ORIGINAL ARTICLE

Incidence of Deferiprone-induced Neutropenia in Patients with Thalassemia and Iron Overload

Kanyaporn Supim MD[1], Oraphan Kongpanvijit MD[2]

[1] Department of Internal Medicine, Faculty of Medicine Vajira Hospital, Navamindradhiraj University, Bangkok, Thailand

[2] Division of Hematology, Department of Internal Medicine, Faculty of Medicine Vajira Hospital, Navamindradhiraj University, Bangkok, Thailand

Background: Thalassemia is an inherited disease that causes abnormal hemoglobin synthesis and the subsequent loss of erythrocytes. Blood transfusions and iron chelators are used as important treatments. Deferiprone, an effective oral iron chelator, can have significant side effects, including neutropenia.

Objective: To determine the incidence of deferiprone-induced neutropenia in patients with thalassemia and assess the efficacy of deferiprone along with other side effects.

Materials and Methods: This retrospective cohort study examined patients with thalassemia aged 15 years who were treated with deferiprone between January 2011 and December 2019. The reported incidence rate of neutropenia is 100 per 100 person-year. Basic variables were compared between patients with or without neutropenia, with the correlation being significant at $p<0.05$.

Results: In total, 162 patients with thalassemia aged 15 years or older were treated with deferiprone. The mean age of patients was 42.19±19.05 years, and 92 patients (60%) were female. Beta-thalassemia HbE was present in 92 patients (56.8%). In total, 81 patients (50%) were dependent on blood transfusions, and 109 patients (67.3%) had not undergone splenectomy. Deferiprone-induced neutropenia occurred in 26 patients, and were categorized as three cases of agranulocytosis, 5 cases of moderate neutropenia, and 18 cases of mild neutropenia. The incidence rates of agranulocytosis and neutropenia were 0.38 and 3.22 per 100 person-year, respectively. The dosage of deferiprone that caused neutropenia was 35.4 mg/kg/day (20 to 50 mg/kg/day). The period of occurrence was 664 days (363 to 1,176 days). Deferiprone reduced serum ferritin levels from baseline by 15.92±29.71, and 18.41±39.65 ng/mL after 6 and 12 months of treatment. Common side effects included nausea (4.3%) and joint pain (3.7%).

Conclusion: Incidence rates of agranulocytosis and neutropenia were 0.38 and 3.22 per 100 person-year, respectively. Deferiprone reduced serum ferritin levels from the baseline by 16% and 18% after 6 and 12 months of treatment, respectively.

Keywords: Neutropenia; Deferiprone; Iron Overload Thalassemia; Agranulocytosis

Received 8 September 2023 | Revised 12 March 2024 | Accepted 2 May 2024

J Med Assoc Thai 2025;108(Suppl.1):S1-9

Website: http://www.jmatonline.com

Thalassemia is a genetically inherited disease that causes abnormal hemoglobin synthesis, erythrocyte loss, and anemia. Thalassemia occurs in 1% of the Thai population[1] with an overall estimation of 434,460 people; 9,853 new patients with thalassemia are diagnosed per year, according to the number of 800,000 newborns per year[2].

Iron overload is commonly observed in patients with thalassemia. One unit of blood contains 250 mg of iron. However, in patients with thalassemia, iron is increasingly absorbed in the intestines, and the subsequent iron overload leads to abnormal functioning of organs and can cause death[3]. Treating iron overload in patients with thalassemia can reduce side effects from iron overload and prolong lifespan.

Deferiprone is an oral iron chelator that is efficient in treating iron overload in patients[4]. The medication can be produced domestically by the Government Pharmaceutical Organization (GPO) under the commercial name "GPO-L-ONE". A phase III study of GPO-L-ONE in Thailand in 73 patients with thalassemia aged 3.2 to 19 years with deferiprone usage of 79.1±4.3 mg/kg/day and following up the efficacy of medication at 12 months found that 45% of patients had 15% lower serum ferritin levels than at the baseline. The level of serum ferritin decreased to 1,065 ng/mL on average. The side effects of deferiprone (GPO-L-ONE) are gastrointestinal irritation (20.5%), transaminitis

Correspondence to:

Kongpanvijit O.

Division of Hematology, Department of Internal Medicine, Faculty of Medicine Vajira Hospital, Navamindradhiraj University, Bangkok 10300, Thailand.

Phone and Fax: +66-2-2443590

Email: oraphan@nmu.ac.th

How to cite this article:

Supim K, Kongpanvijit O. Incidence of Deferiprone-induced Neutropenia in Patients with Thalassemia and Iron Overload. J Med Assoc Thai 2025; 108(Suppl.1):S1-9.

DOI: 10.35755/jmedassocthai.2025.S01.S1-S9

(16.4%), and neutropenia (6.8%). The incidence rate of neutropenia is 7.5 per 100 patient-years, but death or infection cases were not found. Most cases of neutropenia were found at eight weeks, but neutropenia was not observed in patients who had undergone splenectomy[5].

A study on the efficacy of deferiprone in treating 87 patients with thalassemia and iron overload who were older than 15 years in Chiang Rai province found that the medication was efficacious in significantly reducing serum ferritin levels within 1 year from 3,357±2,586 to 1,551±1,179 ng/mL ($p<0.001$). Side effects of the medication were found mostly in the gastrointestinal system (25.28%) and neutropenia (1.15%), with mild neutropenia with an absolute neutrophil count (ANC) of 1,483/mm^3 occurring at the 12th month[6].

A study on the efficacy of deferiprone in treating iron overload neutropenia in patients with thalassemia between 18 and 50 years old at Siriraj Hospital found that the medication could significantly reduce the iron overload incidence in 12 months. The present study found cases of neutropenia and agranulocytosis at 6.6%, where neutropenia occurred five days after medication and agranulocytosis occurs five months after medication[7].

In Canada, deferiprone has the commercial name of Ferriprox® (ApoPharma Inc., Canada). A study collected data from 1,127 patients from clinical drug trials and postmarketing surveillance programs and found that for those in clinical drug trials, 5.5% of patients experienced neutropenia and 1.5% experienced agranulocytosis, constituting an incidence rate of 1.1 per 100 patient-years. For postmarketing surveillance programs, the incidence rates of agranulocytosis were 0.24 per 100 patient-year. The median time from receiving medication to the occurrence of neutropenia was 242 days (9 days to 17 years) and to the occurrence of agranulocytosis was 147 days (9 days to 17 years). The incidence of neutropenia did not depend on the dosage of medication. The incidence was found to be threefold higher in females, more prevalent in children than in adults, and more common in patients who had not undergone splenectomy compared with those who had[8].

An Italian study of 532 patients with thalassemia found that the side effects included joint pain (3.9%), gastrointestinal symptoms (3.2%), increased ALT level (2.8%), and neutropenia (3.9%). The incidence rate of neutropenia was 2.08 per 100 patient-years and that of agranulocytosis was 0.9% (0.43 per 100 patient-year). The average time from receiving medication to the occurrence of neutropenia was 175 days (10 to 775 days) and for recovering from neutropenia was 29 days (2 to 92 days). Neutropenia was more likely in patients who had not undergone splenectomy and who were ≤18 years old[9].

Deferiprone is commonly used in Thailand and is accessible by all healthcare schemes, and therefore most studies in Thailand have not evaluated the incidence of neutropenia and agranulocytosis in patients with thalassemia who are older than 15 years, and no studies have assessed the factors influencing the occurrence of neutropenia. Consequently, in this study, data was collected from patients with thalassemia who received treatments at Vajira Hospital, which is a tertiary care hospital. The present study evaluated the incidence and risk factors of neutropenia, side effects of deferiprone, and the efficacy of medication in reducing the level of serum ferritin in patients with thalassemia who are older than 15 years to assess the benefits of treating these patients and surveil any side effects.

Objectives

Main objective: To study the incidence and risk factors of deferiprone-induced neutropenia in patients with thalassemia aged 15 years and older.

Secondary objectives: To study the deferiprone-associated side effects such as nausea, vomiting, abdominal pain, abnormal liver function test results, joint pain, headache, and rash. In addition, to study the efficacy of deferiprone in reducing serum ferritin levels after 6 and 12 months of treatment.

Materials and Methods

This research was approved by the Institutional Review Board of the Faculty of Medicine Vajira Hospital and is in full compliance with the International guidelines for human research protection (COA 213/2564).

Research Methodology: This research is a retrospective cohort study.

Inclusion Criteria: Patients with thalassemia who were 15 years old or older and had been diagnosed via hemoglobin typing from laboratories and examined by a hematologist at the Hematology Department and General Ambulatory Medicine Department of Vajira Hospital, Navamindradhiraj University. Patients with either transfusion-dependent or nontransfusion-dependent thalassemia who have an iron overload condition requiring the use of deferiprone with conditions according to the variable definition from January 1, 2011 to December 31, 2019.

Exclusion Criteria: Patients with hematologic malignancies and bone marrow diseases such as Leukemia, lymphoma, aplastic anemia, and myelodysplastic syndrome. Patients who received chemotherapy or immunosuppressants that can cause neutropenia. Patients who experienced neutropenia before receiving deferiprone therapy. Patients with acute hepatitis, hypersplenism, or liver transaminase fivefold higher than the highest normal rate or ALT concentration >250 IU/L([5]). Patients infected with human immunodeficiency virus([5]). Patients who received iron

chelators other than deferiprone.

Number of volunteers or sample size

In total, 162 patients with thalassemia who were 15 years old or older with iron overload and had been treated with deferiprone from January 1, 2011 to December 31, 2019 at the Hematology Unit and Medicine Department of Vajira Hospital, Navamindradhiraj University.

Variable definition

The targets of the prtesent study were defined as: iron overload condition, which indicates the use of an iron chelator for treatment. The indication for the use of iron chelator in transfusion-dependent thalassemia is a serum ferritin level >1,000 ng/mL with at least two examinations conducted at least 1 to 3 months apart with a history of continuous blood transfusion of >1 year or >10 times. The indication for the use of iron chelators in nontransfusion-dependent thalassemia is a serum ferritin level >800 ng/mL with at least two examinations performed at least 1 to 3 months apart. A neutropenia condition means an ANC of <1,500 cells/mm^3[8,9], which can be divided into mild neutropenia of 1,000 to 1,500 cells/mm^3, moderate neutropenia of 500 to 1,000 cells/mm^3, and agranulocytosis of <500 cells/mm^3[8,9]. Febrile neutropenia is a condition where the body temperature is ≥38.3°C for ≥1 h together with an ANC <500 cells/mm^3 or has the potential to decrease to <500 cells/mm^3 within 48 h[10]. Patients who are responsive to deferiprone in reducing serum ferritin have a decreased level of serum ferritin at least 15 % of the previous level of serum ferritin[5] within 6 and 12 months.

Data analysis

Population descriptions including qualitative variables such as gender, splenectomy, types of thalassemia, blood transfusion dependency are treated as categorical data and are presented in frequency and percentage while quantitative variables such as age, dosage of medication are continuous data and are presented by mean and standard deviation if data are normally distributed and by median and ranges if data are not normally distributed.

The incidence of neutropenia is presented in incidence rates. Comparison of basic factors, such as gender and splenectomy that have effects on clinical description between patients with thalassemia with or without neutropenia who receive differential treatment were evaluated using Chi-square or Fisher's exact test if the factors are qualitative data. Comparison of basic factors that are continuous data such as dosage of medication that have effects on clinical description between patients with thalassemia with or without neutropenia who receive deferiprone were evaluated with an independent t-test or a Mann–Whitney U test. An efficacy study on iron chelator deferiprone in reducing serum ferritin levels was performed by comparing serum ferritin level (mean and SD) at baseline at 6 and 12 months of treatment. Data recording and analysis were performed using STATA/IC Software version 17.0 (Stata Corp, College Station, Texas, USA) with two-way or one-way analysis. Significance was determined at a p=0.05.

Results

The study collected data from electronic medical records at Vajira Hospital, Navamindradhiraj University from January 1, 2011 to December 31, 2019 on the incidence of deferiprone-induced neutropenia in patients with thalassemia and iron overload who are 15 years old or older. A total of 162 patients with thalassemia and iron overload met the inclusion and exclusion criteria for iron overload patients and were administered deferiprone (Figure 1).

Among the 29 patients with neutropenia, three experienced neutropenia due to other causes besides deferiprone treatment. Two patients experienced neutropenia due to the use of other medications, including interferon and hydroxyurea, along with deferiprone. In these cases, the patients could discontinue the other medications and resume deferiprone therapy as usual. One patient developed Salmonella septicemia. Following recovery from the infection, the patient was able to resume deferiprone use. Thus, 26 patients experienced deferiprone-induced neutropenia.

The general data of 162 patients with thalassemia who were 15 years old or older and received deferiprone is shown in Table 1. The median followup time was 1,586 days (IQR 649 to 2,710). The present study included 98 female patients (60.5%) and 64 male patients (39.5%. The average age of the patient was 42.29 years (42.19±19.05 years). The average weight was 49.17 kgs (49.17±13.94 kg) and the average height was 155.32 cm (155.32±12.61 cm). For genetic variants, 92 patients carried beta-thalassemia HbE (56.8%), 42 patients carried HbH, 14 patients carried homozygous beta-thalassemia (8.6%), and another 14 patients carried HbH with coinheritance of Hb constant spring (8.6%).

The present study included 81 nontransfusion-dependent patients (50%), and 109 patients had not undergone splenectomy (67.3%). Most patients have normal viral exam results. Twelve patients had natural immunity to hepatitis B (7.4%), eight had anti-HBc antibodies (4.9%), five had anti-HCV antibodies (3.1%), and four were HbsAg positive.

The initial administration of deferiprone was 20.23 mg/kg/day (11.63 to 38.46 mg/kg/day). Before deferiprone administration, the serum ferritin level was 1,943 ng/mL (1,240 to 3,131 ng/mL), and the ANC was 3,672 cells/mm^3 (2,773 to 5,121.1 cells/mm^3).

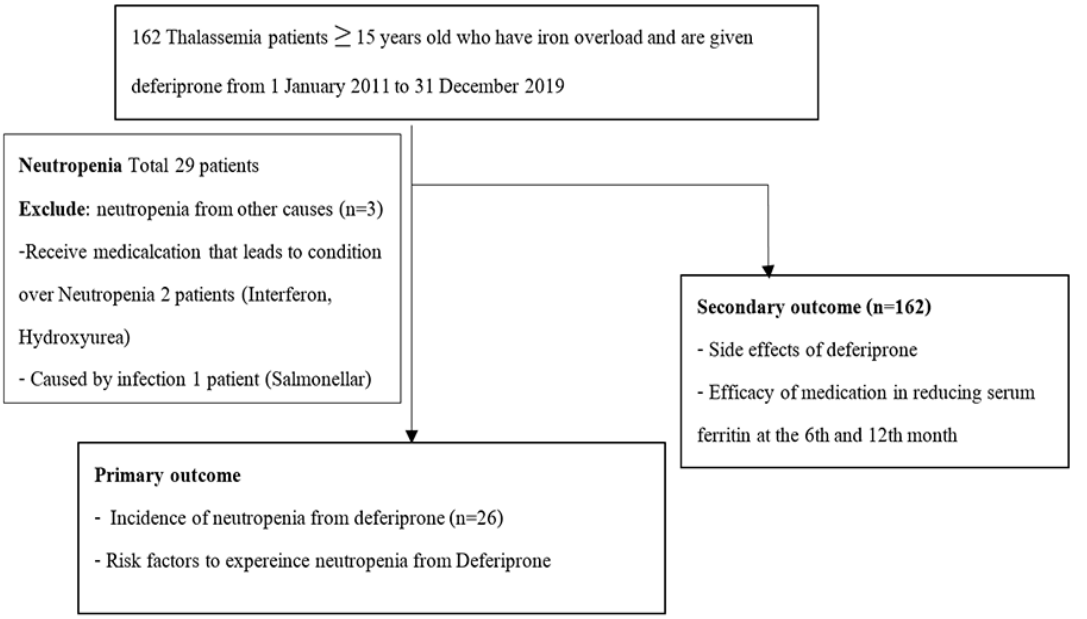

Figure 1. Selection criteria for patients thalassemia and iron overload who received deferiprone.

A total of 26 patients had deferiprone-induced neutropenia (16.05%) in whom the severity of neutropenia was categorized for ANC as follows: 18 patients had mild neutropenia (11.1%), with an incidence rate of 2.22 per 100 person-year; five patients had moderate neutropenia (3.1%), with an incidence rate of 0.62 per 100 person-year; and three patients had severe neutropenia or agranulocytosis (1.8%), with an incidence rate of 0.38 per 100 person-year (Table 2).

The incidence rate of deferiprone-induced neutropenia in patients with thalassemia and iron overload was 3.22 per 100 person-year. The median time taken to experience neutropenia was 664 days (IQR 363 to 1,176 days), and the median dosage was 35.4 mg/kg/day (range: 20 to 50 mg/kg/day). Most cases were found in females (18 patients; 69.2%). Most patients had normal serology (18 patients; 69.2%). Eighteen patients had not undergone splenectomy (69.2%). Fourteen patients were transfusion-dependent (53.8%), with the most common type of thalassemia being beta-thalassemia Hb E found in 13 patients (50%), followed by HbH, which was present in nine patients (34.6%). Thirteen patients discontinued medication after experiencing neutropenia (50%), eleven patients switched medications (42.2%), and four patients were admitted to the hospital (15.4%). Three patients died (11.5%); two were diagnosed with agranulocytosis and one with moderate ANC. The cause of death in all cases was sepsis.

Three patients were diagnosed with agranulocytosis (1.8%). The incidence rate of agranulocytosis was 0.38 per 100 person-year. The median time taken to experience agranulocytosis was 630 days (with a range of 71 to 958 days for the development of agranulocytosis). The median dosage was 50 mg/kg/day (range of dosage was 5.9 to 51.4 mg/kg/day). Most cases were found in females with three patients (100%). Most patients had normal serology with three patients (69.2%). Two patients had not undergone splenectomy (66.7%), and two patients were transfusion-dependent (66.7%). The type of thalassemia found was equal, i.e, one from homozygous beta-thalassemia disease, one from beta-thalassemia HbE disease, and one from HbH disease (33.3%). Three patients discontinued their medication and were admitted after experiencing agranulocytosis (100%). Two patients used granulocyte colony-stimulating factor (66.7%). Two patients died (66.7%) of febrile neutropenia. One patient survived (33.3%) and had changed the iron chelator to replace deferiprone.

The study on factors influencing the severity of deferiprone-induced neutropenia in patients with thalassemia and iron overload identified a significant correlation between patients who had undergone splenectomy and the severity of neutropenia (p=0.02). Patients with mild or severe neutropenia were more commonly found among those who had not undergone splenectomy than among those who had. In addition, patients with moderate neutropenia or severe neutropenia were significantly correlated with hospital admission and death (p=0.009 and 0.01, respectively).

Table 1. General data characteristics, clinical description, and laboratory results of patients with thalassemia before treatment of iron overload

Characteristic	Percent (n=162)
Gender	
Male	64 (39.5%)
Female	98 (60.5%)
Age (mean±sd, years)	42.19±19.05
Weigh (mean±sd, Kg)	49.17±13.94
Height (mean±sd, cm)	155.3±12.6
Type of Thalassemia	
Homozygous beta-thalassemia	14 (8.6%)
beta -thalassemia Hb E	92 (56.8%)
Hb H disease	42 (26%)
Hb H with Cs	14 (8.6%)
Blood transfusion dependence	
Transfusion dependence	81 (50.0%)
Non-Transfusion dependence	81 (50.0%)
Splenectomy	
Yes	53 (32.7%)
No	109 (67.3%)
Serology	
HBsAg positive	5 (3.1%)
Isolated anti-HBc	8 (4.9%)
Anti-HCV positive	5 (3.1%)
Isolated anti-HBc with anti-HCV positive	2 (1.2%)
Natural immune of hepatitis B	12 (7.4%)
Immunization of hepatitis B	12 (7.4%)
Normal serology	118 (72.8%)
Dose of Deferiprone (dose/kg/day) median (IQR)	20.23 (11.63 to 38.46)
Serum ferritin (ng/ml) median (IQR)	1,943 (1,240 to 3,131)
ANC (cells/mm^3) median (IQR)	3,672 (2,773 to 5,121.1)
ANC <500 (severe neutropenia)	3 (1.8%)
ANC 500 to <1,000 (moderate neutropenia)	5 (3.1%)
ANC 1,000 to <1,500 (mild neutropenia)	18 (11.1%)
ANC ≥1,500	136 (63.6%)

ANC=absolute neutrophil count

No correlations were present between the severity of neutropenia and gender, type of thalassemia, transfusion condition, dosage of medication, or age (Table 3).

Subgroup analysis in patients with neutropenia was conducted to study the risk factors that correlated with the incidence of neutropenia. Gender, type of thalassemia, transfusion condition, splenectomy, and age receiving deferiprone were found to differ with the occurrence of neutropenia.

Based on laboratory test analysis before administration, the serum ferritin level was 1,943 ng/mL (1,240 to 3,131 ng/mL), hemoglobin level was 7.4 g/dL (6.4 to 8.3 g/dL), ANC was 3,672 cells/mm^3 (2,773 to 5,121.1 cells/mm^3), platelet count was 220×103/mm^3 (151 to 374×103/mm^3), and serum creatinine level was 0.63 mg/dL (0.5 to 0.89 mg/dL).

At the 12 month followup, the dosage of deferiprone had significantly ($p<0.001$) increased from a median of 20.23 mg/kg/day (range: 11.63 to 38.46 mg/kg/day) to 23.26 mg/kg/day (range: 16.03 to 42.86 mg/kg/day) Furthermore, the administration of deferiprone reduced the median serum ferritin level from 1,943 ng/mL (range: 1,224 to 2,850 ng/mL) to 1,337 ng/mL (range: 914 to 1,940 ng/mL) over 12 months. At the 12-month followup, serum ferritin levels significantly decreased by 18% from the initial baseline ($p<0.001$). Hemoglobin, ALT, and AST levels changed significantly, whereas the levels of ANC, platelets, and serum creatinine did not (Table 4).

The administration of deferiprone in patients with thalassemia and iron overload tended to reduce the average level of serum ferritin after 3 months by11.86±23.56 ng/mL. The average level of serum ferritin at 6 months was reduced by 15.92±29.71 ng/mL, and the average level of serum ferritin at 12 months was reduced by 18.41±39.65 ng/mL. Thus, patients with thalassemia and iron overload who had received deferiprone were found to have significant changes in the median serum ferritin level during the 12 months of treatment ($p<0.001$) (Figure 2).

The commonly found side effects included nausea in seven patients (4.3%), arthralgia in six patients (3.7%), vomiting in five patients (3.1%), and abdominal pain in five patients (3.1%) (Table 5).

Discussion

Thalassemia is a genetically inherited disease[3] that causes abnormal hemoglobin synthesis, resulting in the destruction of erythrocytes and anemia. Furthermore, iron overload is commonly found in patients with thalassemia and can occur via both transfusion and nontransfusion dependence. Deferiprone is an oral iron chelator that can be produced by the GPO in Thailand[4]. This drug has important side effects that must be monitored, including neutropenia (ANC <1,500 cells/mm^3) and agranulocytosis (ANC <500 cells/mm^3). Studies in Thailand and abroad[5-9] found the occurrence rate of deferiprone-induced neutropenia at approximately 1.15% to 6.8% where the incidence rate of neutropenia was 2.08 to 7.5 per 100 person-years of exposure, whereas the occurrence rate of agranulocytosis was approximately 0.5% to 3.6% with an incidence rate of 0.24 to 1.1 per 100 person-years of exposure. The current study, conducted from January 1, 2011, to December 31, 2019, involved 162 patients with thalassemia and iron overload aged ≥15 years. The occurrence of deferiprone-induced neutropenia was 16%, with an incidence rate of approximately 3.22 per 100 person-year of exposure. Agranulocytosis occurred in 1.8% of cases, with an incidence rate of approximately 0.38 per 100 person-year

Table 2. General data on deferiprone-induced neutropenia in patients with thalassemia and iron overload and factors influencing the severity of neutropenia

Characteristic	Mild neutropenia (n=18)	Moderate neutropenia (n=5)	Severe neutropenia (n=3)	Total neutropenia (n=26)	p-value
Neutropenia patient* (%)	18 (11.1%)	5 (3.1%)	3 (1.8%)	26 (16%)	
Incidence rate* (100-person year)	2.22	0.62	0.38	3.22	
Time to event, day (median, IQR)	733.5 (281 to 1,351)	399 (378 to 1.176)	630 (71 to 958)***	664 (363 to 1,176)	0.640****
Dose mg/kg/day, median (IQR)	27.9 (20 to 48.6)	37 (13.2 to 37.6)	50 (5.9 to 51.4)***	35.4 (20 to 50)	0.900****
Age, year (mean ± SD)	48.8±4.3	31.6±7.0	50.3±5.6	46.3±18.5	0.601****
Sex					0.657
Male (%)	6 (33.3)	2 (40)	0	8 (30.8)	
Female (%)	12 (66.6)	3 (60)	3 (100)	18 (69.2)	
Serology status					0.809
Isolated HBc	1 (%)	0	0	1 (4.8%)	
Anti-HCV positive	1 (5.6%)	1 (20%)	0	2 (7.7%)	
Natural immune Hepatitis B	2 (11.1%)	0	0	2 (7.7%)	
Immunization Hepatitis B	2 (11.1%)	0	1 (33.3%)	3 (11.5%)	
Normal serology	12 (%)	4 (80%)	2 (66.7%)	18 (69.2%)	
Splenectomy					0.022*
Splenectomy	3 (%)	4 (80%)	1 (33.3%)	8 (30.8%)	
Non-splenectomy	15 (%)	1 (20%)	2 (66.7%)	18 (69.2%)	
Transfusion dependent					0.128
Transfusion dependent	10 (55.6%)	4 (80%)	1 (33.3%)	14 (53.8%)	
Non-Transfusion dependent	8 (44.4%)	1 (20%)	2 (66.7%)	12 (46.2%)	
Type of thalassemia					0.565
Homozygous beta-thalassemia	2 (11.1%)	1 (20%)	1 (33.3%)	4 (15.4%)	
Beta-thalassemia Hb E	8 (44.4%)	4 (80%)	1 (33.3%)	13 (50%)	
HbH disease	8 (44.4%)	0	1 (33.3%)	9 (34.6%)	
Treatment event					
Change new medication	8 (44.4%)	2 (40%)	1 (66.7%)	11 (42.2%)	0.489
Use GCSF**	0	0	2 (66.7%)	2 (7.7%)	-
Stop deferiprone	8 (44.4%)	2 (40%)	3 (100%)	13 (50%)	0.249
Hospitalization	0	1 (20%)	3 (100%)	4 (15.4%)	0.009*
Death	0	1(20%)	2(66.7%)	3(11.5%)	0.010*

* A total of 162 patients were included; ** G-CSF= Granulocyte colony-stimulating factor; *** Report median (Min-Max); **** Repeated measurement ANOVA, Chi-square test or Fisher Exact test if expected value <5 any cell and ≥20%

of exposure. Thus, the occurrence of neutropenia and agranulocytosis in this study exhibited similar trends to those observed in previous studies.

Akrawinthawong et al., found that neutropenia could occur within five days to five months after administration of the medication[7]. In a Canadian study, Tricta et al.[8], revealed that the median duration until neutropenia was 242 days (9 days to 17 years), whereas the median time until agranulocytosis was 147 days (9 days to 17 years). In the current study, the median time until neutropenia was 664 days (363 to 1,176 days), and the median time until agranulocytosis was 630 days (71 to 958 days). Another study with a randomized trial of oral chelators in transfusion-dependent pediatric patients demonstrated that neutropenia occurred in 23 of 193 patients in the deferiprone arm; the mean (SD) treatment duration with deferiprone until the diagnosis of neutropenia was 127 (96.1) days[11].

The onset of neutropenia in the current study appears to have occurred later compared with results from other studies. This delay may be attributed to several factors. Variations in monitoring practices, such as the frequency of blood tests used to assess neutropenia, could have impacted the detection and timing of neutropenia onset. Herein, patients were followed-up every 1 to 3 months, with adjustments made by the doctor and appointments scheduled accordingly. Furthermore, the retrospective approach used in the present study might have also influenced the observed timing of neutropenia onset. The present study only included individuals aged 15 years or older, whereas Tricta et al.[8], included both adult and pediatric patients. Therefore, the

Table 3. Factors influencing the severity of deferiprone-induced neutropenia in patients with thalassemia and iron overload

Characteristic	Non neutropenia patients (n=136)	Neutropenia patients (n=26)	p-value
Gender			0.320
Male	56 (87.5%)	8(12.5%)	
Female	80 (81.6%)	18 (18.4%)	
Type of thalassemia			0.060
Homozygous beta- thalassemia	10 (71.4%)	4 (28.6%)	
Beta-thalasemia Hb E	79 (86.8%)	14 (13.2%)	
HbH disease and HbH with Cs	47 (82.5%)	10 (17.5%)	
Transfusion dependence			0.669
Transfusion dependence	67 (82.7%)	14 (17.3%)	
Non-transfusion dependence	69 (85.2%)	12 (14.8%)	
Splenectomy patient			0.817
Yes	45 (84.9%)	8 (15.1%)	
No	91 (83.5%)	18 (16.5%)	
Age (years, mean ± SD)	41.52±19.22	45.69±18.11	0.228

Chi-square test or Fisher's exact test, Mann-whitney U test

Table 4. Laboratory test results during deferiprone medication for 12 months

Factor	Initial	3 months	6 months	12 months	p-value
Dose of deferiprone (mg/kg/day)	20.23 (11.63 to 38.46)	22.32 (12.5 to 45.45)	23.81 (16.12 to 43.43)	23.26 (16.03 to 42.86)	<0.001*
Serum ferritin (ng/ml)	1,943 (1,240 to 3,131)	1,703.5 (1,077 to 2,494)	1,397 (947 to 2,194)	1,337 (914 to 1,940)	<0.001*
Hemoglobin(g/dl)	7.4 (6.4 to 8.3)	7.2 (6.3 to 8.1)	7 (6.2 to 8.25)	7 (6.3 to 8.1)	0.005*
ANC cells/mm^3**	3,638 (2,773 to 5,084)	3,612 (2,623 to 5,105.1)	3,720 (2,548 to 5,457.76)	3,712 (2,738 to 4,992)	0.822
Platelets x103/mm^3	3,672 (2,773 to 5,121.1)	3,612 (2,623 to 5,200)	3,758 (2,549 to 5,357.01)	3,708.2 (2,738 to 4,992)	0.114
AST (IU/L)	220 (151 to 374)	216 (154 to 382)	211 (135 to 427)	210 (144 to 466)	0.013*
ALT (IU/L)	44 (29 to 70)	40 (27 to 64)	40.5 (27 to 59.5)	39 (26 to 57)	0.004*
Serum creatinine (mg/dl)	37 (20 to 61)	35.5 (21 to 52)	29 (17 to 58)	27 (17 to 44)	0.054
Percent change form baseline		11.86% (±23.56)	15.92% (±29.71)	18.41% (±39.65)	<0.001*

* Repeated measurement ANOVA, ** Absolute neutrophil count (ANC)

Table 5. Side effects of iron overload in patients who received deferiprone

Adverse event	Frequency (%)
Nausea	7 (4.3)
Arthralgia	6 (3.7)
Vomiting	5 (3.1)
Abdominal pain	5 (3.1)
Dizziness	4 (2.5)
Headache	1 (0.6)
Skin rash	1 (0.6)
Hepatitis	1 (0.6)

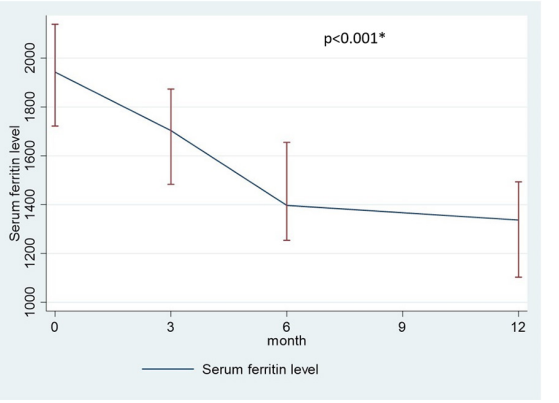

Figure 2. Changes in the median serum ferritin level during the administration of deferiprone for 12 months.

time taken to experience neutropenia and agranulocytosis after receiving the medication does not accurately predict the time of occurrence. The condition can occur after nine days, and several cases were reported at 17 years after receiving deferiprone. Therefore, CBC follow-up at 2 to 4 weeks is necessary[8] because agranulocytosis can lead to death. Herein, agranulocytosis was shown to lead to hospital admission and a mortality rate of 66.7%.

An earlier study found that the occurrence of neutropenia does not depend on the dosage of medication. Neutropenia is more commonly found in patients who have not undergone splenectomy than in those who have undergone this procedure. Furthermore, neutropenia is commonly found in patients who are 18 years old or younger, and more frequently in females than males, but these differences were not significant[8,9]. The current study suggests that the dosage of deferiprone, gender, type of thalassemia, transfusion condition, and splenectomy are not correlated with neutropenia or agranulocytosis. However, neutropenia was confirmed to be more common in females than in males and in patients who have not undergone splenectomy.

The efficacy of deferiprone in reducing serum ferritin level in the study of Viprakasit et al.[5], on the dosage of deferiprone at an average 79.1±4.3 mg/kg/day and follow-up with the patient at 12 months found that 45% of the patients had 15% lower serum ferritin levels from the baseline. In the current study, the initial dosage was 20.23 mg/kg/day (range: 11.63 to 38.46 mg/kg/day) with a serum ferritin level of 1,943 ng/mL (range: 1,240 to 3,131 ng/mL). At the 12-month follow-up, serum ferritin levels decreased by 18% from the initial baseline, indicating the effectiveness of deferiprone in treating iron overload patients.

Agarwal et al., measured urinary iron excretion in patients with thalassemia receiving various doses of deferiprone (25, 50, 75, and 100 mg/kg/day) and found an increasing amount of iron excretion as the dose increased. For example, urinary iron excretion increased from 6.2±4.6 to 42.3±37 mg/24 h at a dose of 25 to 100 mg/kg/day, respectively[12]. The other two studies on iron chelation in patients with thalassemia in Thailand regarding the efficacy of deferiprone demonstrated that a dose of 25 to 50 mg/kg/day can be effective in treating iron overload in patients with nontransfusion-dependent thalassemia[6,13].

The present study included 162 patients, comprising 81 patients with nontransfusion-dependent thalassemia (50%). Among the patients with nontransfusion-dependent thalassemia, 49 (60%) responded to deferiprone treatment with a decrease in serum ferritin levels of at least 15% after 12 months, whereas among the transfusion-dependent patients, 40 (50%) responded to deferiprone. Furthermore, the study found that deferiprone effectively reduced serum ferritin levels in patients with thalassemia and iron overload even when administered at dosages lower than the recommended dose. However, further studies are required to explore this finding in greater detail.

Side effects of neutropenia treatment have been reported as joint pain (3.9%), gastrointestinal symptoms (3.2%) and increasing of aspartate aminotransferase (2.8%[9]. Herein, the commonly found side effects included nausea (4.3%), arthralgia (3.7%), vomiting (3.1%), and abdominal pain (3.1%).

The present study reveals that the incidence of neutropenia in patients with thalassemia in Thailand is nearly identical to that reported in other studies, suggesting that the occurrence rate of deferiprone-induced neutropenia may not be dose-dependent. The limitation of this study lies in its retrospective cohort design. Although the tendency of side effects appears similar, issues might have been present for the comprehensiveness and accuracy of data recording, as well as the limited control over confounding variables.

This research studied the incidence of deferiprone-induced neutropenia in patients with thalassemia who were 15 years old or older, whereas previous studies have more focused more on younger ages; therefore, studies on the incidence of deferiprone-induced neutropenia in adults have not been clearly reported. Furthermore, this research studied the efficacy of deferiprone in reducing serum ferritin levels in patients with thalassemia and iron overload aged 15 years or older. In addition, agranulocytosis is an infrequent condition, and the sample size decreases after categorizing into groups based on the severity of neutropenia, resulting in reduced statistical power, which affects the significance of the results.

Conclusion

The study found that the incidence rate of neutropenia and agranulocytosis was 3.22 and 0.38 per 100 person-years of exposure, respectively, in patients with thalassemia and iron overload who are 15 years old or older and who were evaluated from January 1, 2011 to December 31, 2019 at Vajira Hospital. Agranulocytosis infrequently occurred but is severe and can lead to hospital admission and has a high mortality rate. Therefore, follow-up on the level of leukocytes and continuous monitoring are necessary. Deferiprone was efficacious in treating patients with iron overload because this can reduce serum ferritin levels by an average of 16% and 18% from the initial level after 6 and 12 months of medication, respectively.

What is already known on this topic?

Deferiprone is efficacious in significantly reducing iron overload incidence with 12 months of treatment. The most critical side effects of deferiprone were neutropenia and agranulocytosis.

What this study adds?

Deferiprone, the commercial name of GPO-L1®, is an iron chelator that is commonly used in Thailand and is accessible by all healthcare schemes. The incidence and risk factors of neutropenia, side effects of deferiprone, and the efficacy of medication in reducing the level of serum

ferritin were studied in patients with thalassemia who were older than 15 years and who received treatments at Vajira Hospital, a tertiary care hospital. This study enhances treatment outcomes and monitor side effects in real-world care of patients with thalassemia.

Conflicts of interest

The authors declare no conflict of interest.

References

1. Panich V, Pornpatkul M, Sriroongrueng W. The problem of thalassemia in Thailand. Southeast Asian J Trop Med Public Health. 1992;23 Suppl 2:1-6.
2. Fucharoen S, Weatherall DJ. Progress Toward the Control and Management of the Thalassemias. Hematol Oncol Clin North Am. 2016;30(2):359-71.
3. Mishra AK, Tiwari A. Iron overload in Beta thalassaemia major and intermedia patients. Maedica (Buchar). 2013;8(4):328-32.
4. Society of Hematology of Thailand. Iron overload and iron chelators. Clinical practice guidelines for the treatment of anemia and thalassemia. In: Torcharat K, Charoenkwan P, editor. 2020. Pages 123-32.
5. Viprakasit V, Nuchprayoon I, Chuansumrit A, Torcharus K, Pongtanakul B, Laothamatas J, et al. Deferiprone (GPO-L-ONE®) monotherapy reduces iron overload in transfusion-dependent thalassemias: 1-year results from a multicenter prospective, single arm, open label, dose escalating phase III pediatric study (GPO-L-ONE; A001) from Thailand. American Journal of Hematology. 2013;88(4):251-60.
6. Chueamuangphan N. Effectiveness of Deferiprone (GPO-L-ONE®) Chelation Therapy in Adult Thalassemia Patients with Iron Overload. J Hematol Transfus Med. 2012;22:189-94.
7. Akrawinthawong K, Chaowalit N, Chatuparisuth T, Siritanaratkul N. Effectiveness of deferiprone in transfusion-independent beta-thalassemia/HbE patients. Hematology. 2011;16(2):113-22.
8. Tricta F, Uetrecht J, Galanello R, Connelly J, Rozova A, Spino M, et al. Deferiprone-induced agranulocytosis: 20 years of clinical observations. American Journal of Hematology. 2016;91(10):1026-31.
9. Ceci A, Baiardi P, Felisi M, Cappellini MD, Carnelli V, De Sanctis V, et al. The safety and effectiveness of deferiprone in a large-scale, 3-year study in Italian patients. British Journal of Haematology. 2002;118(1):330-6.
10. Freifeld AG, Bow EJ, Sepkowitz KA, Boeckh MJ, Ito JI, Mullen CA, et al. Clinical Practice Guideline for the Use of Antimicrobial Agents in Neutropenic Patients with Cancer: 2010 Update by the Infectious Diseases Society of America. Clinical Infectious Diseases. 2011;52(4):e56-e93.
11. Tricta F, Felisi M, Della Pasqua O, El-Beshlawy A, Hassab H, Kattamis A, Kreka M, Reggiardo G, Sherief LM, Spino M, Tempesta B. Neutropenia in children treated with deferiprone or deferasirox: a report of the largest randomized trial of oral chelators in transfusion-dependent pediatric patients. Blood. 2019 Nov 13;134:3552.
12. Agarwal MB, Gupte SS, Viswanathan C, et al. Long–term assessment of efficacy and safety of L1, an oral iron chelator, in transfusion dependent thalassaemia: indian trial. Br J Haematol. 1992;82:460–6.
13. Pootrakul P, Sirankapracha P, Sankote J, et al. Clinical trial of deferiprone iron chelation therapy in beta-thalassaemia/haemoglobin E patients in Thailand. Br J Haematol. 2003;122(2):305-310.