

Hydroxyurea in the management of thalassemia intermedia

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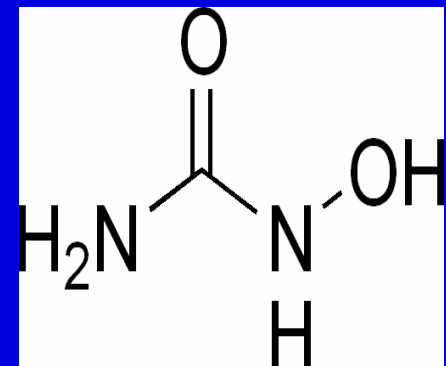
Shiraz University of Medical Sciences, Iran

1-2 May 2009, Syria

Hydroxyurea (Hydroxycarbamide)

- Urea analog → initially synthesized by Dressler and Stein in 1869.
- S-phase specific non-DNA hypomethylation (chemotherapeutic agent)
- Inhibits ribonucleotide reductase (an enzyme that converts ribonucleotide diphosphatase → deoxyribonucleotide

(Important in *de novo* DNA synthesis and DNA repair)



HU is used in the treatment of

- Myeloproliferative disorders
- Some other cancers (squamous cell carcinomas of the head and neck,...)
- Psoriasis
- HIV

Kumar B, et al. *Int J Dermatol.* 2001; 40(8):530-4

Biron F, et al. *J Acquir Immune Defic Syndr.* 2000 Dec 1;25(4):329-36.

Role of HU in Hemoglobin Disorders

- HU stimulates the gamma globins gene. (increased HbF)
- Decreased complications in some hemoglobin disorders.
- The clinical benefits of this compound are shown in sickle cell disease and β -thalassemia.

Karimi M, et al. J Pediatr Hematol Oncol. 2005; 27(7):380-5

Yavarian M, et al. Haematologica. 2004; 89(10): 1172-8

Koren A, et al. Am J Hematol. 2008; 83(5):366-370

Charache et al. NEJM 1995; 332:1317-22

Thalassemia Intermedia (TI)

- TI is a clinical definition applied to patients whose clinical phenotype is milder than that of thalassemia major. The clinical course of TI is characterized by several complications that can be prevented by an accurate follow-up.

Camaschella C. Haematologica. 1995;80(1):58-68.

Effects of HU on β -thalassemia

- The significant benefit is expected in beta-thalassemia by neutralized excess alpha-chains and increased production of gamma-chains which leads to decreased ineffective erythropoiesis.

Koren A, et al. Am J Hematol. 2008; 83(5):366-370

Bradai M, et al. Transfusion. 2007; 47(10):1830-6

Karimi M, et al. J Pediatr Hematol Oncol. 2005; 27(7):380-5

Some recent studies on TI

References	No of patients	HU dose	Length of therapy	Results
Mancuso et al Br J Haematol 2006	18 splenectomized untransfused	5-30 (mg/kg/d)	1 year	Mean Hb ↑ 1.5 gr/dl
Karimi et al J Pediatr Hematol Oncol 2005	163	8-12 (mg/kg/d)	6 year	Group I: 83/120 (69%) transfusion free and ↑Hb to 9.5 gr/dl Group II: ↑Hb to 9.6 gr/dl
Dixit et al Ann Hematol 2005	37	10-20 (mg/kg/d)	4-36 months	45.9% transfusion free or ↑Hb>2gr/dl 24.3%↓transfusion to 50% or ↑Hb 1-2gr/dl
Gamberini et al Pediatr Endocrinol Rev. 2004	6	1000 (mg/d)	3 months	↓ the size of extramedullary hematopoiesis mass and cured leg ulcers

Clinical and paraclinical effects of HU on TI

- **Increased Hb levels**
- **Reduced blood transfusion dependency**
- **Increased MCV and MCH**
- **Decreased the extramedullary hematopoiesis mass and osteoporosis**
- **Decreased splenomegaly**
- **Decreased skeletal deformities**
- **Increased energy state, exercise tolerance and sense of well-being**
- **Cardiac function status**
- **?Decreased pulmonary hypertension**

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Karimi M, et al. Eur J Haematol. 2009; 82(3): 213-8

HU and genotype analysis

- polymorphism for *Gγ XmnI*, homozygous for β -globin mutations [IVS-II 1 (G-A) or IVS-I 5 (G>C)] and carry α -thalassemia deletions have a strong influence on the clinical response to HU therapy.
- There is still not clear direct relationship between clinical and hematological responses to HU with mutation genotype.
- It needs further studies.

Koren A, et al. *Am J Hematol*. 2008; 83(5):366-370

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Adverse Effects of HU

ORGAN SITE	SIDE EFFECT
Neurologic	Peripheral neuropathy Headache, convulsions Drowsiness, dizziness, hallucinations
Dermatologic	Alopecia (rare) Erythema, rash Cutaneous vasculitis/ ulcers and gangrene Dermatomyositis like changes Nail changes Radiation recall reaction (rare) Hyperpigmentation
Gastrointestinal	Mild nausea, vomiting, diarrhea Pancreatitis Constipation Stomatitis, gastric irritation Anorexia
Hematologic	Bone marrow depression (neutropenia, anemia and rarely thrombocytopenia) Immunosuppression Megaloblastosis
Hepatic	Liver failure Abnormal LFT's (rare)
Hypersensitivity	Type III (serum sickness) Hyperpyrexia (low risk)
Neoplastic	Acute leukemia? Skin cancer
Pulmonary	Acute pneumonitis (rare), fibrosis
Other	Fever, chills Fatigue
Renal/metabolic	Elevated BUN and creatinine Hyperuricemia , dysuria

- We studied 143 TI patients who had been treated with HU (8-12 mg/kg/d) for a period of 10 years.
- Adverse effects were seen in 30.7% of patients that dermatologic side effects (21.7%), neurological (16%) and GI (7%) were most adverse effects.
- There were not any reports of leukemia or secondary malignancy, hematologic toxicity or BM suppression in our patients.

- HU tolerates well in β -thalassemia patients.
- It seems safe.
- Nevertheless, the question about the safety of HU treatment in thalassemia patients should not be considered closed and further studies regarding the long-term adverse effects of HU as well as neoplastic and teratogenic risk should be undertaken in the future studies.

Dosage

- High dose of HU may not cause to raise Hb levels as a result of BM suppression.
- It seems that low dose of HU (less than 20 mg/kg/d) is well tolerated without serious side effects and more reasonable hematological responses.

Wang M, et al. Br J Haematol. 2002;119(4):1098-105

Studies on beta-thalassemia major

References	No of patients	HU dose (mg/kg/d)	Length of therapy	Results
Bradi et al. Transfusion 2007	45	16.3±2.3 Raised to 17.4±2.4	1 year	20(44.5%) good response with ↑1.5 gr/dl in Hb level
Korean et al. Am J Hematol 2008	11	10.9±3	46±25 months	9 good response with Hb level of mean 8.2±0.7 gr/dl and transfusion free

Conclusion

- Oral use and easy to take
- Inexpensive
- It has good clinical and hematological (Hb) responses
- Safe (especially at low dose)
- Decreased complications in patients with TI
- No clear indications exist to predict which patients will response

So, HU could be a useful alternative to blood transfusion in some thalassemia patients as well as increased Hb levels in untransfused TI patients.

Thank you for your attention



Perspolis (South of Iran)