did not have pumps, DFO infusions were limited to the days that they received their blood transfusions in the hospital facility. Oral DFX became available through Section 21 motivation of the non-essential drug process in 2005 and was only recently (2016) added to the essential drug list (EDL) for public hospital use.

Data were analysed using Stata version 13.0 software (StataCorp., USA). We employed descriptive analysis to analyse demographic data (age, gender and ethnicity), clinical characteristics and laboratory investigations. We employed Student's *t*-test and the χ^2 test for comparing the adverse effects of iron chelating agents. A *p*-value <0.05 was regarded as significant. Full ethical approval

was granted by the Biomedical Research Ethics Committee of the University of KwaZulu-Natal (ref. no. IRB BE 611/16).

Results

Of the 15 patients who were identified through the electronic data set with transfusion-dependent beta thalassaemia, 3 were excluded because of moving to another province, transferring to another haematology centre within the province, or inadequate data sets owing to loss to follow-up. Of the remaining 12 patients, 6 were male and 6 were female. The median (interquartile (IQR)) age at diagnosis was 2 (0.75 - 3) years and the median (IQR) age of the cohort at the end of the study was 15 (12 - 18) years. All patients in the cohort were of Indian ethnicity. Specific diagnoses included beta thalassaemia major in 9 (75%) cases, beta thalassaemia intermedia in 2 (16.7%) and a single case (8.3%) of haemoglobin E/beta thalassaemia as confirmed on haemoglobin electrophoresis. All 5 cases with a family history of thalassaemia were diagnosed at an earlier age (<1 year of age) compared with the rest of the cohort (median (IQR) age 3 (2 - 3) years). The median (IQR) haemoglobin at diagnosis was 5.7 (4.8 - 6.8) g/dL.

All patients had pallor, failure to thrive and hepatosplenomegaly at diagnosis. Five children presented with fever while 4 had abnormal skeletal changes (i.e. craniofacial anomalies and/or long bone changes). We accessed the records of subjects transitioned to the adult haematology clinic in the same hospital after their 12th birthday, with permission. The median duration of follow-up was 12.5 (IQR 9 - 15) years.

Treatment for thalassaemia and its related complications

All patients received regular red cell concentrate leucocyte-depleted blood transfusions at 3 - 5 weeks' interval, targeting pre-transfusion haemoglobin of 9.5 - 10.5 g/dL. The median (IQR) pre-transfusion haemoglobin of the cohort was 9.5 (8.6 - 10.6) g/dL (Table 1), comparable with the internationally recommended values of 9 - 10.5 g/dL.^[11]

Quantity of red blood cell transfusion

All patients were blood transfusion-dependent for 4 - 17 years, and the median (IQR) quantity of red blood cells given was 165 mL/kg (152 - 274). The median (IQR) transfusion iron intake was 117.5 mg/kg/year (107 - 197) or 0.3 mg/kg/day (IQR 0.25 - 0.5). Only one patient (case 11) had a higher mean transfusion iron intake (239 mg/kg/year/0.7 mg/kg/year) over 4 years (Table 1) correlating with high ferritin levels, abnormal liver MRI R2 (FerriScan) scan and cardiac MRI T2 scan (Table 2).

Iron chelation therapy

All 12 patients received iron chelating therapy to reduce iron overload over the duration of their follow-up (Table 1). ICT was initiated after 10 - 20 regular blood transfusions and/or SF level >1 000 μ g/L as per the available chelation medication (DXO/DFX) in the health facility. Seven (58.3%) patients in the cohort were initiated on parenteral ICT (DFO) then later changed to oral deferasirox in order to improve or reduce iron load as shown in Tables 1 and 2. Two patients (cases 2 and 11) who had iron chelation switch had high mean ferritin levels (1 806 μ g/L and 2 479 μ g/L, respectively) (Table 3), together with abnormal FerriScan and/or cardiac MRI T2 scans. The present study was not able to find conclusive evidence on the reasons for the iron chelation switch beyond the aim to improve or reduce iron load. Five patients who were treated with DFX from the beginning of chelation therapy had satisfactory SF levels of \sim 1 500 μ g/L or less. One patient (case 3), who died at 11 years of age, had high mean SF (3 080 μ g/L)

Table 1. Blood transfusions and iron chelation among transfusion-dependent thalassaemia cases, N=12

Case	Pretransfusion haemoglobin	Transfusion iron intake		DFO	DFO/DFX	DFX
	g/dL	RBC volume (median (IQR)), mL/kg	Iron intake (median (IQR)), mg/kg/day			
1	8.6	160 (136 - 182)	116 (95 - 130)	N	N	Y only
2	9.8	170 (100 - 250)	119 (77 - 176)	Y	N	Y - from DFO
3	9.5	120 (100 - 217)	84 (70 - 152)	Y - no pump	N	Y
4	8.4	267 (208 - 308)	197 (140 - 216)	N	N	Y only
5	10.4	152 (100 - 318)	107 (70 - 223)	Y - no pump	N	Y only
6	11.5	109 (40 - 193)	77 (28 - 236)	Y	N	Y - from DFO
7	9.4	248 (150 - 286)	174 (105 - 200)	N	N	Y only
8	9.3	274 (200 - 287)	192 (140 - 201)	Y - no pump	Y	Y only
9	10.6	281 (243 - 338)	197 (170 - 237)	N	N	Y only
10	8.4	158 (133 - 233)	110 (94 - 164)	N	N	Y only
11	11.2	329 (260 - 341)	239 (183 - 293)	Y - no pump	Y	Y - from DFO
12	9.1	154 (111 - 218)	109 (78 - 153)	Y - no pump	N	Y added

DFO = deferoxamine; DFX = deferasirox; RBC = red blood cell; IQR = interquartile range; Y = received the drug; Y - no pump = patient had no home pump; N = did not receive the drug or combination treatment; Y - from DFO = switched from DFO to DFX.

Table 2. Iron chelation therapy in transfusion-dependent thalassaemia patients

Case	Year of diagnosis	ICT commenced	Year	Iron chelation switch	Year
1	2001	DFX (private)	2005	No	-
2	2003	DFO	2005	DFX	2011
3	2004	DFO	2006	No	-
4	2004	DFX	2007	No	-
5	2004	DFO	2006	DFX	2007
6	2004	DFO	2006	DFX	2007
7	2005	DFX	2008	No	-
8	2008	DFX	2010	No	-
9	2010	DFX	2013	No	-
10	2010	DFX	2012	No	-
11	2011	DFO	2014	DFX	2016
12	2014	DFO	2015	DFX	2017

ICT = iron chelation therapy; DFX = deferasirox; DFO = deferoxamine.

but liver MRI R2 (FerriScan) and cardiac MRI T2 scanning were not performed owing to lack of resources during her follow-up period. Four patients were free from ICT after successful haematopoietic stem cell transplantation.

Haematopoietic stem cell transplantation

Paediatric bone marrow transplants were not performed in KZN in either the public or private health sectors. Patients were referred to Western Cape Province (Cape Town) for transplantation. As transplant bed availability is limited in the public health sector, priority is given to life-threatening conditions (e.g. malignancies and aplastic anaemia).

All patients with human leukocyte antigen (HLA) -matched siblings were eligible for transplantation. To identify a match, HLA typing was done routinely on all patients and their siblings. Patients who had a sibling match (match sibling donor) were referred for transplant. Matched unrelated transplants were not performed.

In all 4 patients who underwent HSCTs no serious complications were noted (Table 3). The average (IQR) age at transplantation was 8.75 (6 - 10.5) years. Timing of the transplant was affected by

Table 3. Outcomes of children undergoing haematopoietic stem cell transplant

N=4	DOB	Year of transplant	Age at transplant (years)	Complications post transplant	Outcomes of transplant
2	Sep. 2000	2014	14	Nil	Remission
5	Nov. 2003	2012	9	Nil	Remission
6	Apr. 2004	2011	7	Nil	Remission
11	Mar. 2010	2015	5	Nil	Remission

DOB = date of birth.

some of the following factors: arrangements made for specialised investigations (i.e. dry iron weight), optimisation of patients with intensive chelation, availability of beds in the transplant unit, availability of the family to travel to transplant unit and or availability of funds including medical aid coverage as well as private funding.

Adverse effects

Serum ferritin levels

The overall median (IQR) SF of the study population was 1 523 (1 037 - 1 807) µg/L. Four patients (33.33%) had SF of 1 000 - 1 500 µg/L and 5 patients (41.67%) had SF of 1 501 - 2 000 µg/L. Only one (8.3%) child each had mean SF >2 500 µg/L (patient 3) and <1 000 µg/L (patient 10) (Table 4).

MRI R2 (FerriScan)

Liver iron concentration (LIC) measured by MRI R2 (FerriScan) was completed in 9 of 12 patients between 2013 and 2018 (Table 4). Access to MRI was not available prior to this. Seven liver MRI R2 scans were normal or optimal. Two patients (cases 8 and 11) had abnormal FerriScans with median ferritin levels of 1 807 µg/L and 2 479 µg/L, respectively. Patient 8 developed a tubulopathy secondary to the oral chelator medication. Patient 11 had gastrointestinal intolerance to the oral chelator.

Cardiac T2 measurements

Cardiac T2 MRI scans were performed in 8 of the 12 cases (Table 4). They were abnormal in 3 of the 8 patients; for 2 patients (cases 2

and 11), abnormalities in either SF or FerriScans or both were also present. For the other patient (case 10), SF was normal at 876 µg/L and the repeat FerriScan changed from optimal to normal.

Liver function

None of the patients had hepatic damage or liver dysfunction, as assessed by ALT levels. The mean ALT level of the cohort was 22 U/L (range 20 - 40). Two patients (cases 5 and 12) had a period of elevated ALT which resolved. The infection screening for viral hepatitis for these cases was negative. Both children had normal MRI R2 FerriScans (Table 4).

Renal function

The cohort had normal renal function measured by serum creatinine. The mean serum creatinine was 35 mmol/L (range 27 - 42) (Table 3). One patient (case 8) developed a tubulopathy which was thought to be due to the oral iron chelator and has required ongoing phosphate supplementation.

Endocrine complications

We did not analyse these owing to lack of data. Monitoring growth, including height and weight, were inadequately documented. Calcium levels were performed but the lack of associated parathyroid and alkaline phosphate levels did not allow interpretation for possible hypoparathyroidism.

Follow-up

One patient died (case 3) and 9 patients transitioned to the adult haematology unit in the same hospital facility. The death occurred in a patient who was in private care and we were unable to determine the cause. Two patients (case 7 and 8) were still receiving regular blood transfusion and ICT in the paediatric haematology unit. The four patients who underwent HSCT achieved haematological remission.

Discussion

Regular blood transfusion therapy together with chelation therapy is the mainstay of treatment of beta thalassaemia in the present study population. These patients require substantially high volumes of blood

transfusion over time, which is not without risks such as blood-borne infection, allo-immunisation, and iron overload. The present study suggests that it is possible to provide regular, appropriate red cell transfusion therapy together with oral chelation therapy in the state health service in SA in keeping with the TIF guidelines.

There have been significant developments in the assessment of iron overload over time, including the use of MRI for measuring liver and cardiac iron load which are useful monitoring tools in the treatment of TDT. Serial measurement of SF levels still appears to be a valuable tool in monitoring iron load owing to its universal availability, especially in low-resource settings. In the present study, findings of SF levels, R2 MRI liver (FerriScan) and cardiac T2 scans were concordant in all but one case (case 10). In this case, the discordant result was corrected on repeat testing MRI R2 (FerriScan), indicating improvement in control of iron overload. In a study of 134 patients, Puliyel *et al.*^[17] reported that trends between SF and liver iron concentration (measured by MRI) might be discordant.

Most of the patients in our study were initiated or changed to oral DFX, possibly because of difficulties in administering parenteral iron chelator medication. Suboptimal iron chelation as demonstrated by raised SF levels enforced the change. It could be assumed but not proven that poor (or no) adherence contributed to these findings, as seen in other studies.^[10,18] There should be emphasis on ensuring adherence to ICT if a patient with thalassaemia requires regular blood transfusions. Patients should be monitored for complications of the disease as well as those that could develop because of chelation therapy. Where available, HSCT is safe and the most effective option in the management of TDT. No serious complications were seen post transplantation. These patients did not require blood transfusions or ICT post transplantation. While monitoring for long-term complications post transplant is necessary, these occur less frequently than in TDT. Transplant patients have notably improved quality of life as evidenced by fewer hospital visits. A substantially reduced cost for medical care post transplant has been observed.^[5] Better medical care has decreased transplant-related mortality to less than 5% in young low-risk children transplanted from HLA-matched siblings.^[5] Studies report long-term overall survival and thalassaemia-free survival of 90 - 96% and 83 - 93%, respectively.^[15,16] However, finding suitable match-related donors for transplantation is difficult and not always available.

Table 4. Adverse effects and safety among the transfusion-dependent thalassaemia cases according to iron chelation therapy, N = 12

N=12	SF, µg/L	SF, IQR	MRI R2 (FerriScan)	Cardiac T2 MRI	Creatinine, mmol/L	ALT, U/L
DFO switched to DFX						
2	1 809	550 - 3 520	Normal	Abnormal	50	20
6	1 626	800 - 2 961	N/D	N/D	35	40
Intermittent DFO, then switch to DFX						
3	3 080	900 - 3 850	N/D	N/D	36	32
5	1 562	928 - 2 928	Normal	Normal	35	93
8	1 807	1 130 - 2 300	Normal	Normal	35	24
11	2 479	971 - 4 599	Abnormal	Abnormal	30	27
12	1 378	421 - 2 662	Normal	N/D	26	92
DFX only						
1	1 037	300 - 1 230	N/D	N/D	45	20
4	1 513	400 - 3 736	Normal	Normal	37	19
7	1 457	383 - 2 850	Normal	Normal	42	20
9	1 037	549 - 1 395	Normal	Normal	25	20
10	876	554 - 1 352	Normal	Abnormal	27	19

SF = serum ferritin; IQR = interquartile range; ALT = alanine transaminase; N/D = not done; DFO = deferoxamine; DFX = deferasirox.

Where possible, cord blood should be collected and stored as a potential source of stem cells should the sibling be a match. If sibling match is available, HSCT should be performed early, preferably by the age of 3 years.

In the present study, the diagnosis of beta thalassaemia was delayed, with a median (IQR) age at diagnosis of 24 (0.75 - 36) months. The clinical features and haematological indices of beta thalassaemia overlap with other conditions, namely iron deficiency anaemia,^[5,19] and therefore healthcare practitioners should have a high index of suspicion to avoid delays in diagnosis. A family history of thalassaemia is useful for early diagnosis but not always present. The clinical manifestations of beta thalassaemia are understood not only to result from the severity of beta globin gene mutations, but also the co-inheritance of modifying factors that alter the relative imbalance of alpha- and beta-globin chains together with their complications. Patients with the same beta globin genotype may have different clinical phenotypes.^[1,20]

Study strengths and limitations

This was a retrospective review and incomplete data sets and loss of clinical and laboratory data were expected. The electronic database of the institutions (Inkosi Albert Luthuli Central Hospital, National Health Laboratory Service and South African National Blood Service) ensured minimal loss of clinical, laboratory and transfusion data. The small sample size (N=12) compared with studies in other thalassaemia-endemic areas is acceptable as the condition is rare in this region. The median duration of follow-up of 12.5 years with detailed descriptions of each case provided reassurance in interpreting the data. Limited availability of MRI in the region resulted in some cases not having the study performed according to the frequency recommended by international thalassaemia guidelines.

Conclusion

The study confirms that haemoglobin-level-driven blood transfusions with adequate oral chelation therapy is possible in the public health service in SA. Close monitoring for iron overload using SF is essential. MRI R2 (FerriScan) and T2 MRI scanning are useful non-invasive tools for monitoring iron overload. There should be emphasis on ensuring adherence with ICT if a patient with thalassaemia requires regular blood transfusions. Oral ICTs are the preferred agents for reducing iron overload. Early HSCT, preferably by the age of 3 years, is the treatment of choice for TDT to obviate the need for regular blood transfusion and associated iron load. Where possible, cord blood from siblings should be collected and stored as a potential source of stem cells should the sibling be a match.

Declaration. The manuscript was submitted in partial fulfilment of the requirements for the MMed (Paed) degree.

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Author contributions. MTM, YG and PMJ designed and developed the study. MTM collected the data, performed analyses and prepared the manuscript. YG and PMJ supervised the study, and revised and edited the manuscript.

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