Side effects of hydroxyurea in patients with major and intermediat β-thalassemia

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Abstract

Introduction: Patients referred to as having thalassemia major are usually those who come to medical attention in the first year of life and subsequently require regular transfusions to survive. Those who present later or who seldom need transfusions are said to have thalassemia intermedia
Hydroxyurea, an s-phase-specific and non-DNA-hypomethylating chemotherapeutic agents is capable of inducing HbF synthesis.

Patients & Methods: The study evaluated hydroxyurea complications in a cohort of 28 patients with major (n=20) and intermediate thalassemia (n=8). HU was started in a dose of 10 mg/kg daily and then increased by 5 mg/kg daily every 4-6 weeks until toxicity occurred or clinical response was achieved.

Results: We reviewed the records of 28 patients with intermediate and major β-thalassemia. The statistical analysis did not show a significant correlation between age at diagnosis, age of starting HU, duration of HU treatment, dose of HU and ethnicity.Side effects of HU have been recorded in 21 (75%) patients.Adverse effects were hair loss (n=8; 28.57%), hyper pigmentation (n=4; 14.28%), nausea and vomiting (n=2; 7.14%), abdominal pain (n=4; 14.28%), and increase in hepatic enzymes (n=2; 7.14%).Neurologic complications were headache (n=7; 25%), vertigo (n=1; 3.57%) and drowsiness (n=1; 3.57%).

Conclusion: According to the results of this and other studies, it seems that HU therapy in thalassemic patients can be safely used but can be started at low doses and increased slowly , monitoring the patient's response.

Key words: Side effects, Hydroxyurea, β-thalassemia

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Introduction

In 1925, Thomas Cooley and Pearl Lee described a form of severe anemia, occurring in children of Italian origin and associated with splenomegaly and characteristic bone changes (1).

In β-thalassemia intermedia, although patients are homozygous or doubly heterozygous, the resultant anemia is milder than in thalassemia major (2). Patients with thalassemia intermedia are usually able to maintain stable hemoglobin levels of about 8 gr/dl or even higher, allowing a normal physical development without the need for regular transfusions (3).

The terms thalassemia major and intermedia have no specific molecular correlate but encompass a wide spectrum of clinical and laboratory abnormalities (2).

Patients referred to as having thalassemia major are usually those who come to medical attention in the first year of life and subsequently require regular transfusions to survive. Those who present later or who seldom need transfusions are said to have thalassemia intermedia (4).

Hydroxycarbamide, also known as hydroxyurea, an s-phase-specific and non-DNA-hypomethylating chemotherapeutic agent is capable of inducing HbF synthesis. The effect of hydroxycarbamide and other antimetabolits on HbF synthesis is mainly mediated by their cytotoxic properties. In fact, they preferentially kill dividing cells, permitting

the emergence of primitive erythroid progenitors more highly committed HbF synthesis. Hydroxycarbamide may also have a more general role in increasing globin synthesis (5).
Hydroxyurea effects on fetal hemoglobin production via a reactivation of Y genes as a result of some unknown molecular mechanisms (6). Significant benefit is also expected in severe β-thalassemia patients because the increased production of Y chains can balance the lack of β chains, neutralize excess of α chains and provide improvement. The beneficial results in thalassemia major patients have not been very encouraging (7-12); however, many studies have documented good response in thalassemia intermedia patients (13).

Patients & Methods

Patients were selected using simple random sampling. The questionnaire was used for data collection for this research. The study evaluated hydroxyurea complications in a cohort of 28 patients with major (n=20) and intermediate thalassemia (n=8).Laboratory tests including CBC (complete blood count) and liver enzymes were performed monthly. HU was started in a dose of 10 mg/kg daily and then increased by 5 mg/kg daily every 4-6 weeks until toxicity occurred or clinical response was achieved. The variables such as gender, age, ethnicity, age of diagnosis, age of starting HU, history of blood transfusion, duration of HU treatment, and dose of HU were recorded. The correlation between variables and dermatologic, neurologic, hematologic, and hepatic side effects were then compared.
Data were analyzed using SPSS software, version 16. P values < 0.05 were considered significant.

Results

We reviewed the records of 28 patients with intermediate and major β-thalassemia, 15 males (46.9%) and 13 females (54.2%). Eleven (39.9%) patients were ethnic Arabs and 17 (60.7%) were non-Arabs.
The median age of the patients was 17.47±9.42 (range: 4-52 years). The median age of initial diagnosis was 5.43±8.27 years. Hydroxyurea was started at a median dose of 15.4± 4.16 mg/kg.
The age of starting HU was 15.37±9.59 and the duration of HU treatment was 1.93±2 years.
The statistical analysis did not reveal a significant correlation between age at diagnosis (P=0.307), age of starting HU (P=0.94), duration of HU treatment (P=0.688), dose of HU (P=0.586) and ethnicity.
Twenty-three (82.1%) patients had history of blood transfusion .No correlation was found between blood transfusion and side effects (p=0.500).
Side effects of HU have been recorded in 21 (75%) patients.
Adverse effects were hair loss (n=8; 28.57%), hyper pigmentation (n=4; 14.28%), nausea and vomiting (n=2; 7.14%), abdominal pain (n=4; 14.28%), and increase in hepatic enzymes (n=2; 7.14%).
Neurologic complications were headache (n=7; 25%), vertigo (n=1; 3.57%) and drowsiness (n=1; 3.57%).
Hematologic side effects including decrease in PLT count and the Hb level were found in 1(3.57%) and 2 (7.14%) patients, respectively

Table1. Side effects of hydoxyurea

Side effects		Patients (%)
Neurologic 9(32.1%)	Headache	7(25)
	Vertigo	1(3/57)
	Drowsiness	1(3/57)
Dermatologic 8(28.5%)	Hair Loss	8(28/5)
	Hyper pigmentation	4(14/28)
	Skin ulcer	1(3/57)
	Skin rash	1(3/57)
Gastrointestinal 7(25%)	Abdominal Pain	4(14/28)
	Nausea and vomiting	2(7/4)
	Increase in LFT	2(7/4)
	Constipation	1(3/57)
	Anorexia	1(3/57)

Discussion

The most common side effects were headache and hair loss in 25% and 28.57% of patients, respectly.
The most common adverse effects of HU were neurologic complications which occur in 32.1%

(9) of patients. The dermatologic manifestations and gastrointestinal adverse effect occurred in 28.5% (n=8) and 25% (n=7) of our patients, respectively.

Kosarian and co-worker (2007) reported 295 patients received HU 15.5±6.4 mg/kg, and the median duration was 5.2±2 years (range: 0.5-9 years). The side effects of HU were nausea, palpitation, transient leukopenia and transient rise in creatinine (14).

Khushnooma and co-worker treated 79 patients with HU and followed them for 20-24 months. Among the frequently transfused patients, 58% became transfusion independent and 16% showed a 50% reduction in transfusions (15).

Chick and co-workers did not find any abnormalities in renal and liver function (16).

In zargari study, hyperpigmentation was the most common skin adverse effect (17).

Karimi and co-workers showed that dermatologic complications were the most common side effects followed by neurological and gastrointestinal adverse effects.

There were not any reports of hematologic toxicity or any signs of bone marrow suppression.

The statistical analysis showed a positive correlation between advancing age and adverse effects (18). In our study, neurologic, dermatologic and gastrointestinal complications were most common side effects.

Conclusion:

Side effects of HU were common but mild to moderate, benign and transient.

The statistical analysis did not show a significant correlation between occurrence of HU side effects and variables such as HU dose, duration of drug consumption, gender, ethnicity and history of transfusion.

According to the results of this and other studies, it seems that HU therapy in thalassemic patients can be safely used but can be started at low doses and increased slowly , monitoring the patient's response.

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