

The use of combination chemotherapy has been developed successfully over several decades for the treatment of cancer and, more recently, HIV infection. However, the principles of treatment with multiple drugs that have distinct and additive or synergistic mechanisms of action and non-overlapping toxicity have not been applied to the treatment of sickle cell disease. In Project 1 we propose the combination of hydroxyurea, which stimulates fetal hemoglobin synthesis, and magnesium, which improves red cell hydration, in Phase I and Phase II trials in children and adolescents with sickle cell disease. Patients eligible for this trial will have been treated with hydroxyurea for a minimum of 6 months before they are begun on oral magnesium pidolate. In Specific Aim 1, the Phase I trial, we will determine the maximum tolerated dose (MTD) of magnesium pidolate, beginning at a dose of 0.5 mEq/kg/day. Specific Aim 2 is to determine the effect of combination treatment including magnesium at the previously determined MTD, on prevention or reversal of CNS complications in a preselected population of patients identified in a screening phase to have a silent infarct on MRI or a stenotic lesion on MRA. Patients in the Phase II study will be followed to detect decreases in the rate of new or more extensive silent infarcts and new overt strokes and improvement in stenotic lesions in the respective populations. In Specific Aim 3 we will determine the effect of the combination of hydroxyurea and magnesium on hematologic parameters and red cell characteristics by distributing serial blood samples to 4 investigators whose research laboratories will examine red cell metabolism, ionized magnesium levels, red cell adhesion, and whole blood viscosity. In particular, the studies of Dr. Carlo Brugnara will elucidate the combined effects of hydroxyurea and magnesium on red cell K and Mg content, K-Cl co-transport, and the fraction of dense red cells. In summary, through Phase I and II studies, Project 1 will determine the MTD of magnesium when used in combination treatment with hydroxyurea and will assess the efficacy of this combination on red cell physiology.