PART I — DISEASE-MODIFYING THERAPY

1. Hydroxyurea

Principles

- To identify patients who are likely to benefit from hydroxyurea therapy.
- To initiate hydroxyurea therapy and adjust the dose according to clinical results and results of laboratory monitoring.
- To facilitate optimal patient adherence to hydroxyurea therapy.

Recommendations

Indications and patient counseling

- All adult HbSS or HbS-beta^0-thalassemia patients with a history of three or more crises per year should be counseled on the potential benefits and risks of chronic hydroxyurea therapy and strongly encouraged to begin taking it.
- All other HbSS or HbS-beta^0-thalassemia patients ≥9 months of age should be counseled on the potential benefits and risks of chronic hydroxyurea therapy, and encouraged to begin taking it.
- After a discussion of the potential benefits and risks, adult patients with HbSC and other compound heterozygous sickle cell disease should be offered hydroxyurea.

Administration and monitoring (modified from Platt 2008)

- Prior to starting hydroxyurea, measure CBC, reticulocyte count, HbF level, renal and liver function.
- For adult patients, consider a starting dose of 1,000 mg. For children, consider a starting dose of 20 mg/kg.
- If creatinine clearance is <60 mL/minute, the starting dose should be reduced.
- After 2 to 4 weeks of daily hydroxyurea, CBC should be performed to look for the expected decrease in white blood cell and platelet count and increase in mean corpuscular volume. If these have not changed:
  - Check that original dose calculation was accurate;
  - Review dosing regimen with patient;
  - Assess adherence and assist with finding strategies for compliance.
- Repeat CBC and reticulocyte count every 2 to 4 weeks, and adjust hydroxyurea accordingly to achieve the patient's maximum tolerated dose.
  - If blood cell counts are acceptable, strongly consider incremental dose increase(s). If 1 or more parameters fall(s) into unacceptable range at any time (e.g., absolute neutrophil count <1.0, platelet count <80, hemoglobin <50 g/L or decrease in reticulocyte count below 80 x 10^9/L), hold hydroxyurea until recovery, and consider resuming hydroxyurea therapy at a reduced dose.
  - Individual treatment centres must define their own thresholds for unacceptable hematologic values.
- Once the patient is on a stable dose, monitoring can take place less frequently (e.g., every 3 months).
- HbF levels may be monitored every 3 to 6 months to assess the efficacy of treatment.
- Patients who, despite dose adjustment, active management, and evidence of good adherence, do not respond to hydroxyurea can be considered for enrollment in high-quality clinical trials of other inducers of fetal hemoglobin.
- Contraception is advised for both men and women taking hydroxyurea.
- Women planning a pregnancy should discuss alternative therapeutic options with their treating hematologist, due to concern about teratogenicity of hydroxyurea. (*see Part III, section 2 for further details*)
- Hydroxyurea is contraindicated in lactating mothers, as it is excreted in breast milk.

Background

Hydroxyurea has been used for almost 20 years and is currently the only disease-modifying agent proven to prevent complications in patients with sickle cell disease (SCD).

Fetal hemoglobin (HbF) has long been observed to have a protective effect in SCD patients. Higher levels of HbF correlate with a less severe course in SCD patients, including fewer painful episodes, and lower risk of early death.[1,2] This result is due to decreased polymerization of sickle hemoglobin (HbS) in the presence of high concentrations of HbF. In the 1980s, a series of small studies in patients with SCD confirmed the ability of hydroxyurea to increase HbF levels.[3,4] Additional mechanisms of hydroxyurea in SCD include reduced neutrophil counts; decreased adhesiveness of circulating reticulocytes and neutrophils; improved red blood cell (RBC) hydration; decreased adhesiveness; and improved rheology.[5]

In 1995, the Multicenter Study of Hydroxyurea (MSH) was published, in which nearly 300 adult patients with sickle cell anemia and a history of three or more sickle pain episodes per year were randomized to receive either hydroxyurea at maximal hematological tolerated dose, or placebo. After a mean follow-up of 21 months, the hydroxyurea group had significantly fewer crises per year, fewer episodes of chest syndrome, and required fewer transfusions. The medication was well tolerated overall, without any important side effects.

Improved Survival in Adults

Since that landmark paper, there have been numerous additional studies demonstrating the benefits of hydroxyurea in SCD. Long-term follow-up of MSH study participants found an association of hydroxyurea use with improved survival.[6] Long-term follow-up of a similar European study demonstrated a significant reduction in 10-year overall mortality in patients with sickle cell anemia (HbSS) and HbS-beta^0-thalassemia.[7]

Infants and Children

Studies in children have shown reduced frequency of vaso-occlusive episodes[8,9] and blood transfusion,[8-10] improved transcranial Doppler flow velocities,[11] and reduced rates of hospitalization[9,10,12,13] after starting hydroxyurea, with no unexpected toxicity. Rare episodes of transient neutropenia were reported.[9,13]

The BABY HUG trial was a prospective clinical trial of liquid hydroxyurea (20 mg/kg/day) versus placebo in 193 infants and children with SCD.[14,15] Any child with HbSS or HbS-beta^0-thalassemia aged 9 to 18 months was eligible for the study, regardless of clinical severity. Although the study's primary endpoint was not achieved, there were significant reductions in the rates of acute chest syndrome, pain, dactylitis, transfusion, and hospitalization among patients who received hydroxyurea. There were also significant increases in hemoglobin concentration and hemoglobin F levels. There was increased mild-to-moderate neutropenia in the hydroxyurea group, but no increased risk of bacteremia or serious infection. Growth rate was not affected by hydroxyurea. Whether hydroxyurea may have some neuro-protective effect in infants and children remains to be defined.

Hemoglobin SC disease (HbSC)

Although most studies have evaluated patients with more severe forms of sickle cell disease, such as HbSS or HbS-beta^0-thalassemia, the few treatment studies in patients with HbSC found similar benefit.[16] To date, however, there have been no high-quality, prospective studies in patients with HbSC.

Hydroxyurea Administration and Monitoring

The goal of hydroxyurea is to titrate to the maximal tolerated dose for each patient, based on maintaining safe blood counts.[17] Laboratory testing of complete blood count (CBC), reticulocyte count, HbF levels, and renal- and liver-function tests should be performed prior to initiating hydroxyurea, and should be repeated at regular intervals thereafter (*see Recommendations box for details*).

Although the expected decrease in WBC and platelets and increase in HbF can be seen within weeks to months, a clinical response may only be evident after 3 to 6 months of treatment. In addition to laboratory monitoring and dose adjustment, follow-up appointments should be used to assess symptoms and to encourage continued adherence.

The younger the age when first commencing hydroxyurea, the deeper and more sustained the response to the medication.[18] A liquid formulation may be administered to infants and young children.

Once a patient is started on hydroxyurea, the current model of care is to continue this therapy indefinitely. Ongoing research and development of new anti-sickling agents brings hope for future alternatives, however.

Patient Counseling

Prior to initiation of hydroxyurea, patients should be counseled about potential reversible side effects, including nausea, rash, nail changes, hair thinning, and headache.

Concern has existed about the theoretical risk of malignancy after long-term use of hydroxyurea, because of possible increased rates of leukemia and skin cancers in patients with other hematologic conditions who had taken hydroxyurea. Laboratory studies, however, have shown no increased genotoxicity in hydroxyurea-exposed blood from patients with SCD compared with control subjects,[19] and no increased rate of malignancy has been observed in adults or children with SCD who have taken hydroxyurea for up to 20 years.[20,21] Furthermore, there is growing evidence that long-term hydroxyurea therapy is associated with decreased overall mortality, and may have a significant impact on the life expectancy of patients with SCD.[6,7]

Although unsubstantiated in human studies,[22] concern remains about possible teratogenesis based on animal studies. As a result, contraception is advised for both men and women. Patients planning conception should discuss therapeutic options with their treating hematologist. In women for whom the balance of potential risk to the fetus versus benefit to the patient with ongoing hydroxyurea use is uncertain (e.g. a woman with history of severe sickle cell disease complications who has been optimized on hydroxyurea), informed decision-making may include consultation with Motherisk and/or knowledgeable maternal-fetal medicine specialists. When hydroxyurea is discontinued in pregnancy, chronic transfusion may be considered as an alternative means of preventing maternal sickle complications.

Hydroxyurea is also contraindicated in lactating mothers, as it is excreted in breast milk and therefore could potentially lead to adverse effects in the infant.

Some patients and their families may have questions or misperceptions about the balance of risks and benefits of hydroxyurea therapy in SCD. It is important to outline the strong evidence of clinical benefit, and the lack of clear evidence of increased rates of malignancy and teratogenicity. Having a frank and open discussion about these issues is an important element in increasing medication acceptance and adherence.

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