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HydroxyureaTherapy in Patients with Sickle Cell Disease

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Abstract

Sickle cell anemia is associated with several systemic complications and life-threatening crises. The use of hydroxyurea, which increases hemoglobin F level in patients with sickle cell disease, is associated with reduction in disease severity, diminution in the frequency of veno-occlusive crises and other complications as well as improvement in the quality of life. There are specific indications for the use of hydroxyurea in patients with sickle cell disease and there are certain tools to monitor its effectiveness.

Hydroxyurea has been shown to be a safe medication even on long-term administration. However, close monitoring and regular follow up of patients from clinical and laboratory sides are essential to ensure early discovery of toxicity, adherence to the prescribed treatment in addition to continued and long-lasting response to therapy. In this literature review: the complications of sickle cell anemia as well as the available therapeutic modalities will be highlighted and the role of hydroxyurea in the management of patients with the disease will be discussed thoroughly.

Introduction

Sickle cell disease (SCD) is a very devastating medical condition caused by an autosomal recessive inherited hemoglobinopathy. This genetic defect is characterized by production of an abnormal hemoglobin (Hb) called Hb S which is poorly soluble and becomes polymerized when deoxygenated [1]. The pathophysiological hallmark of SCD is intracellular polymerization of Hb S upon deoxygenation [2]. Hb S results from point mutation in β-globin chain of human Hb (Glu 6 Val) where the sixth amino acid, glutamine, is substituted by valine[1,3-5]. This genetic mutation causes red blood cells (RBCs) to acquire a sickle shape under conditions of hypoxia resulting in a wide range of complications such as veno-occlusive crises, hemolytic episodes, stroke, acute chest syndrome and susceptibility to various infections [4].

Worldwide, Hb S is the commonest pathological Hb mutation and is one of the most common genetic causes of illness and death [5,6]. Recently, SCD has been recognized as a global health problem by the United Nations (UN) and the world health organization (WHO) [6]. Currently, the global burden of SCD is increasing and is expected to increase further in the coming decades [6,7]. SCD occurs throughout sub-Saharan Africa and in small pockets in the: Middle East, Indian subcontinent and Mediterranian and Caribbean regions [8,9]. Worldwide, approximately 300,000 to 400,000 children are born every year with SCD and up to 90% of these births occur in low-or middle-income countries [5,8].

Complications of SCD and General Outline of Management

Patients with SCD are at risk of developing a number of life-threating crises and the disease may be complicated by adverse consequences that may involve any body organ (Table 1)[1-4,10,11]. A study that wasperformed in both the United Kingdom (UK) and the United States of America (USA) which included 632 patients showed that the risk factors for death in patients with SCD include: age > 47 years, male gender, chronic blood transfusions, WHO class III-IV, and elevated hemolytic markers, serum ferritin and serum creatinine level [12]. Care of patients with SCD is a difficult task that requires a multidisciplinary approach [1,3,11,13]. Management of patients with SCD can be divided into: (1) general measures that can serve as long-term care as well as crisis intervention, (2) specific and targeted therapies that are gaining particular interest and are aimed at prevention of complications and management of these complications once they are encountered, (3) potentially curative therapies and (4) preventive measures (Table 2) [1,3,11,14-21].

Targeted Therapies in the Management of SCD

There are several classes of targeted and specific therapies that have been utilized in the treatment of patients with SCD. Examples of these drug categories include: drugs that increase Hb F production, Gardos channel inhibitors, anti-oxidants and vascular tone targeting agents (Table 2)[3,22-25]. Amongst the targeted therapies, agents that increase production of Hb F have received especial attention. Hydroxyurea is the most commonly studied and used agent [3,22,23]. Gardos channel inhibitors, such as ICA-17043, have been reported to improve RBC survival but only minimal improvement on pain episodes has been achieved. These drugs modulate the transport systems that are involved in cellular dehydration [1,3]. Because many factors in sickle-cell-induced ischemic injury are regulated by nitrous oxide (NO), the role of NO has been explored in patients with SCA. While pilot studies treating individualswith NO initially showed beneficial effects, larger studies did not show similar benefits [3].

Hydroxyureain the Treatment of SCD

Hydroxyurea was initially synthesized in Germany in 1869. It is an oral chemotherapeutic agent that has traditionally been used in the treatment of: chronic myeloproliferative neoplasms, certain types of leukemia, melanoma and ovarian cancer [26]. Hydroxyurea was first tested in SCD in 1984. In the USA, the drug was approved

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Complication or organ involved	Examples and details
Infections	* Pneumonia ** Organisms: * Urinary tract infection - *Streptococcal pneumoniae* - *Salmonella species* * Pyelonephritis - *Neisseria meaningitidis* * Meningitis - *Hemophilus influenzae* - *Chlamydia pneumoniae* * Acute cholecystitis - *Staphylococus aureus* * Bacteremia and septicemia - *Myloplasma pneumoniae* - *Parvovirus B-19*
Sickle cell crises	* veno-occlusive * Hemolytic * Aplastic * Splenic sequestration
Bone involvement	* Dactylitis * Avascular necrosis of bone e.g. femoral head (osteonecrosis) * Osteomyelitis
Renal involvement	* Hyposthenuria * Glomerulopathy - End stage renal disease * Microalbuminuria * Renal insufficiency- Contrast and analgesic nephropathies
Pulmonary involvement	- Pulmonary emboli - Restrictive lung disease - Acute chest syndrome - Pulmonary hypertension - Lung infections
Cardiac complications	- Cardiomyopathy - Myocardial infarction - Heart failure
Neurological sequelae	- Ischemic stroke - Silent cerebral infarctions - Convulsions
Chronic hemolysis	- Anemia (may be severe) - Cholelithiasis - Priapism - Risk of aplasia - Hyperbilirubinemia - Leg ulcers - Pulmonary hypertension
Miscellaneous Complications	* Delayed growth * Drug toxicity * Delayed sexual maturation * Narcotic dependence / abuse * Proliferative retinopathy * Priapism * Iron overload and hemochromatosis * Hyposplenism, splenic dysfunction and auto-splenectomy * Organ dysfunction and failure

Table 1: Complications of sickle cell anemia.

General Measures	Specific and targeted therapies	Potentially curative therapies	Preventive measures
* Analgesia for pain * Oral and intravenous hydration * Folic acid supplements * Penicillin prophylaxis * Antimicrobials for infectious complications * Blood transfusion * Exchange blood transfusion * Oxygen supplementation * Mechanical ventilation in respiratory distress * Joint replacement therapy for avascular necrosis e.g. hip joint * Chelation therapy for iron overload	** Drugs that increase HbF production - Hydroxyurea - Vorinostat - Valproic acid - Panobinostat - Erythropoietin - Kit ligand - Histone deacetylase inhibitors: butyrate, scriptade, apicidin, tricistatin A and hydroxyamide. - Hypomethylating agents: decitabine and 5- azacytidine - Anti-angiogenic agents: thalidomide, pomalidomide and lenalidomide ** Anti-oxidant therapies: * Glutamine *N-acetylycystine * Alpha-lipoic acid * Omega - 3 fatty acids ** Gardos channel inhibitors ** Vascular tone targetting: IV magnesium ** Anti - sicking agents e.g. Aes - 103 ** Blockade of adhesive pathways: * Intravenous immunoglobulin * Anti - selectins * Propranolol * Tinzaparin ** Anticoagulants for vascular thrombosis ** Anti-platelet agents: prasugrel ** Anti - inflammatory agents: regadenoson ** Statins; for vascular protection ** Phytomedicines; including plant mixtures *** Investigational therapies e.g. nitrous oxide	** Gene replacement therapy ** Various forms of stem cell therapies	** Avoidance of: - dehydration - extremes of temperture - physical exhaustion - high altitude without oxygen supplementation - certain medications: * Meperidine *Granulocyt-colony stimulating factor (G-CSF) ** Health education ** Screening programs ** Family and genetic counselling

Table 2: Management outlines in patients with SCA.

by the Food and Drug Authority (FDA) for use in adults with SCD in February 1998 and the National Heart Lung and Blood Institute (NHLBI) recommended the use of hydroxyurea therapy on daily basis in selected patients with SCD in 2002 [26-29].Hydroxyurea stimulates Hb F production. Additionally, some of the clinical benefits of the drug may be mediated through other mechanisms:

(1) Reduction of sickle erythrocyte-endothelial cell adhesion and (2) reduction of vasoconstrictive stimulus [24-30]. Approaches to understand the impact of hydroxyurea treatment on Hb F production and its other therapeutic effects on SCD include the use of: single nucleotide polymorphisms (SNPs), pharmacokinetics, gene expression-based analysis and epigenetic studies in humans in addition to through studies in existing murine models [31]. Genetic polymorphisms can modify the laboratory and clinical phenotypes even in very young patients with SCD [32]. Secretion-associated and RAS-related protein (SAR) has recently been shown to play a pivotal role in HGB induction and erythroid maturation by causing cell apoptosis and G1/S-phase arrest [33]. Variation within SAR1A regulatory elements may contribute to inter-individual differences in the regulation of Hb F expression and the responses to hydroxyurea treatment in patients with SCD [33]. Thegenotoxicity of hydroxyurea in patients with SCD is low. However, individual receiving the drug should be constantly monitored [34,35]. Hydroxyurea does not appear to have significant deleterious effects on the immune functions of infants and children with SCD. Therefore, no changes in immunization schedules are recommended [36]. It exerts dose-dependent anti-proliferative effect on T-cells, but has no direct impact on T-cell activation [37].

Body organ / system	Specific adverse effects
Hematopoeitic system	* Variable degrees of myelosuppression, usually reversible:
	- mild thrombocytopenia - severe anemia - mild to moderate neutropenia
	* Megaloblastic erythropoiesis
Gastrointestinal tract	- Nausea - Vomiting - Diarrhea - Constipation
Liver	* Hyperbilirubinemia * Elevated liver enzymes
Skin, hair and nails	** Various skin eruptions: - Erythematious rash - Facial erythema
	- Maculopapular rash - Hyperpigmentation
	** Skin ulcerations ** Hair loss ** Nail changes
Fertility in males	* Reduced sperm count - semen impairment appears to be proportional to the duration of hydroxyurea therapy.
	* Reduced sperm motility
	* Abnormal sperm morphology -semen impairment is usually irreversible in the majority of cases.
Miscellaneous side effects	* Renal tubular dysfunction ** Headache ** Fever ** Weight loss
	* Pulmonary fibrosis - rarely
	* Parvovirus-B19 infection ** Few reports of leukemia in humans.
Adverse effects in animal studies	** Carcinogenesis ** Teratogenesis ** Exacerbation of SCD - induced hypogonadism and development of gonadal failure ultimately.

Table 3: Adverse effects of hydroxyurea in humans and animal studies.

Indications	Details and examples
(1) Acute veno-occlusive complications	- Recurrent painful events - Dactylitis
	- Acute chest syndrome - Frequent hospitalizations
(2) Laboratory markers of severity	- Low hemoglobin - High white blood cell count
	- Low hemoglobin F level - High lactic dehydrogenase level
(3) Organ dysfunction	- Renal disease; proteinuria
	- Pulmonary disease; hypoxemia
	- Brain: * Elevated TCD velocities
	* Silent MRI or MRA changes
	* Stroke prophylaxis
(4) Miscellaneous	- Poor growth parameters
	- Patient or family request
	- Sibling on treatment

- TCD: transcranial doppler
- MRI: magnetic resonance imaging
- MRA: magnetic resonance angiography

Table 4: Potential clinical indications for using hydroxyurea in the treatment of patients with sickle cell disease

The use of hydroxyurea has been associated with adverse effects that can involve any body organ, but these side effects are not usually severe (Table 3)[21,30,38-42]. The effect of hydroxyurea on renal function is controversial. One study showed that the drug decreases glomerular hyperfiltration in children with SCD, while two other studies showed that the use of hydroxyurea in patients with SCD is associated with not only preservation but also improvement in renal concentrating ability and even reduction in renal enlargement [43-45]. A three year follow up of patients with SCD treated with hydroxyurea showed no major short or medium-term toxicity and a 9 year follow up study showed that no serious adverse effects were encountered on long-term use of the drug [39,46]. Due to the safety and efficacy of hydroxyurea in very young children, it is recommended to consider hydroxyurea therapy for all children with SCD regardless the presence or absence of clinical symptoms [47-49].

The potential indications for the use of hydroxyurea in infants, children and adults with SCD are included in Table 4 [22,50-53]. Several studies on the use of hydroxyurea in patients with SCD have shown the following beneficial effects: (1) increased production of Hb F with a concomitant reduction in the intracellular concentration of Hb S that can lead to an increase in total Hbconcentration and decreased hemolysis with the release of free Hb, (2) reduction in white blood cell (WBC) count and reduction in the expression of cell adhesion molecules that contribute todiminution of veno-occlusive crises and other complications, (3) reduction in the rate of transfusion requirements, (4) reduction in the number of visits to the emergency room and in the frequency of hospital admissions, (5) reduction in the rate of infectious complications, (6) significant reductions in the costs of medical care, and (7) reduction in the severity of SCD, decreased mortality, improved survival and improvement in the quality of life [22,30,46,50,51,54-56]. Hence, the use of hydroxyurea in patients with SCD is cost-effective [60,61]. A prospective, two arm, single center study on the effect of long-term administration of hydroxyurea on morbidity and mortality in adults with SCD that included 330 patients showed: the probability of 10 year survival was 86% and 65% for hydroxyurea and non-hydroxyurea treated patients respectively ($p=0.001$) although hydroxyurea patients had more severe forms of SCD. Multivariate analysis showed that Hb F values at baseline and percentage change in lactic dehydrogenase (LDH) between baseline and 6 months were independent predictors of survival in the hydroxyurea group of patients [56]. Therefore, hydroxyurea treatment is not only beneficial in patients with SCD, but its long-term use can also modify the natural history of the disease [53]. However, the use of hydroxyurea in children with SCD is significantly associated with: (1) sickle genotype, (2) better parental knowledge about the major therapeutic effects of the drug, and (3) institution of this therapy by hematologists and provision of the drug to symptomatic patients [23].

Blood parameters	Details
Neutrophils	Absolute neutrophil count < 0.1 × 10^9 / L
Hemoglobin	< 7.0 g/dL with low reticulocyte count [absolute reticulocyte count > 100 × 10^9 / L] or Decrease in hemoglobin by > 20% from previous level
Reticulocytes	< 80 × 10^9 / L unless hemoglobin concentration is > 8.0 gram / dL
Platelets	Platelet count < 80 × 10^9 / L

- L: liter
- dL: decilite

Table 5: Hematological toxicity thresholds requiring hydroxyurea dose modification.

Predictors of response to hydroxyurea therapy include: (1) decrease in the number of veno-occlusive crises and reduction in the complications of SCD, (2) increase in normal Hb level, Hb F level, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean reticulocyte volume and percentage of F-cells, and (3) increase in the urinary level of hydroxyurea as measured by mass spectrometry [62-68].Otherparameters that can predict the response to hydroxyurea therapy include: duration of treatment with hydroxyurea, certain haplotypes such as Senegal haplotype, gender and weight of patient, WBC count, platelet count and reticulocyte count [68]. Sometimes, the dose of hydroxyurea may need to be modified due to the evolution of certain adverse effects that may be encountered on the long-term use of the drug. Hematological toxicity thresholds that require modification of the dose of hydroxyurea in patients with SCD are included in Table 5 [22,52].

Adherence to a medication is defined as the extent to which patients take medications as prescribed by their health care providers. Adherence to drug therapy can be measured by direct and indirect methods, but none of them is considered the gold standard. Direct methods include: directly observed therapy (DOT) and measurement of drug levels or biologic markers in blood. Indirect methods include: pill counts, pharmacy refills, electronic drug monitoring, patient diaries and patient self-reports the form of questionnaires [69]. The modified version of Morisky medication adherence scale (MMAS) is relatively simple, practical to use in clinical settings and is preferred to interviews. The eight items included in the scale aid in identifying patients with adherence problems and can be utilized to monitor adherence over the course of drug therapy [70-73]. Adherence to hydroxyurea can be measured by: (1) pharmacy refills, (2) MMAS, (3) visual analogue scale, (4) medical provider report, (5) clinic visits and (6) electronic DOT [74,75]. Pharmacy refills and MMAS may be helpful in identifying children at risk of poor response due to non-adherence and children with good adherence but having poor response due to biologic factors such as pharmacodynamics [74]. Studies have shown that close adherence to prescribed hydroxyurea therapy is necessary to maximize the efficacy of the drug and that adherence to treatment improves health-related quality of life [74,76-78]. In a largeretrospective study which was conducted in North Carolina in the USA and that included 312 patients with SCD treated with hydroxyurea, the following results were obtained: (1) adherence to treatment was generally suboptimal, as nearly two thirds of the study population were classified as non-adherent to therapy, and (2) adherence to hydroxyurea was associated with: reduced risk of hospitalization, reduction in the number of visits to the emergency room, reduction in the frequency of veno-occlusive crises and reduction in health care costs [77]. In a multicenter, double-blinded, placebo-controlled study on the efficacy of hydroxyurea therapy in SCA patients which included 150 patients treated with hydroxyurea and that was performed in USA in 1995, the results of follow up for 2 years showed: (1) half of the hydroxyurea-assigned patients had long-term increment in Hb F, and (2) bone marrow reserve or ability to withstand hydroxyurea therapy was important for sustained Hb F

increase during treatment with hydroxyurea[62]. Extended follow up of patients for 17.5 years showed significant reduction in mortality and safety of the drug on long-term use [55].

Barriers to adherence to hydroxyurea treatment include: high frequency and length of clinic visits, disruption of school and work and lack of resources [78]. Provider-related barriers to prescribing hydroxyurea include: patient adherence to the prescribed medication, patient adherence to blood tests and lack of contraception in females [79]. Facilitators of adherence include: health benefits of therapy, social support systems, medication reminders and positive clinic experiences [78]. In addition to health education, the following methods have been shown to improve adherence to treatment: (1) multimedia communication for hospitalized patients with their teachers and work colleagues, (2) integration of interactive web-based technology to assess adherence to therapy, (3)electronic DOT, and (4) coaching very young children for swallowing hydroxyurea capsules [75,78,80-82].

Over the last 30 years, substantial experience has accumulated regarding the safety and efficacy of hydroxyurea in patients with SCD and strong evidence supports its efficacy in reducing the frequency of veno-occlusive crises, acute chest syndrome, hospitalizations and blood transfusions in patients with SCD [29,50,51,53,54]. Thus, hydroxyurea is considered an important advance in the treatment of patients with SCD as it is the only widely used drug that modifies the pathogenesis of the disease [29,51-53,55]. Although questions remain regarding its long-term risks and benefits, current evidence suggests that many young patients with SCD should receive hydroxyurea[29,50,51,53,54].

Curative And Potentially Curative Therapies

Potentially curative therapies in patients with SCD include: gene replacement therapy and hematopoietic stem cell transplantation (HSCT) [1,3,16,18-21]. Gene replacement therapy, using either pluripotent stem cells or autologous gene correction in stem cell designs, has been studied in animal models with promising results [17,18]. Induced pluripotent stem cells (iPSCs) have the potential to correct the Glu-6-Val mutation in the abnormal hemoglobin (Hb S). However, safety issues are of a concern [3,16-19]. The only curative therapy for SCD is allogeneic HSCT. Traditionally this procedure has been limited to children below 16 years of age with severe pre-existing complications [1,19-21]. Use of HLA-matched sibling donor myeloablative allogeneic HSCT has been associated with: overall survival >90% and cure rate up to 85% [19-21]. However, HSCT particularly myeloablative allogeneic transplantation carries significant morbidity and mortality [19-21,83]. In sibling allografts, stem cells can be obtained from a normal donor or a sickle celltrait. Sibling allogeneic HSCT may be available for 30% of patients, while matched unrelated donor (MUD) allografts can be available for 60% of patients [20,21]. Recently, reduced-intensity conditioning therapy has been introduced in HSCT for patients with SCD and this form of HSCT allows older patients and those with organ dysfunction to be transplanted. Alternative donors such as unrelated cord blood HSCT as well as related haploidentical bone marrow and

peripheral blood HSCT have also been successfully used [19-21,83-85]. Interestingly, the use of hydroxyurea in patients with severe SCD prior to allogeneic HSCT does not have a negative impact on the outcome of HSCT as it seems to be associated with lower incidence of rejection and absent engraftment [86].

Conclusions and Recommendations

Hydroxyurea treatment is effective in reducing the complications of SCD in infants, children and adults and it has significantly improved the quality of life in patients receiving it. However, adherence to the prescribed medication is essential to achieve the expected response. Close follow up of patients and regular monitoring of their clinical and laboratory parameters is vital to predict the response to hydroxyurea treatment. Adopting a multidisciplinary approach and incorporation of continued health education are important to guarantee regular intake of the drug in order to prevent complications of SCD before they evolve.

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