Sickle and Thalassaemia Training days

September 2017

Hydroxycarbamide

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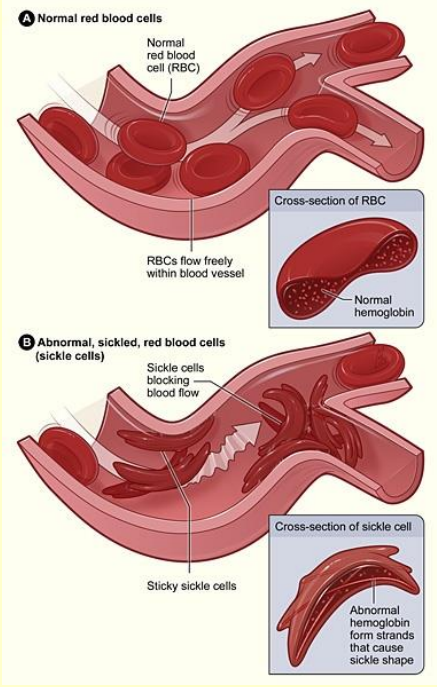
Why do sickle cells cause pain and organ damage?

Under certain conditions, haemoglobin S forms long rigid strands causing
red cell to sickle

Rigid red blood cells block small blood vessels

Lack of blood supply results in release of inflammatory chemicals, activation of pain fibres

…and **organ damage**



Sickle patients' life expectancy is improving…

- 1973 HbSS – **14 years** (Diggs et al)
- 1994 HbSS **45 years**, HbSC 65 years (Platt et al)
- 2016 **67 years** (versus 82 years for local population) for KCH patients (Gardner et al)

- **Improving due to:**
  - Safe available blood transfusion
  - Early diagnosis, vaccination and antibiotics
  - Improved medical care and patient education

– Hydroxycarbamide

Hydroxycarbamide = Hydroxyurea (HU)

- **Only medication licensed for prevention of recurrent painful episodes in SCD**
  - **Reduces frequency and severity of pain**
  - **Reduces number of hospital admissions and blood transfusions**
  - **Reduces stroke, lung damage and incidence of chest syndrome**
  - **Improves quality and length of life**

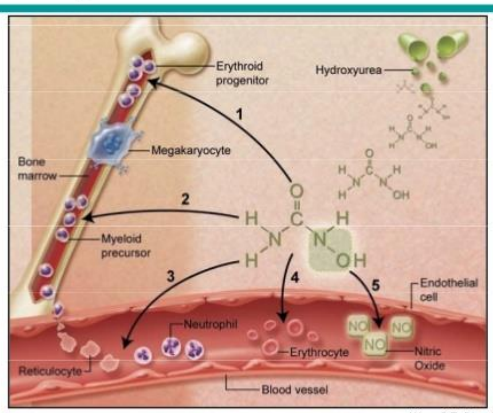
HYDROXYCARBAMIDE in SCD

- **HU for SCD first reported in 1984** - increased HbF
- **>30 years of laboratory and clinical effectiveness** in children and adults
- **Long-term use reduced SCD morbidity and mortality**
  - 9 yr F/U (MSH observational study JAMA 2003), 40% reduction in mortality
  - 17.5 yr F/U (Am J Med 2010) overall mortality 43%, 87% in non-HU patients
- **BABY HUG Phase 3 clinical trial** (Lancet 2011)

BABY HUG: decade-long phase III double blind, placebo-controlled randomised clinical trial

- 96 received HU, 97 placebo
- **HU significantly reduced:**
  - Pain (177 events in 62 HU patients vs 375 events in 75 placebo patients, p=0·002)
  - Dactylitis (24 events in 14 HU pts vs 123 events in 42 placebo pts, p<0·0001)
  - Acute chest syndrome
  - Hospitalisation rates
  - Transfusion rates
- **Conclusion: Consider HU for all young SCD children** Ware et al 2011

Hydroxyurea in SCD: multiple mechanisms of action



Ware RE. Blood. 2010;115: 5300-11.

HU mechanisms of action:

Increased HbF production

(foetal haemoglobin doesn't contribute to sickle haemoglobin stranding and cell distortion)

Improved red cell hydration

(raised MCV, reduces sickling)

Reduced neutrophil count

(fewer large sticky cells to slow down microcirculation and precipitate sickling)

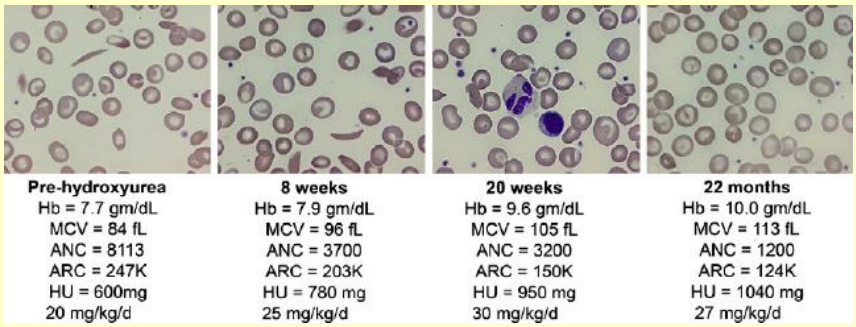
Modifies endothelial cell interactions

(reduced interactions between lining of blood vessels and red blood cells so cells don't get stuck)

Acting as a Nitric Oxide donor

(NO is a chemical which helps blood vessels to open wider to help blood flow)

Changes in blood film morphology before and after hydroxycarbamide



Pre-hydroxyurea	8 weeks	20 weeks	22 months
Hb = 7.7 gm/dL	Hb = 7.9 gm/dL	Hb = 9.6 gm/dL	Hb = 10.0 gm/dL
MCV = 84 fL	MCV = 96 fL	MCV = 105 fL	MCV = 113 fL
ANC = 8113	ANC = 3700	ANC = 3200	ANC = 1200
ARC = 247K	ARC = 203K	ARC = 150K	ARC = 124K
HU = 600mg	HU = 780 mg	HU = 950 mg	HU = 1040 mg
20 mg/kg/d	25 mg/kg/d	30 mg/kg/d	27 mg/kg/d

Fertility

- Teratogenicity in animal studies, but normal outcomes reported after accidental use during pregnancy
- Effects on spermatogenesis

Advise contraception during and for 3 months after cessation

Offer sperm banking

HU Monitoring and dosing

- 15 mg/kg od (5-10mg/kg/day of renal impairment)
- Max 35mg/kg/day
- **Myelosuppression** - monitor FBC, kidney and liver function, reticulocyte count 2-12 weekly
- **New BCSH HU guidelines imminent, including dosage, treatment thresholds etc.**

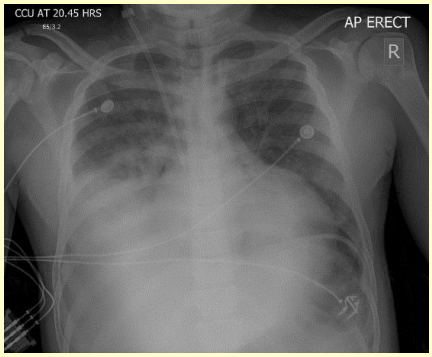
Blood monitoring on HU :

BSH Guideline in progress 2017

- **If blood parameters**
  - Neutrophils <1.25 x 10^9/l
  - Platelets <80
  - Retics <80 or 20% reduction in Hb
- **Stop HU and repeat FBC weekly until**
  - Neutrophils >1.25 x 10^9/l
  - Platelets >80
  - Retics >80
  - Re-start same dose or reduce by 5mg/kg/day

Who used to be offered HU?

- **Recurrent acute pain**
  - >3 admissions/year
  - Very symptomatic at home
- 2 or more **acute chest syndrome**, or one requiring ICU support
- **Severe anaemia**
- **Organ dysfunction**



Who should now be offered HU?

BSH Guideline in progress 2017

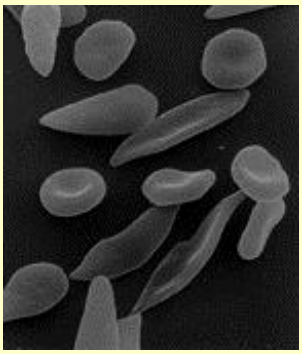
- **Infants 9-42 months**
  - offer Rx regardless of clinical severity
- **Children > 42 months, adolescents and adults**
  - consider Rx regardless of clinical severity
- **Recurrent acute pain**
  - >3 moderate to severe pain episodes in 12/12
  - SCD pain that interferes with daily activities and QOL
- **Severe or recurrent acute chest syndrome**
- **Children with abnormal TCD**
  - Offered after 1 year of blood transfusion
- **Children with conditional risk TCD velocities (MTD)**
- **Second line for children & adults with ischaemic stroke Hx**

Also …

BSH Guideline in progress 2017

- **Sickle nephropathy** with persisting proteinuria despite ACE1/ARB therapy
- **Pulmonary hypertension** or chronic hypoxia
- **Symptomatic chronic anaemia** interfering with daily activities or QOL
- Discuss possible benefits of HU in **prevention and treatment of other chronic disease complications**

Should everyone with with HbSS or HbSβ^o consider hydroxycarbamide?



Hydroxycarbamide improves quality and length of life in SCD

- **Reduces morbidity and mortality**
  - Reduces need for blood transfusion, number and severity of painful episodes, stroke, lung damage and chest syndrome
- **Well tolerated**
  - No significant short-term toxicities or long-term safety concerns
  - No evidence for leukaemogenesis or MDS
  - Mild GI symptoms, darkening of skin and nails (dose dependent)
- **"Disease-modifying therapy for all SCA patients regardless of age or clinical severity"**
  Ware et al 2011

HU side effects

- **Well-tolerated** with little significant toxicity
- Occasional **GI discomfort** - take dose at night
- **Skin ulceration** - <u>not</u> reported in SCD HU use
- Transient and reversible **bone marrow suppression**, esp. mild neutropenia and low reticulocyte count (hence need for routine blood monitoring)

Increased **pigmentation of nails and skin** – cosmetic and dose dependent

HU treatment is an inclusion criteria for stem cell transplantation and gene therapy trials

Inclusion Criteria - Recipient

Age ≥ 18 years	□ **Yes**	□ **No**
Haploidentical relative donor available	□ **Yes**	□ **No**
Ability to comprehend and willing to sign an informed consent	□ **Yes**	□ **No**
Negative serum β-HCG	□ **Yes**	□ **No**
Ejection Fraction ≥ 35 %	□ **Yes**	□ **No**
Glomerular Filtration Rate > 60 mL/min/1.73m^2 by cystatin C-based GFR testing	□ **Yes**	□ **No**
DLCO ≥ 35%	□ **Yes**	□ **No**

Disease Specific Inclusion Criteria

Patients with any type of sickle cell disease who are at high risk for disease-related morbidity or mortality, defined by having severe end-organ damage (A, B, or C) or **potentially modifiable complication(s) not ameliorated by hydroxyurea (D):**

A. Stroke defined as a clinically significant neurologic event that is accompanied by an infarct on cerebral MRI or cerebral arteriopathy requiring chronic transfusion therapy; OR	□ **Yes**	□ **No**
B. Tricuspid regurgitant jet velocity (TRV) of ≥ 2.5 m/s at baseline (without vaso-occlusive crisis); OR	□ **Yes**	□ **No**
C. Sickle hepatopathy defined as EITHER ferritin > 1000mcg/L OR direct bilirubin > 0.4 mg/dL AND platelet count < 250,000/uL at baseline (without vaso-occlusive crisis); OR	□ **Yes**	□ **No**
D. Any one of the below complications:	□ **Yes**	□ **No**

Complication	Eligible for hydroxyurea*	Eligible for HSCT
Vaso-occlusive crises	At least 3 hospital admissions in the last year	**More than 1 hospital admission per year while on maximal tolerated dose of hydroxyurea***
Acute chest syndrome	2 prior ACS	**any ACS while on hydroxyurea***

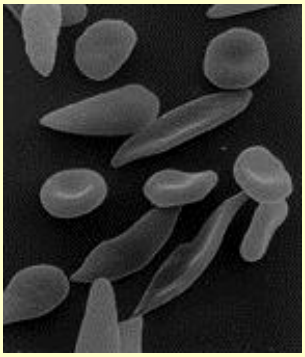
***hydroxyurea at maximum tolerated dose for at least 6 months**

Safety concerns?

- >30 years clinical experience and trials shows:
  - **No significant long-term toxicities associated with HU therapy for SCA**
  - **No cases of myelodysplasia or leukaemia in HU-treated SCA patients**
  - **No increase in cancer or stroke**
  - Did not identify any long-term toxicities

Conclusion

- HU **reduces mortality** in sickle cell disease:
  - **Adult trials** (LaSHS survival 86% for HU-group, 65% non-HU group and MSH)
  - **Paediatric study** (Brazilian cohort) 4.6-fold decreased risk of death (despite selection of severely affected children for HU, 44 deaths in untreated children , only 2 in HU treatment group)
- HU is **safe**: HUSTLE protocol:
  - Minimal genotoxicity or carcinogenicity with long-term HU exposure
  - Decades of evidence shows acceptable long-term safety profile
- HU treatment is an **inclusion criteria for trials of stem cell transplantation and gene therapy**
- **Consider HU as standard care**



>14,000 people in England live with Sickle Cell Disease

~4000 adults & children in South East London Network

How many are on Hydroxycarbamide?

~4000 adults + children in South East London Network:

Hospitals	Children with SCD	Adults with SCD
Guy's Hospital, Evelina Children's Hospital	520	828
King's College Hospital, Princess Royal Hospital	502	600
Croydon University Hospital	245	150
Queen Elizabeth Hospital	370	250
University Hospital Lewisham	200	180
Princess Royal Hospital, Royal Sussex County Hospital	5	20
Darent Valley Hospital	60	20
Kent and Canterbury Hospital	5	-
Eastbourne District General, Conquest Hospital	5	-
Maidstone Hospital, Tunbridge Wells Hospital	7	-
Medway Hospital	25	<10

Hospital	No. of HbSS/ HbSb°	Adults or children	No. on HU	% on HU	No. of HbSS/HbSb° on regular transfusion	NHR/local database/other?	Target HbSS/HbSb° on HU
Guy's Hospital	397+8	adults	120+/-7	**40%**	4 top up 102 EBT	NHR & local database	No target
King's College Hospital	293	children	108	**37%**	27	NHR & recent audit	50%
	455+10	adults	101	**25%**	62 EBT+11	NHR & database	40%
Croydon University Hospital	81+3	adults	9	**11%**	4	Local database	No target
	125+2	children	30	**24%**	0	Local database	No target
Queen Elizabeth	130	adults	44	**34%**	2	NHR & database	50%
University Hospital Lewisham	146+5	children	36	**25%**	7	Local database	No target
	120	adults	18+	**15%-58%**	11(+1 HbSC)	NHR & recent audit	No target
Darent Valley Hospital	21+0	adults	10	**48%**	0	Local and NHR	60%
	70+	children	7-10	**14%**	2	Rough estimate	No target
Maidstone, Tunbridge Wells	3+1	children	2	**50%**	0	local	?
Medway Hospital	No data reported						
Kent and Canterbury Hospital							
Eastbourne District General, Conquest Hospital							

HU Audit Summary

- **11% - 58% (mean 31%) of eligible patients are on HU**
- Wide range in HU uptake in STSTN hospitals – need equity of provision
- **Male:female ratio 1:1**, where data available
- **Wide age range** from infancy to age 67

Conclusion

- **Hydroxycarbamide is the only UK licensed medication for the prevention of recurrent painful episodes in sickle cell disease**
- **It is safe and effective**
- **Pre-treatment with HU for at least 12 months is prerequisite for entry into gene therapy and stem cell transplant trials**


Any Questions?