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Use of iron chelator therapy in Miri Hospital

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Abstract

Introduction: Globally, it'sestimated that more than 300 million people are Thalassemia trait carriers, with most of the population residing in South East Asia. Thalassemia is a heterogenous group of blood disorders which affects the production of haemoglobin resulting in decreased synthesis of α or β globin chains. The mainstay of treatment for thalassemia is regular blood transfusion. However, regular blood transfusions often lead to iron overload. Hence, iron chelating agents employed to remove excess iron in transfusion- dependent β-thalassaemia patients. The aim of this study is to analyse the prescribing trend and cost-effectiveness between iron chelators (Deferiprone, Deferoxamine, and Deferasirox) as well to evaluate the treatment efficacy between the iron chelators in reducing serum ferritin levels.

Methods: The analysis examined usage of iron chelators (Deferiprone, Deferoxamine, and Deferasirox) available in Miri Hospital from January 2016 until December 2017 to establish the prescribing trend of iron chelators in Miri Hospital. Information regarding the number of prescriptions, packs and cost of the drugs obtained through Pharmacy Information System

(PhIS). A patient level analysis obtained through PhIS used to examine the age, race and sex of the patients.

Results: Majority of the β-thalassemia patients on iron chelator therapy in Miri Hospital were Malay (64%), followed by Chinese which constituted 27% while the other races comprise another 9% of the patient base. Based on the data collected across both years (2016-2017), generally the iron chelator most commonly prescribed was Deferasirox (DFX), followed by Deferiprone (DFP) and lastly Deferoxamine (DFO).

Conclusion: Effective chelation therapy attained when iron chelators remove enough excess iron, equivalent to that accumulated in the body from transfusion. Hence, due to its high chelation efficacy and patient-friendly dosing regime, DFX remains the highest prescribed oral iron chelator in Miri Hospital.

Keywords*: Iron chelator therapy, transfusion dependent β-thalassemia, serum ferritin*

Introduction

Thalassemia is a heterogenous group of blood disorders which affect the production of haemoglobin resulting in a decreased or in the absence of synthesis of α or β globin chains (1). Thalassemia is one of the most common genetic disorders which afflict approximately 300 million people worldwide (2,3).Alike many other countries, thalassemia also poses a significant public health burden in Malaysia. Malaysia is an emerging country in South East Asia with a population of 32 million, which comprises of most of Malay (50.8%) and other ethnic groups, mainly Chinese (23.0%), indigenous people of Sabah and Sarawak (11.0%), Indian (6.9%), and other minority groups making up the remaining 8.3% of the population (2).

In the year 2014, there were 6,088 thalassemia cases registered with the Malaysian Thalassemia Registry, with the highest number of thalassemia cases from Sabah (2). Approximately 4.5%-6% of Malaysians are carriers of the β-thalassemia trait and an estimated 2.1 per 1,000 births affected annually, with an estimated 5,600 patients being transfusion dependent (5,6). β-thalassemia patients who are transfusion-dependent, require regular blood transfusions to survive and without adequate transfusion support, they would suffer several complications and a shorter life span (4). As a result of these regular transfusions, these population of patients often require iron chelator therapy to remove excess iron from accumulating and damaging vital organs such as the heart, liver, pancreas and pituitary glands (4).

Available iron chelation therapies include Deferoxamine (DFO), Deferiprone (DFP) and Deferasirox (DFX) (3,4,7). DFO was the first iron chelator introduced clinically and was the standard therapeutic option for thalassemia over the past 40 years (3,4,7).DFO is administered parenterally, either via the intravenous route or subcutaneous route (3,4,7).The recommended mode of administration for DFO is via slow subcutaneous infusion over 8-12 hours, using an infusion pump for a minimum of 5 days per week (3,4,7).The standard dosing

regimen used for children is 20-40 mg/kg/day and up to 50-60 mg/kg/day for adults (3,4,7). The main disadvantage of DFO therapy, is that it is expensive, and it must be administered parenterally which is uncomfortable and time-consuming, leading to issues with patient compliance (3,4,7).Due to difficulty in establishing long-term compliance to DFO therapy, the demand to develop an oral chelating agent became more apparent, hence, leading to the introduction of the first oral iron chelator, Deferiprone (DFP) in the market (3,4,7).The daily dose for DFP with the most body of evidence is 75 mg/kg/day in 3 divided doses (3,4,7).However, due to notable serious adverse events caused by DFP such as agranulocytosis and neutropenia, the novel oral iron chelator, Deferasirox (DFX) was developed. DFX is a once-daily oral monotherapy which is patient-friendly (3,4,7). Due to its long half-life, DFX confers 24 hours of protection from plasma labile iron (3,4,7).It was also the first iron chelator to be officially evaluated in the use of paediatric patients as young as 2 years old (3,4,7). Recommended dosing range for DFX is 10-30mg/kg/day (3,4,7).

Methods

Data was extracted from the Pharmacy Information System (PhIS) to examine the usage of iron chelators (Deferiprone, Deferoxamine, and Deferasirox) available in Miri Hospital over a 2-year period; 2016 and 2017. Data obtained was used to establish a prescribing trend of iron chelators in Miri Hospital. Furthermore, information regarding the number of prescriptions, stock keeping unit (SKU) and cost of the drugs obtained through PhIS to evaluate the cost-effectiveness of the iron chelator therapy prescribed. ATC code set by World Health Organization (WHO ATC) assigned to the corresponding medication based on generic name and drug class. Additionally, a patient level analysis obtained through PhIS used to examine the age, race and sex of the patients**.**

Results

Demographic

Data extracted from PhISshowed that there were 13 patients with β-thalassemia on iron chelator therapy in the year 2016, with these numbers increasing to 20 patients in 2017.Among the patients on iron chelator therapy in Miri Hospital (2016-2017), 64% of the patients were Malay, followed by Chinese (27%) while indigenous races comprise another 9% of the patient base as illustrated in Figure 1.

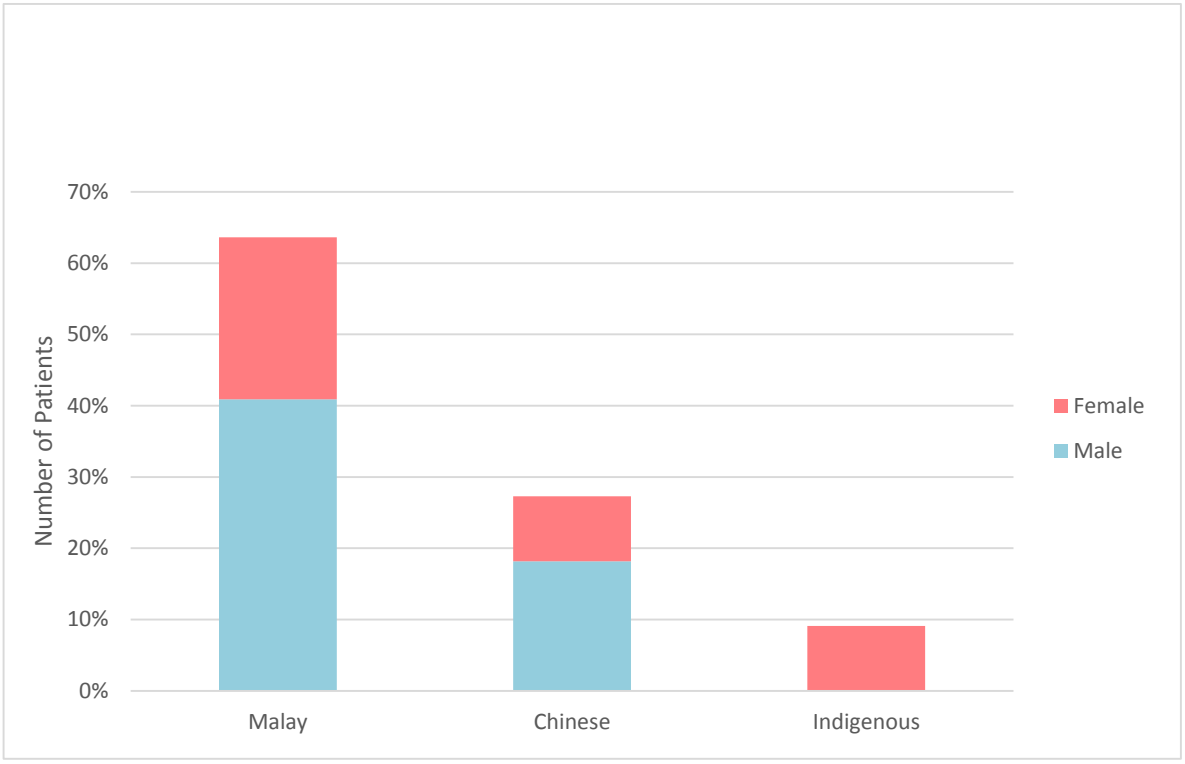

Figure 1. Patient demographics

Prescribing trend

As illustrated in Figure 2, majority of the patients were prescribed with DFX. Based on the data obtained, it can be observed that there is a notable increasing in trend of DFP being prescribed; 12% increment. In comparison, the iron chelator recording a reduction in prescribing trend was the combination DFO and DFP; 3% reduction. As patients further stratified into respective age groups, it was evident that DFX was the preferred iron chelator in patients younger than 20 years old.

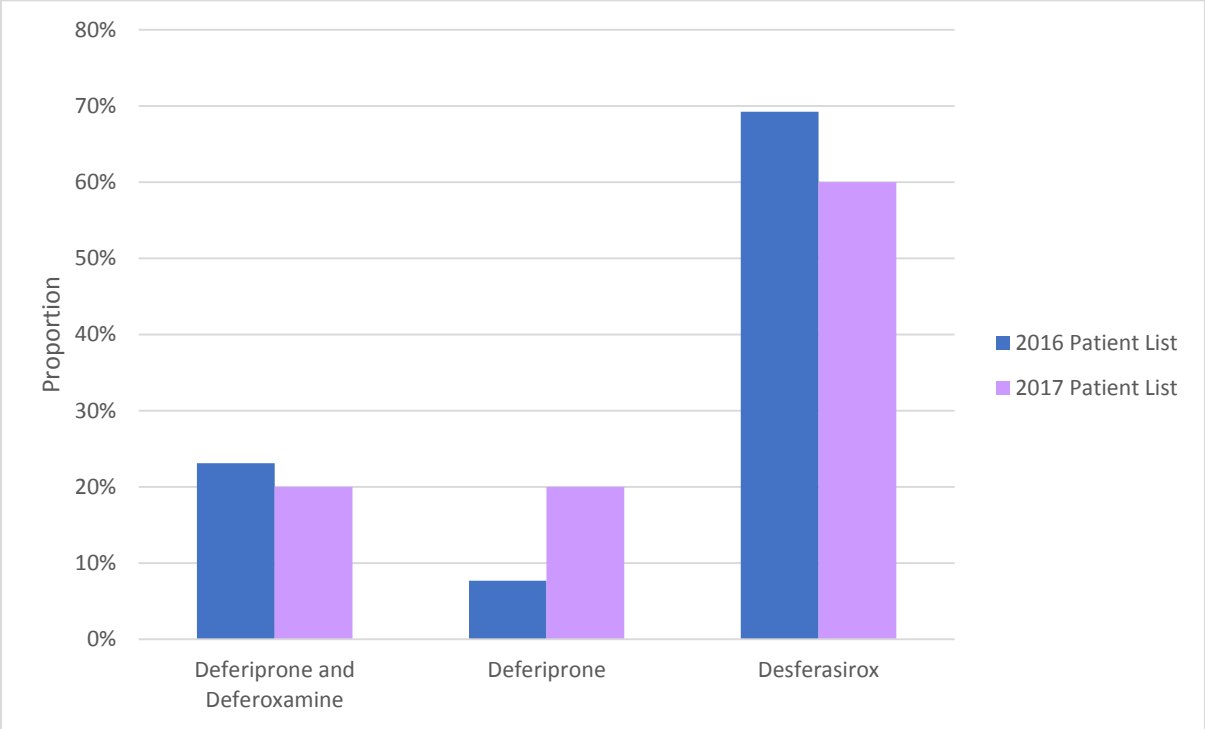

Figure 2. Proportion of patient receiving iron chelator therapy from 2016 to 2017

Table 1. Number and proportion of patient receiving iron chelator therapy according to age group

Age Group	2016			2017		
	Combination of DFO and DFP	DFP	DFX	Combination of DFO and DFP	DFP	DFX
< 10	0	0	4 (44.4%)	0	0	5 (55.5%)
10 - 20	1 (6.3%)	0	5 (31.2%)	1 (6.3%)	2 12.5%)	7 (43.8%)
>20	2 (25%)	1 (12.5%)	0	3 (37.5%)	2 (25%)	0

DFO: Deferoxamine; DFP:Deferiprone; DFX: Deferasirox

Table 2. Total expenditure of Miri Hospital for iron chelator therapy

ATC Code	Treatment	Total Expenditure (2016)	Total Expenditure (2017)
V03AC01 & V03AC02	Combination of DFO and DFP	RM 30,406.32	RM 20,512.17
V03AC01	DFP	RM 14.58	RM 1,720.44
V03AC03	DFX	RM 201,871.84	RM 320,824.18

DFO: Deferoxamine; DFP:Deferiprone; DFX: Deferasirox

Cost-effectiveness

Across both years (2016 &2017), there was an overall increasing trend of expenditure for both DFX monotherapy and DFP monotherapy as in Table 1. On the other hand, there was a reduction in the total expenditure spent on the combination therapy DFO and DFP.

Discussion

In Malaysia, optimal management of patients with transfusion dependent thalassemia remain a challenge for healthcare professionals due to limited accessibility and availability of oral iron chelator therapy (3,8). Less than 20% of patients receive adequate iron chelator therapy, with life expectancy significantly reduced due to complications which stem from iron overload (3,8).

The population who mainly affected by this autosomal recessive genetic disorder are mainly Malay and Chinese (1,5,6,9).It is estimated that 4.5-6% of these ethnic groups are carriers of this trait (1,5,6,9). This reflected in the data obtained from Miri Hospital showing that majority of the patient population with β-thalassemia on iron chelator therapy to comprise mainly of these ethnic groups.

From the prescribing trend in Miri Hospital, it was observed that oral iron chelators (DFP and DFX) are preferred compared to DFO due to ease of administration. DFO, being a subcutaneous infusion, long-term compliance is difficult to maintain due to patient-related factors such as inconvenience of the regime, pain and discomfort as well as cost of treatment. Furthermore, it has a short half-life; with chelation of iron only occurring during the time it is being infused and hence, leaving the patient with 12 or more hours without iron chelation.

On the other hand, the notable reduction in the number of patients on combination therapy (DFP & DFO) can be explained through a systematic review conducted by Fisher, showing that there is an increased rate of adverse events in patients being treated with DFP compared with DFO and in patients on combination therapy with DFP and DFO compared to DFO alone (4).

Despite DFX being significantly more expensive compared to DFO and DFP, DFX recorded the highest percentage in prescribing trend, possibly due to its high chelation efficacy at 27%, followed by DFO 13% and lastly DFP 7% (4).Aside from its high chelation efficacy, the long half-life conferred by DFX provides a longer coverage to chelate excess plasma labile iron (4).This enables it to be prescribed as a single daily dosing as compared to DFP which is usually a multiple daily dosing regimen. Hence, due to the simplicity in regimen, compliance rate to DFX treatment is notably higher compared to the other two iron chelators available.

Limitations

This study collects data from 13 β-thalassaemia patients in 2016 and 20 patients in 2017 from Miri Hospital. The races of patients studied comprise of Malay, Chinese and the Sarawak indigenous population. The small number of patients and the limited patient race studied may not be an accurate representation of the Malaysia population. Involvement of other tertiary hospitals throughout Malaysia may give a better picture of selecting iron chelators and the treatment results in the Malaysian population. In addition, the study results collected were from January 2016 till December 2017. Longer study duration may be required to reflect the true prescribing trend throughout the years.

Conclusion

Effective chelation therapy attained when iron chelators remove enough excess iron, equivalent to that accumulated in the body from transfusion. Hence, due to its high chelation efficacy and patient-friendly dosing regime, DFX remains the highest prescribed oral iron chelator in Miri Hospital.

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References

1. Pauzy LHM, Esa E, MokhriNM ,Yusoff YM , Jamaludin NA, Zakaria Z. Thalassemia Distribution Based on Screening Programs in the Population of the East Malaysian State of Sabah. J Blood DisordTransfus. 2018;9(1). Available from: https://www.omicsonline.org/peer-reviewed/thalassemia-distribution-based-on-screening-programs-in-the-population-of-the-east-malaysian-state-of-sabahp-98079.html [Accessed on 12th December 2018].
2. Yap YT, Suan MAM, Ismail CK, Chin SC, Khor CH, Abdullah SAW. Assessing Healthcare Providers' Knowledge of Deferasirox at District Hospitals in Kedah State, Malaysia. J Pharm Pract Community Med. 2017;3(4):240-5.
3. Viprakasit V, Chan LL, Chong QT, Lin KH, Khuhapinant A. Iron chelation therapy in the management of thalassemia: the Asian perspectives. Int J Hematol. 2009;90: 435-445.
4. Ministry of Health Malaysia. Management of Thalassaemia [Internet]. 2017 [cited 21 December 2018]. Available from: http://www.moh.gov.my/update2017/727.pdf.
5. Wong LP, George E, Tan JMA. Public perceptions and attitudes toward thalassaemia: Influencing factors in a multi-racial population. BMC Public Health. 2011,11:193. Available from: https://bmcpublichealth.biomedcentral.com/articles/10.1186/1471-2458-11-193 [Assessed on 18th December 2018].
6. Tan JMA, Lee PC, Wee YC, Tan KL, Mahali NF, George E, et al. High prevalence of Alpha- and Beta-Thalassemia in the Kadazandusuns in East Malaysia: Challenges in providing Eeffective health care for an indigenous group. J Biomed Biotechnol. 2010;706872.
7. Wu HP, Lin CL, Chang YC, Wu KH, Lei RL, Peng CT, et al. Survival and complication rates in patients with thalassemia major in Taiwan. Pediatr Blood Cancer. 2017;64: 135-8.
8. George E. Beta-Thalassemia Major in Malaysia, an on-going public health problem. Med J Malaysia. 2001;56(4): 397-400.
9. Dahlui M, Hishamshah MI, Rahman AJA, Aljunid SM. Quality of life in transfusion dependent thalassaemia patients on desferrioxamine treatment. Singapore Med J. 2009; 50(8): 794-9.