

Medical management of β -thalassaemia without blood transfusion: a myth or a reality?

Tahir Shamsi, Saqib Ansari

Beta (β)-thalassaemia major is a transfusion dependent anaemia that results from absent or reduced synthesis of beta-globin chains. The mainstay of treatment is palliation with blood transfusion and iron chelation therapies. The only definitive and curative treatment available is bone marrow transplant from an HLA-identical donor.¹ The observation that hydroxyurea (HU) can cause a rise in foetal haemoglobin (HbF) in sickle cell disease led many investigators around the globe to exploit its potential in other haemoglobinopathies.² The precise mechanism of action is not yet clear, but it appears that HU increases nitric oxide levels, causing soluble guanylyl cyclase activation with a resultant rise in cyclic GMP, and the activation of gamma-globin synthesis necessary for HbF.³ These newly-formed gamma-globin chains competitively bind with alpha-globin chains.

In thalassaemia, children make normal quantities of Hb during foetal life. At birth their gamma-globin gene gets methylated and they progressively stop making sufficient quantities of gamma-globin chains to bind with alpha chains.¹ Due to a mutation in the beta-globin gene, there is no or minimal beta-globin chain synthesis. This leads to excessive accumulation of alpha chains, which precipitate and cause lipid peroxidation of red cell membrane leading to haemolysis, ineffective erythropoiesis and severe anaemia.¹

Administering HU in this group of patients switched on the gamma-globin gene.⁴ The re-synthesis of gamma-globin chains allows the coupling of alpha-globin chains, which leads to effective erythropoiesis and a rise in the total Hb concentration (all of it would be HbF).

A local study showed that 40% patients will not need blood transfusion and maintain Hb level between 7-9 gm/dl long-term.⁴ Earlier studies from Thailand and Italy showed a minimal clinical benefit of raising HB level 0.5-1.0gm above the baseline.^{5,6} Meanwhile reports from India, Iran and France showed independence from blood transfusion in many patients.⁷⁻⁹

There has been scepticism on the use of HU by many clinicians and many concerns have been raised. A major

.....
Department of Haematology, National Institute of Blood Diseases & BMT, Karachi.

Correspondence: Saqib Ansari. Email: muddasirsaqib@yahoo.com

concern raised was based on earlier reports from Italy, Greece and Thailand, which showed that HU in haemoglobinopathies did not show any benefit and its efficacy was only noted in sickle cell disease.^{5,6}

Many investigators reported clinically significant effects of HU in β -thalassaemia major patients. These include a rise in Hb above 9 gm/dl and a reduction in packed red blood cell transfusion requirement. HU treatment was well-tolerated and it did not cause any haematopoietic suppression except in one patient who developed transient thrombocytopenia that resolved after a short period of HU cessation. The authors did not encounter any malignancies including leukaemia in the five-year follow-up period. Many genetic factors (e.g. XmnI polymorphism, the T-allele in linkage to the haplotype I and coinheritance of alpha thalassaemia gene) were found to predict a response in these studies.⁷⁻⁹

Another concern discussed commonly is that "the increment of Hb in these trials was marginal ranging from 0.5 to 1.5 gm and we all know that 0.5 to 1.0 gm variation in Hb is noted in many conditions including diurnal variation. In most of these trials the main focus was on Hb increment without considering the side effects which include nausea, vomiting and life-threatening neutropenia. On the same note, as these patients were deprived of blood transfusions so they must have developed extramedullary haematopoiesis, which lead to hepatosplenomegaly and skeletal abnormalities that is missing in the clinical findings of these trials."

The explanation of concerns in the above-mentioned studies is that these patients maintain an Hb level of 7-9 gm without transfusion, and it's not 0.5-1.5 gm rise. All the 7-9 gm of Hb is produced by their bone marrow. In β -thalassaemia setting, a very low dose of HU (8-20 mg/kg per day) was used. Although there is a potential to develop nausea/vomiting or neutropenia but grade 4 neutropenia is not observed in any of the trials. One important observation reported by most studies is the improved quality of life / well-being experienced by the patients. None of the trials reported any signs of extramedullary haematopoiesis, worsening of hepatosplenomegaly or skeletal abnormalities. Published data consistently reported an increase in the size of spleen and liver from baseline and at different timelines suggesting "extramedullary haematopoiesis" does not develop in these

subjects. The reason is two-fold: one is effective erythropoiesis due to a reduction in alpha: non-alpha chain imbalance, and the second is the cyto-reductive effect of HU.⁴

Another very important concern is that "HU carries mutagenic potential although its safety is established in sickle cell disease. What will happen to β -thalassaemia major patients after 30 or 40 years of exposure to this potentially mutagenic compound?" The explanation of this concern is that in animal models, HU has proven mutagenic potential. But in long-term follow-up of over 17.5 years and in a statistical model of clinical and biological benefits and safety of HU over 654 patient-year exposure, no malignancy was observed.^{12,13} With a clear pattern of response of HU in different type of mutations in beta-globin gene, published papers have pointed out that its inadvertent use cannot be justified.

Thalassaemia is a major genetic and hereditary disorder of public health in the country. Every year, 6,000-10,000 new patients are added to the existing population.¹⁵ There are 10 million carriers of this disease who spread this disease to their next generation.¹⁶ This enormous disease burden warrants special attention to develop and implement thalassaemia prevention programme. Side by side, allowance should be made for those who suffer from this disease by providing comprehensive care, safe blood, iron chelators, bone marrow transplant and extend this newly discovered indication of HU to eligible patients.

Management of thalassaemia has a major bearing on different aspects of healthcare delivery, economics and social well-being of our nation. It is gratifying to see a major development in the treatment of thalassaemia in which 40% patients do not require blood transfusion while a significant number have more than 50% reduction in blood transfusion requirements.⁴ This seems to be a major breakthrough and a ray of hope for thousands of parents who suffer from the misery, financial hardship, complications of the disease and treatment-related iron overload in their affected children. Most important discovery of these researchers is their ability to identify the 5 genetic mutations in which HU has been found to be preferentially beneficial.

Economic cost of treatment of thalassaemia is enormous.¹⁷ Comprehensive treatment of 60,000 registered patients cost 7.8 billion rupees per year. On an average, blood transfusion cost is Rs 30,000 per year per child and cost of iron chelation is Rs 150,000 per year per child. Most of this cost is covered by NGOs, government and affected families. When 40-50 % of these patients can be managed without blood, at least 3.5 billion rupees could be saved. It will also reduce the shortage of blood in the country and blood banks will be able to provide this blood in cases of trauma and to women who die

because of massive blood loss during childbirth.

Thalassaemia care requires a concerted effort and a public-private partnership to manage its menace. We hope that every stake-holder will feel its responsibility and play an important role in addressing this national health issue.

References

1. Weatherall DJ, Clegg JB. The thalassaemia syndromes. 4th ed. Oxford: Blackwell Science; 2001; pp 288-9.
2. Perrine SP. Fetal globin induction: Can it cure β -thalassaemia? Hematology Am Soc Hematol Educ Program 2005; pp 38-44.
3. Charache S, Terrin MI, Moore RD, Dover GJ, Barton FB, Eckert SV, et al. Effect of hydroxyurea on frequency of painful crisis in sickle cell anaemia. Investigators of the Multicenter Study of Hydroxyurea in Sickle Cell Anaemia. N Engl J Med 1995; 332: 1317-22.
4. Ansari SH, Shamsi TS, Ashraf M, Perveen K, Farzana T, Borhany M et al. Efficacy of hydroxyurea in providing transfusion independence in β -thalassaemia. J Pediatr Hematol Oncol 2011; 33: 339-43.
5. Rodgers GP, Sauntharajah Y. Advances in experimental treatment of β -thalassaemia. Expert Opin Invest Drugs 2001; 10: 925-34.
6. Olivieri NF. Reactivation of fetal haemoglobin in patients with β -thalassaemia. Semin Hematol 1996; 33: 24-42.
7. Fucharoen S, Siritanaratkul N, Winichagoon P, Chowthaworn J, Siriboon W, Muangsup W, et al. Hydroxyurea increases haemoglobin F levels and improves the effectiveness of erythropoiesis in β -thalassaemia/haemoglobin E disease. Blood 1996; 87: 887-92.
8. Bradai M, Abad MT, Pissard S, Lamraoui F, Skopinski L, de Montalembert M. Hydroxyurea can eliminate transfusion requirements in children with severe β -thalassaemia. Blood 2003; 104: 114-7.
9. Zamani F, Shakeri R, Eslami SM, Razavi SM, Basi A. Hydroxyurea therapy in 49 patients with major β -thalassaemia. Arch Iran Med 2009; 12: 295-7.
10. Yavarian M, Karimi M, Bakker E, Hartevelde CL, Giordano PC. Response to hydroxyurea treatment in Iranian transfusion-dependent β -thalassaemia patients. Haematologica 2004; 89: 1172-8.
11. Italia KY, Jijina FJ, Merchant R, Panjwani S, Nadkarni AH, Sawant PM, et al. Response to hydroxyurea in β -thalassaemia major and intermedia: experience in western India. Clin Chim Acta 2009; 407: 10-5.
12. Nzouakou R, Bachir D, Lavaud A, Habibi A, Lee K, Lionnet F et al. Clinical follow-up of hydroxyurea-treated adults with sickle cell disease. Acta Haematol 2011; 125: 145-52.
13. Steinberg MH, McCarthy WF, Castro O, Ballas SK, Armstrong FD, Smith W et al. The risks and benefits of long-term use of hydroxyurea in sickle cell anaemia: A 17.5 year follow-up. Investigators of the Multicenter Study of Hydroxyurea in Sickle Cell Anaemia and MSH Patients' Follow-Up. Am J Hematol 2010; 85: 403-8.
14. Ansari SH, Shamsi TS, Khan MT, Borhany M, Farzana T, Perveen K et al. Genotype of β -Thalassaemia Patients As Predictors for Prognosis & Management without Blood Transfusion. ASH Annual Meeting Abstracts 2011; 118: (Abstract No: 3199).
15. Ahmed S, Saleem M, Modell B, Petro M. Screening extended families for genetic haemoglobin disorders in Pakistan. N Engl J Med 2010; 347: 1162-8.
16. Ahmed S, Saleem M, Sultana N, Raashid Y, Waqar A, Anwar M et al. Prenatal diagnosis of β -thalassaemia in Pakistan: experience in a Muslim country. Prenat Diagn 2000; 20: 378-83.
17. Faulkner LB. Extending access to Bone Marrow Transplantation for severe Thalassaemia. (Online). (Cited 2012 October 2). Available from URL: http://www.thalassaemia.org.cy/antalya_presentations/12th/Lawrence%20Faulkner.pdf.