Mast cell disease and Hydroxyurea

Mast cell activation syndrome (MCAS) is a more common but only recently recognized form of the rare, proliferative mast cell (MC) disease mastocytosis) and typically causes a chronic inflammatory syndromes. The MC activation seen in either mastocytosis or relatively non-proliferative MCAS often results in migratory soft tissue and/or bone pain which frequently responds poorly to typical (narcotic and non-narcotic) analgesics as well as atypical analgesics such as antidepressants and anticonvulsants.

Hydroxyurea (HU) is an oral ribonucleotide reductase inhibitor with antimetabolic and antineoplastic properties. First used clinically in the 1960s for chronic myeloproliferative neoplasms (MPNs), HU was shown to raise fetal hemoglobin (HbF, $\alpha_2\gamma_2$) levels in sickle cell disease (SCD) in 1985. Continued clinical research culminated in a Phase 3 double-blind randomized controlled trial published in 1995 clearly establishing the utility of the drug in reducing the severity of sickle cell anemia (SCA). It also inhibits replication of human immunodeficiency virus-1 (HIV-1) and has been used in cyanotic congenital heart disease. The efficacy of HU for these varied clinical conditions appears to be due, at a minimum, to its potent inhibition of ribonucleotide reductase, a ubiquitous intracellular enzyme that converts ribonucleotides to deoxyribonucleotides, which are required for DNA synthesis and repair. A 2018 study of children with SCA was reassuring with respect to cancer risk (Rodriguez). From this study conclusions reached included: 1) In the non-malignant setting of SCD, data on the safety of long-term HU use have been reassuring; 2) SCD increases, slightly but significantly, DNA damage in lymphocytes from patients with SCD; 3) Patients with SCD treated with HU do not present more nucleoid damage than patients with SCD not treated with HU; 4) Good responders to the HU treatment have significantly less nucleoid damage than poor respondersand 5) HU treatment at ≤30 mg/kg/day does not expose patients to a genotoxic plasma concentration. In male with SCA, there is risk of reduced fertility rate of sperm (DeBaun 2014)

HU has been used in the treatment of mastocytosis, too, and has been associated with reductions in MC load and symptoms as well as reductions in symptoms without clear reduction in MC load (e.g., malaise and pruritus; progressive decrease in clinical symptoms and the need for intensive anti-mediator therapy; weight loss, severe night sweats, abdominal pain, and pruritus; facial flushing and bone pain; and pruritus, flushing, ascites, and hepatosplenomegaly). These reports suggest HU might be able to modulate MC mediator expression in some patients independent of its anti-proliferative effects.

In an article by Dr. Afrin entitled Utility of hydroxyurea in mast cell activation syndrome (Exp Hematol Oncol. 2013; 2: 28.) efficacy was reported in five cases of MCAS to reduce symptoms. All five patients responded to assorted sets of MCAS-directed therapies. Of note, in all five patients modest doses of HU promptly, markedly reduced their diffuse aching, though cytopenias required stopping the drug in one patient, and reactions to one formulation of the drug in another three patients required trials of an alternative formulation.

HU appears able to modulate MC mediator expression in MCAD, including MCAS, and may be particularly useful to treat pain in patients refractory to, or intolerant of, other typical and atypical analgesics. Although all of the patients reported here were already on some anti-mediator therapy at the time HU was begun, the fact that initiation of HU was the only medication change

preceding the observed further symptomatic improvements strongly suggests HU was solely responsible for these improvements.

HU appears useful in treating an assortment of mediator-driven symptoms in some patients with MCAS. In particular, HU may be useful in addressing otherwise refractory soft tissue and/or bone pain in MCAS. Further study is needed to define HU's mechanisms of action in MCAD/MCAS, optimal dosing strategies, and which patient subpopulations are most likely to benefit. Further study may also be warranted to characterize the prevalence and behavior of MCAS in SCD patients, particularly those with comorbidities not easily attributable to erythrocyte sickling.

Nonetheless HU can be used for innovative therapy for patients severely affected by mast cells especially for patients who have tried all basic therapy.

Consent:

I have read the above information and wish to take Hydroxyurea (HU) therapy. I will comply with lab monitoring.** I understand and accept the risks and understand that this therapy is used in cases of mast cell diseases where the symptoms have not responding to numerous treatments and the quality of life is so impaired that innovative therapy is required. I have been given this form in advance of taking the medication and was allowed to read it and ask my physician questions regarding this medication.

Signature/date: _____ _____

**Labs: Baseline CBC, CMP. During therapy have CBC (complete blood count) weekly for the first month, biweekly for the second month, and then monthly; CMP (complete metabolic panel) monthly

References:

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Rodriguez A. et al. Hydroxyurea (hydroxycarbamide) genotoxicity in pediatric patients with sickle cell disease. Pediatr Blood Cancer. 2018 Mar 7. doi: 10.1002/pbc.27022.

DeBaun MR.Hydroxyurea therapy contributes to infertility in adult men with sickle cell disease: a review. Expert Rev Hematol. 2014 Dec;7(6):767-73.