Thalidomide has a significant effect in patients with thalassemia intermedia

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ABSTRACT

Objective: To investigate the effect of thalidomide in patients with thalassemia intermedia.

Methods: We observed the effect of thalidomide in seven patients with thalassemia intermedia requiring blood transfusion. Four of the patients were transfusion-independent, and three patients were transfusion-dependent.

Results: For the four transfusion-independent patients, hemoglobin concentration increased significantly (≥2 g/dl) in three and moderately (1–2 g/dl) in one. After 3 months of treatment, hemoglobin concentration increased 3.2 ± 1.2 g/dl compared to pretreatment. Among the three transfusion-dependent patients, transfusion was terminated after one month of treatment in one patient and decreased >50% in the other two patients, accompanied by an increase in the average hemoglobin concentration.

Conclusion: Thalidomide had a significant effect in patients with thalassemia intermedia. Further studies of a larger scale and more rigorous design are warranted.

KEYWORDS

Thalassemia intermedia; thalidomide; effect; transfusion

Thalassemia is the most common single gene hereditary disease worldwide. Depending on the gene involved, thalassemia is classified as either α thalassemia or β thalassemia. Beta thalassemia can be further divided into thalassemia major (TM) and thalassemia intermedia (TI) based on the severity of the disease [1]. Due to a shortage of β globin, free α globin aggregates and takes part in the formation of reactive oxygen species, causing red blood cells (RBCs) to be destroyed in the bone marrow (ineffective erythropoiesis, IE) or peripheral circulation (hemolysis) [2]. Different from patients with TM, TI patients can survive without regular blood transfusions and iron chelating, but multiple complications, such as pulmonary hypertension, extramedullary hemopoiesis, diabetes mellitus, leg ulcers and osteoporosis may occur due to anemia, IE or secondarily to iron overload [3,4]. Blood transfusion is effective in ameliorating IE, improving anemia and alleviating related complications [5]. In a retrospective investigation of 165 patients with TI, 28% ultimately became transfusion-dependent in adulthood [6]. However, iron overload will inevitably be aggravated after blood transfusion, and consequent iron chelating therapy is costly.

Guangxi province in the southwestern region of China is economically underdeveloped and an area with a high prevalence of thalassemia [7,8]. In Guangxi, there is a shortage of blood product supply, and many patients with thalassemia are not sufficiently transfused [9]. Additionally, iron chelators are expensive and generally not affordable due to economic difficulties [10]. It is important to investigate medicines that could possibly improve anemia in patients with TI in Guangxi. Hydroxyurea is the most commonly prescribed drug, and although it is effective in majority patients with TI [11], its ability to improve anemia is moderate [12]. In 2008, a dramatic effect of thalidomide in the treatment of one patient with TM was reported by Aguilar-Lopez et al. [13]. Subsequently, four additional patients with β thalassemia were reported [14–16], suggesting that thalidomide may be more effective than hydroxyurea in patients with thalassemia. Nevertheless, data is limited and publication bias cannot be ruled out, hence the effect of thalidomide on patients with TI remains to be explored. We investigated the effect of thalidomide in patients with TI who could not afford blood transfusion or chelation therapy in our center from May 2016, and data on seven patients is summarized below.

Patients and methods

Patients

From May 2016 on, adult patients with TI requiring blood transfusion but unable to afford regular transfusions or iron chelation due to economic or other reasons were recommended for thalidomide treatment. The indications for blood transfusion included the following: (1) continuous hemoglobin (Hb) concentration <7.0 g/dl, (2) complications such as extramedullary hemopoiesis, leg ulcers, facial deformities, and pulmonary hypertension, and (3) limited physical activities due to anemia [17]. Patients were informed of the side effects and possible benefits of thalidomide

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treatment. Full informed consent was required before treatment initiated. Pregnancy was ruled out in female patients. All female patients were informed that pregnancy should be prevented during treatment and until 6 months after the withdrawal of medicine. The thalidomide protocol for patients with TI was approved by the Medical Ethics Committee of the 303rd People’s Liberation Army Hospital.

Drug administration and clinic observation

Patients were divided into two groups before treatment: the transfusion-independent (group 1) and transfusion-dependent group (group 2). Patients requiring blood transfusion every 1–2 months in the year before treatment were classified as transfusion-dependent. In group 1, no patients received blood transfusions within 3 months before or during treatment.

Thalidomide (Changzhou Pharmaceutical Factory, Changzhou, Jiangsu, China) was begun at 50 mg orally per night. A dosage adjustment was performed in one patient in Group 2. To prevent thrombosis, aspirin (100 mg/d) was prescribed for post-splenectomy patients who had platelet counts >500 × 10⁹/l.

Red cell parameters, including Hb concentration, reticulocyte count, and nucleated red blood cell (NRBC) count, were analyzed using an XE 5000 automatic blood cell analyzer (Sysmex Corporation, Kobe, Japan). The levels of HbF and HbA were quantified using a BioRad Variant II high-pressure liquid chromatograph (BioRad, Hercules, CA, U.S.A.). Biochemical tests, including measurement of aspartate aminotransferase, alanine aminotransferase, bilirubin, and blood glucose, were assessed using a multichannel analyzer (Abbott Aeroset, Abbott Diagnostics, Bohemia, NY, U.S.A.).

Standard for efficacy judgment

For patients in group 1, Hb levels were measured after 3-month treatment and compared with pretreatment levels. A minor response was defined as an increment in the Hb concentration of 1–2 g/dl; the major response was Hb increment >2 g/dl. For patients in group 2, average Hb levels and blood transfusions 6 months before and after treatment were recorded. A minor response was defined as a 50% reduction in blood transfusions; the major response was defined as the need for a blood transfusion [11,18].

Statistical analysis

All data were analyzed using SPSS v13.0 (SPSS Inc., Chicago, IL, U.S.A.). For patients in group 1, a paired t-test was used to compare the changes in Hb concentration and other parameters before and after treatment. For patients in group 2, the mean Hb level and the difference in blood transfusion 6 months before and after treatment were compared using a two-sample t-test. P < 0.05 was considered statistically significant.

Results

Between May 2016 and February 2017, seven patients received thalidomide treatment. Among the seven patients, four were in group 1 and three were in group 2. At the time of the last follow-up (12 February 2017), patients had been treated for >3 months in group 1 and >6 months in group 2. The clinical data of the seven patients are shown in Table 1.

Effect of thalidomide on patients in group 1

As shown in Figure 1, for each patient in group 1, the Hb concentration increased after treatment with thalidomide. The Hb concentration increased after two weeks of treatment (1.0 ± 0.5 g/dl, P = 0.032), and continued to increase incrementally in three patients (except case 4).

Table 1. Clinical characteristics of seven patients who received thalidomide.

| Case no. | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|----------|---|---|---|---|---|---|---|
| Gender   | M | M | M | F | F | F | M |
| Age (y)  | 25| 28| 28| 30| 34| 35| 26|
| Genotype | β41/42-28 | β41/42-28 | β41/42-28 | β41/42-28 | β41/42-28 | β41/42-28 | β41/42-E |
| Age at time of diagnosis (y) | 25 | 8 | 3 | 6 | 1 | 4 | 1 |
| Age at time of first transfusion (y) | 25 | 23 | 3 | 8 | 5 | 4 | 1 |
| Splenectomy | Yes | No | No | Y | Y | N | Y |
| Age at time of surgery (y) | 7 | 9 | 9 | 9 | 9 | 9 | 9 |
| Transfusion | Seldom | Seldom | Seldom | Seldom | Frequent in recent 1 y | Frequent in recent 1 y | Frequent in recent 1 y |
| Iron chelator | Never | Never | Irregular | Seldom | Irregular | Irregular | Irregular |
| Indication for treatment | EH | EH, Poor physic status | EH, Poor physic status | Poor physic status | EH, DM | EH | EH |

EH: extramedullary hemopoiesis; DM: diabetes mellitus.
The hematologic and biochemical parameters of the four patients before and 3 months after treatment were compared. All four patients responded to treatment with thalidomide. Among the four patients, there were three major responses and one minor response. Hb concentration increased significantly after 3 months of treatment (3.2 ± 1.2 g/dl), while the reticulocyte and NRBC counts were not significantly changed. Hb analysis showed that the increased Hb was mainly composed of HbF; HbA was not significantly improved. Bilirubin was also not significantly changed (Table 2).

**Effect of thalidomide on patients in group 2**

In case 6, hemoglobin concentration increased after 1 month of treatment, and the patients transformed from transfusion-dependent to transfusion-independent. From then on, Hb concentration remained at approximately 10 g/dl without transfusion. Her Hb concentration decreased at 4 months of treatment when the dosage of thalidomide decreased from 50 to 25 mg/d, but recovered when the dose of thalidomide increased.

In cases 5 and 7, the amount of blood transfusion and average Hb concentration 6 months before and after thalidomide treatment were recorded. After treatment, blood transfusion decreased from 13 units to 6 units in case 5, and from 23.5 units to 10.5 units in case 7. Simultaneously, average Hb concentration increased from 7.1 ± 1.3 g/dl to 8.5 ± 0.9 g/dl in case 5, and from 7.2 ± 1.3 g/dl to 8.4 ± 0.9 g/dl in case 7 (Figure 2).

**Side effects**

Two patients complained of mild constipation and improved after diet modulation. No other side effects occurred during treatment. Dosage adjustments due to adverse reactions were not needed.

**Discussion**

Although the extant literature suggests a significant effect of thalidomide in patients with TI and TM, only five cases had been documented in four reports [13–16]. The favorable effect of thalidomide was confirmed by the high response ratio (100%) in the seven patients treated in this study. Among the seven patients, four reached major response and three reached minor response. This suggests better efficacy than hydroxyurea monotherapy. Among 100 patients with TI studied by El-Beshlawy et al. [11], the overall response ratio and major response ratios of hydroxyurea were 79 and 33%, respectively. In another report by Karimi et al. [19], which consist of 106 patients TI, the overall response ratio and major response ratios of hydroxyurea were 47 and 3%, respectively. For patients with TI blood transfusion-dependent, the efficacy of hydroxyurea was further disappointing, with the overall response ratio and major response ratios as low as 30 and 0%, respectively [20].

The effect of thalidomide seems to be comparable to regimens consisting of erythropoietin alone (overall response ratio 95% and major response ratio

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**Table 2.** Indices of anemia and hemolysis in group 2 patients before and after 3 months of treatment with thalidomide.

|                     | Case 1       | Case 2       | Case 3       | Case 4       | Comparison pre- and post-treatment |
|---------------------|--------------|--------------|--------------|--------------|-----------------------------------|
|                     | Pre | Post | Pre | Post | Pre | Post | Pre | Post | Pre | Post | d   | t   | P     |
| **Complete blood count** |     |      |     |      |     |      |     |      |     |      |      |     |       |
| Hb (g/dl)           | 7.8 | 11.9 | 5.5 | 9.7  | 7.4 | 10.0 | 6.4 | 8.2  | 3.2 | 1.2 | 5.414 | 0.012 |
| Ret (10^9/l)        | 219 | 69   | 87  | 269  | 661 | 551  | –   | –    | –   | –   | –19.5 | 0.263 |
| NRBC (10^9/l)       | 1.5 | 0.2  | 0.2 | 0.4  | 52.2| 20.1 | –   | –    | –   | –   | –8.2  | 0.374 |
| WBC (10^9/l)        | 4.2 | 5.3  | 3.5 | 5.2  | 25.6| 25.2 | 9.4 | 11.4 | 1.1 | 1.0 | 2.06  | 0.131 |
| Plt (10^9/l)        | 206 | 183  | 160 | 287  | 714 | 697  | 817 | 734  | 1.0 | 89.1| 0.022 | 0.984 |
| **Hemoglobin peptide** |     |      |     |      |     |      |     |      |     |      |      |     |       |
| HbF (%)             | 61.8| 61.0 | 59.0| 76.2 | 61.6| 74.7 | 50.7| 59.1 | 8.4 | 8.1 | 2.081 | 0.129 |
| HbF (g/dl)          | 4.8 | 7.3  | 3.2 | 7.4  | 4.6 | 7.5  | 1.3 | 2.0  | 3.3 | 1.6 | 4.210 | 0.024 |
| HbA (%)             | 35.2| 36.3 | 38.2| 21.0 | 34.2| 22.2 | 75.2| 71.2 | –8.0| 8.1 | 1.968 | 0.144 |
| HbA (g/dl)          | 2.7 | 4.3  | 2.1 | 2.0  | 2.6 | 2.2  | 4.8 | 5.8  | 0.5 | 0.9 | 1.12  | 0.344 |
| Liver function      |     |      |     |      |     |      |     |      |     |      |      |     |       |
| TBLI (μmol/l)       | 51  | 57   | 49  | 63   | 63  | 43   | 53  | 49   | –1.05| 14.5| –0.144| 0.895 |
| IBIL (μmol/l)       | 45  | 59   | 38  | 53   | 50  | 16   | 35  | 50   | 2.8  | 24.5| 0.228 | 0.834 |

Ret: reticulocyte; Plt: platelet; TBLI: total bilirubin; IBIL: indirect bilirubin; NRBC: nucleated red blood cell.
67%) [21] or in combination with hydroxyurea (overall response ratio 92.5% and major response ratio 50%) [20]. However, thalidomide was more convenient and more economically feasible. For a 60-kg patient with TI, if blood transfusions are required every 3 months, the cost of thalidomide is about 1440 RMB Yuan (equal to 209 dollars) per year, while the yearly cost of erythropoietin is about 36,000 RMB Yuan, and the yearly cost of blood transfusion together with iron chelator is more than 40,000 RMB Yuan. It is also noteworthy that in the group 1 patients, Hb concentrations increased by an average of 3.2 g/dl after 3 months of treatment, which was much better than what would be expected from hydroxyurea (0.7–1.6 g/dl) [11,16,22] or hydroxyurea combined with erythropoietin (1.6 g/dl) [20].

To explore the possible mechanism underlying thalidomide in the treatment of patients with TI, changes in Hb concentration were analyzed before and after treatment in group 1 patients. The increased Hb concentrations increased by an average of 3.2 g/dl after 3 months of treatment, which was much better than what would be expected from hydroxyurea (0.7–1.6 g/dl) [11,16,22] or hydroxyurea combined with erythropoietin (1.6 g/dl) [20].

In conclusion, our observations suggest that thalidomide has a superior therapeutic effect in patients with TI. Thalidomide is convenient for oral administration and inexpensive in China. In this area, patients with TI may benefit from thalidomide treatment. Future more-standardized clinical trials are required to verify the efficacy and safety of thalidomide in treating patients with TI, to explore the suitable dosage for treatment, and the possible index for predicitng responses.

Disclosure statement
No potential conflict of interest was reported by the authors.

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