HYDROXYCARBAMIDE IN SICKLE CELL DISEASE

Adult South Thames Sickle Cell and Thalassaemia Network guideline

Dr Tullie Yeghen

For the
South Thames Sickle Cell and Thalassaemia Adult Network Meeting
27 January 2012

Hydroxycarbamide

- First synthetised in 1869
- Ribonucleotide reductase inhibitor
- MSH study (Charache *et al*) terminated early in January 1995 due to significant superiority of HU arm
- Increases Hb F, reduces neutrophils, alters red cell adhesion, increases red cell water contents
- The only widely available disease modifying drug
- Remains somewhat unpopular with patients

Indications

Adults and children with Sickle Cell Disease who have:

- >3 admissions with painful crises in the previous 12 months
- >1 admission with painful crisis in the previous 12 months, and are symptomatic in the community
- >1 life threatening complications of the disease such as acute chest syndrome
- other indications (such as secondary stroke prevention, pulmonary hypertension) must be discussed with the consultant in charge of the patient.

Exclusions and requirements

- Pregnancy or not practicing active contraception (if sexually active)
- Active hepatitis
- Discuss the possible risks of infertility with male patients and offer sperm count and banking.
- Counsel patient re neutropenic sepsis, need for regular monitoring, teratogenicity, side effect profile. ?? Risk of secondary malignancy (4 leukaemia, 1 HD, no causality)
- ?? Consent form

Regimen details

- Commence at 15mg/kg to nearest 500mg
- If there is a good clinical response continue on this dose (Minimal effective dose)
- If clinical response is sub-optimal, increase by 2.5mg/kg every 8 weeks until toxicity seen.

Toxicity

- Neutrophils $< 1.5 \times 10^9/l$
- Platelets $< 80 \times 10^9/l$
- Retics $< 10 \times 10^9/l$
- Haemoglobin <3g/dl from baseline
- If any of the above problems with FBC encountered, stop hydroxycarbamide, until full blood count has recovered.
- Restart at 2.5mg/kg (or 1 capsule – 500mg) lower. This is the maximum tolerated dose (MTD)

Cautions

- If there is a significant rise in Hb (>11g/dl in HbSS) stop the hydroxycarbamide and consider venesection
- If there is a downwards trend in FBC parameters, increase frequency of monitoring
- Use with caution in renal & hepatic impairment: start at a lower dose and increment more cautiously
- If Creatinine Clearance < 60ml/min, commence at 50% dose (7.5mg/kg)

Monitoring

Day 1	Fbc and reticulocytes HbF% U+Es and LFTs Urate LDH Alpha genotype if not known (optional)
Day 14 (and every 14th day until dose stable)	Fbc Hb F% U+Es LFTs Reticulocytes
Once stable every 8–12 weeks	Fbc Hb F% U+Es LFTs Reticulocytes, LDH

Toxicities

- Common: Bone marrow suppression and cytopenias.
- Hyperpigmentation of nails and skin
- Nausea and vomiting
- Diarrhoea
- Skin rash
- Uncommon: Alopecia
- Teratogenicity
- Leg ulcers
- Decreased sperm count and function
- Low risk of second malignancy

Dose modifications

Haematological Toxicity

- **Neutrophils** ≥ 1.5 x 10^9/L & **Platelets** ≥ 80 x 10^9/L: 100% dose
- **Neutrophils** < 1.5 x 10^9/L or **Platelets** <80 x 10^9/L: Stop treatment and recheck FBC until N>1.5 and Plt >80. Restart treatment at 2.5mg/kg or 500mg daily lower.