Sickle Cell Disease: Hydroxycarbamide
STSTN guideline: Hydroxycarbamide (Hydroxyurea) - Guidelines for treating Adults with Sickle Cell Disease

Profile	
Version:	*V2.0*
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Executive/Divisional sponsor:	*Dr Lisa Pickering, Divisional Chair* *DGB February 2019*
Applies to:	*All staff involved in the care of patients with Sickle Cell*
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Approval	
Approval person/Committee:	*MedCard Divisional Governance Board*
Date:	*14th February 2019*

Contents

Policy Gateway

Please complete the checklist and tables below to provide assurance around the policy review process.

☒ I have involved everyone who should be consulted about this policy/guidance

☒ I have identified the target audience for this policy/guidance

☒ I have completed the correct template fully and properly

☒ I have identified the correct approval route for this policy/guidance

☒ I have saved a word version of this policy/guidance for future reviews and reference

Please set out what makes you an appropriate person to conduct this review:
Consultant for adult haemoglobinopathy service

Please set out the legislation, guidance and best practice you consulted for this review:
Reference: Guidelines for the use of Hydroxycarbamide in children and adults with sickle cell disease 2018 181, 460-475

Please identify the key people you involved in reviewing this policy why, and when:

Summarise the key changes you have made and why:
Updated in accordance with national guidelines

Executive Summary

This document contains the STSTN guidance for the use of hydroxycarbamide in adults with sickle cell disease (SCD).

1. Introduction

Sickle cell disease (SCD) is a life-long condition characterised by chronic red cell haemolysis leading to multi-organ dysfunction. Patients may also suffer from acute events often referred to as crises. Hydroxycarbamide (also known as hydroxyurea) is currently the only medication licensed in the UK for the prevention of recurrent painful vaso-occlusive crises in patients with SCD. It works by increasing fetal haemoglobin levels and reducing intercellular adhesion to improve blood flow.

This guideline provides detailed guidance on hydroxycarbamide treatment in patients with SCD.

2. Status and Purpose

This document is part of the Haematology Department's guidelines on the management of patients with SCD and is applicable to all staff involved in the care of these patients.

3. Definitions

Sickle Cell Disease – inherited lifelong condition due to abnormal haemoglobin variant.

4. Scope

This guideline is relevant to the care of patients with SCD requiring elective and emergency surgery at St.George's.

5. Roles and Responsibilities

5.1 Haemoglobinopathy team (Consultant haematologists, Clinical Nurse Specialist and Clinical Health Psychologist) – Responsible for the care of these patients, developing and updating guidelines to be reflective of good practice and to deliver the training to ensure good safe care.

5.2 Medical staff involved in the care of patients with SCD. Responsible with the oversight of the haemoglobinopathy team to deliver the care to these patients in line with guidelines where possible.

5.3 Nursing staff and allied health professionals involved in the care of patients with SCD on wards, day unit and other areas of St George's responsible with the oversight of the haemoglobinopathy team to deliver the care of these patients in line with guidelines where possible.

6. Content

6.1 Patient selection

The benefits of hydroxycarbamide should be discussed with all patients with SS/Sβ^0 to enable informed joint decision-making. It may also be useful in other types of sickle cell disease such as HbSC disease in selected patients.

Indications:

As a standard of care, Hydroxycarbamide should be discussed with all patients with HbSS/Sβ^0-thalassemia, and the information revisited at a later date as appropriate. It can be routinely offered from 9 months of age, irrespective of clinical severity.

It should also be offered to patients with severe complications:

- 3 or more episodes of acute vaso-occlusive painful episodes each year
- Recurrent or severe Acute Chest Syndrome

Other indications include:

- persistent low haemoglobin (<60g/l)
- hypoxaemia
- significant proteinuria
- patients keen to avoid blood transfusions if at all possible, those with alloantibodies or a history of severe transfusion reactions
- preoperative preparation when blood transfusions are not acceptable
- Patients changing from regular blood transfusions to maximum tolerated dose hydroxycarbamide for primary stroke prevention (see section below).
- significant cerebral vasculopathy when blood transfusions are unacceptable
- progressive cerebral vasculopathy despite adequate blood transfusions

6.2 Parent/patient information and Consent

Patient information leaflets should be given in addition to a full discussion of risks, benefits and side effects, including dose dependent bone marrow suppression. There is no available evidence in females or males that hydroxycarbamide affects fertility. In males, the effect of hydroxycarbamide on spermatogenesis remains unclear. Most studies are case reports with few prospective studies, making evidence-based counselling of the risk of developing sperm abnormalities or infertility challenging.

In view of these uncertainties it has been suggested that it is reasonable to offer post–pubertal male patients sperm analysis and cryopreservation prior to starting treatment with hydroxycarbamide .

Many patients and carers may want to think about the issues and discuss things further, a follow-up appointment to discuss things further should be offered.

Contacts:
Andrology Unit, Hammersmith Hospital:
Tel: 020 3313 34680. Email:lia.joannou@imperial.nhs.uk (Andrology Laboratory Manager)

Hydroxycarbamide is a form of chemotherapy and informed consent is essential; discussions should be recorded in the notes but it is not necessary for the patient to sign anything.

Hydroxycarbamide at high (superpharmacological) doses is teratogenic in animals leading to abnormalities in the central nervous system, vertebral bodies, craniofacial tissue, skull and limbs in mammals. There is limited data on adverse outcomes in pregnant women, including early fetal loss or anomalies. An expert panel report from the NTP in the USA expressed concern about potential teratogenicity with hydroxycarbamide and possible harmful effects to the baby when breastfeeding (NTP-CERHR, 2008). If women do conceive whilst taking hydroxycarbamide, stopping the drug should be considered in the first trimester and a detailed anomaly scan should be performed at 20 weeks gestation.

At present, until further data are available, the use of contraception is recommended for both male and female patients whilst taking hydroxycarbamide. Despite this precautionary measure, some women have become pregnant while they or their male partners were on hydroxycarbamide.

However, in men and women who have a severe disease phenotype and/or are difficult to transfuse, the risks of stopping hydroxycarbamide prenatally and for women during pregnancy may outweigh any possible risks of teratogenicity. If hydroxycarbamide is stopped prenatally and during pregnancy, consider a transfusion programme if there is a severe clinical phenotype as an alternative to hydroxycarbamide treatment**.** These risks should be carefully discussed with the patients to enable them to make an informed choice.

The importance of adherence to the effectiveness of Hydroxycarbamide should be discussed. If patients miss a dose they should not take a double dose.

6.3 Toxicity

- Reversible increase in skin and nail pigmentation, alopecia
- Haematological – myelosuppression – see below
- Renal
- Hepatic
- Gastrointestinal – rarely - nausea and vomiting, diarrhoea – antiemetics not usually required
- Teratogenic – Hydroxycarbamide may, theoretically harm the unborn fetus although there is no clear human evidence of this.
- Fertility in boys – some evidence of reduced fertility in males with sickle cell anaemia – exact role of Hydroxycarbamide unclear
- Long term marrow effects uncertain
- No evidence of increase in malignancy in patients with SCD taking Hydroxycarbamide.
- Drug interactions

6.4 Baseline investigations

Prior to commencing hydroxycarbamide these should include:

- FBC and reticulocytes with differential count
- HbF%
- Renal function
- Hepatic function including ALT

The Clinical Nurse Specialist should be informed of all patients starting hydroxycarbamide to record them for follow up and monitoring.

6.5 Administration and Formulation

Hydroxycarbamide is given orally once a day. If a dose is missed, a double dose should not be taken.

Hydroxycarbamide is available as:

- Hydroxycarbamide capsules 500mg
  Hydroxycarbamide capsules can be opened and the powder taken with a small amount of water or juice. This works well for some patients, but it should be explained that hydroxycarbamide is a form of chemotherapy and should not come into contact with skin or anybody other than the patient; this will mean washing the spoon very carefully and wiping up any spills immediately.
  Because the capsules are only available as 500mg, giving the exact calculated daily dose can be difficult, and in general it is satisfactory to give alternating day doses such as 500mg alternating with 1g to achieve an average daily dose, although this should be explained carefully to the patient and/or carers.

- SIKLOS 100mg tablets is used in paediatric practice and not usually available for adult sickle patients. When patients transition on the medication they are currently switched to the capsules.
- Where it is used SIKLOS tablets can be mixed with a small amount of water just before being taken.

- Hydroxycarbamide Liquid (100mg/ml)
  Liquid preparation is available and may be more suitable for some patients, although it has a short-shelf life, and can be difficult to obtain from local hospitals for shared-care patients. It is possible to arrange for local hospitals or pharmacies to dispense the drug, and this should be discussed with the pharmacists here.

6.6 Recommended Dose

The therapeutic dose range of hydroxycarbamide is 15-35 mg/kg daily and for some indications clinical response at the lower end of the range is sufficient (Lowest Effective Dose), whilst for other indications, particularly involving cerebrovascular disease, the dose is escalated to the higher end of the range, or until myelosuppression occurs (Maximum Tolerated Dose – MTD).

Most adults start at a dose of 15mg/kg daily (to the nearest 500mg), unless there is particular concern about the risk of myelosuppression, when lower doses should be used.

6.7 Dose Adjustment and Monitoring

For most patients, the dose is increased by 5mg/kg every 8-12 weeks until there is evidence of clinical benefit, which is the Lowest Effective Dose.

FBC, reticulocytes, renal and hepatic function and HbF% should be checked 2 weeks after starting, and after any dose increase, until the dose is stable and then every 8–12 weeks.

Assess clinical response and if sub-optimal, increase by 5mg/kg every 8 weeks (maximum dose 35mg/kg/day) until target ranges are reached or stopping if haematological toxicity (see below):
Target ranges:

- Neutrophils 2.0-3.0 x 10^9/l
- Platelets ≥ 100 x 10^9/l
- Reticulocytes ≥ 80 x 10^9/l

If cytopenias occur a dose adjustment should be made - see table below for dose adjustment for haematological toxicity. This is particularly important in patients where the aim is to increase the dose to Maximum Tolerated Dose (MTD) who are more likely to experience myelosuppression.

Neutrophils (x 10^9/l)	Reticulocytes	Platelets (x 10^9/l)	Dose Adjustment
>1.0	≥1% or ≥ 80 x 10^9/l	≥ 80	Continue current dose
< 1.0	<1% or <80 x 10^9/l (unless Hb >90g/l)	< 80	Stop treatment and recheck FBC weekly until Neutrophils >1.0 x 10^9/l platelets >80 x 10^9/l, Hb >45g/ and reticulocytes >80 x 10^9/l (unless Hb>90g/l) Restart at lower dose: reduce by either • 2.5-5mg/kg/day or • 500mg/day (1 capsule) or • 100mg/day (SIKLOS 1 capsule) Monitor FBC after 2 weeks and follow as above for dose modifications. This is the Maximum Tolerated Dose (MTD)

Other toxicities:
Renal: Increase in serum creatinine ≥ 50% baseline
Hepatic: > 100% increase in ALT
Stop Hydroxycarbamide, contact the family directly with instructions and arrange further tests to monitor recovery.

6.8 Dose adjustment to Maximum Tolerated Dose (MTD) for patients with cerebrovascular disease

For some indications, such as those involving cerebrovascular disease, the dose should be increased every 6-8 weeks by increments of 5mg/kg/day, to a maximum of 25-35mg/kg/day (maximum dose 2000mg) or until limited by myelosuppression (Maximum Tolerated Dose – MTD):
Target blood results for MTD:
Target neutrophil count 2.0-3.0 x 10^9/l
Total daily dose 25-30mg/kg/day

If neutrophils < 1.0 x 10^9/l, platelets <80 x 10^9/l or reticulocytes <80 x 10^9/l, discontinue for 2 weeks or until recovered (see above for monitoring), and restart a lower dose (usually the dose prior to the most recent dose increase). This is the Maximum Tolerated Dose.

Parents should also be advised to attend hospital for assessment and urgent blood tests if they develop symptoms suggestive of sepsis, or unusual bruising or bleeding, because of the possible risk of bone marrow suppression and neutropenia or thrombocytopenia.

Inform the GP/Shared Care Hospital team/in writing of any dose adjustments and blood test results

6.9 Admission to Hospital

Hydroxycarbamide therapy should be continued during hospitalizations or illness unless due to febrile neutropenia or bleeding with thrombocytopenia

6.10 Withdrawal of Hydroxycarbamide

Patients should usually be treated for at least six months before deciding to stop hydroxycarbamide because of lack of benefit. When hydroxycarbamide is associated with clinical improvement, it is typically continued lifelong.

7. Dissemination and implementation

7.1 Dissemination:
Guidelines will be available on the departmental intranet page and available in paper form in the junior doctor office in haematology.

7.2. Implementation
Guidelines will be promoted by the haemoglobinopathy team.

8. Consequences of Breaching the Policy

Failing to follow this policy could lead to action under the Trust's disciplinary policy.

9. Monitoring compliance
The table below outlines the process for monitoring compliance with this document.

Monitoring compliance and effectiveness table					
Element/ Activity being monitored	**Lead/role**	**Methodology to be used for monitoring**	**Frequency of monitoring and Reporting arrangements**	**Acting on recommendations and Leads**	**Change in practice and lessons to be shared**
WMQRS peer review quality standards	*Consultant haematologist*	*As required (every 2-3 year)*	*The lead or committee is expected to read and interrogate the report to identify deficiencies in the system and act upon them. Consider stating this responsibility in committee terms of reference.*	*Required actions will be identified and completed in a specified timeframe. Consider stating this responsibility in committee terms of reference.* *These will be discussed at Divisional governance board*	*Required changes to practice will be identified and actioned within a specific timeframe. A lead member of the team will be identified to take each change forward where appropriate. Lessons will be shared with all the relevant stakeholders.*

7. Associated documentation

8. References

Qureshi A, et al.Guidelines for the use of Hydroxycarbamide in children and adults with sickle cell disease. Br J Haematol 2018; 181, 460-475