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Real-life experience with hydroxyurea in sickle cell disease: A multicenter study in a cohort of patients with heterogeneous descent

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ABSTRACT

We conducted the first nation-wide cohort study of sickle cell disease (SCD) in Italy, a Southern European country exposed to intense recent flux migration from endemic areas for SCD. We evaluate the impact of hydroxyurea on a total of 652 pediatric and adult patients from 33 Reference Centers for SCD (mean age 24.5 ± 15 years, 51.4% males). Hydroxyurea median treatment duration was 7 years (range: < 1 year to 29 years) at a mean therapeutic dose of 18 ± 4.7 mg/kg/day. Hydroxyurea was associated with a significant increase in mean total and fetal hemoglobin and a significant decrease in mean hemoglobin S, white blood and platelet counts, and lactate dehydrogenase levels. Hydroxyurea was associated with a significant reduction in the incidence of acute chest syndrome (− 29.3%, $p < 0.001$), vaso-occlusive crisis (− 34.1%, $p < 0.001$), hospitalization (− 53.2%, $p < 0.001$), and bone necrosis (− 6.9%, $p < 0.001$). New silent cerebral infarction (SCI) occurred during treatment (+ 42.4%, $p < 0.001$) but not stroke (+ 0.5%, $p = 0.572$). These observations were generally consistent upon stratification for age, descent (Caucasian or African), genotype (βS/βS, βS/β^0 or βS/β^+) and duration of treatment (< or ≥ 10 years). There were no new safety concerns observed compared to those commonly reported in the literature. Our study, conducted on a large population of patients with different descent and compound state supports the benefits of hydroxyurea therapy as a treatment option. Registered at clinical trials.gov (NCT02709681).

1. Introduction

With the ongoing search for targeted and curative therapeutics for sickle cell disease (SCD) and its manifestations, hydroxyurea remains a cornerstone of conventional management owing to its oral efficacy and low toxicity [1,2]. The disease modifying properties of hydroxyurea were initially attributed to its ability to induce fetal hemoglobin and decrease hemoglobin S polymerization [3,4] which should theoretically ameliorate downstream pathophysiologic mechanisms, acute and long-term clinical morbidity. Other beneficial effects have subsequently emerged including increasing total hemoglobin levels, decreasing platelet and white blood cell counts, changing expression of adhesion molecules, and nitric oxide generation [1,5,6]. Thirty years of clinical experience through randomized clinical trials and large observational studies established that hydroxyurea is safe and effective in decreasing the frequency of acute complications like painful vaso-occlusive crisis and acute chest syndrome, while also decreasing the need for blood transfusion and hospitalization in SCD adults and children as young

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9 months of age [7–13]. Long-term follow-up studies have also established continued benefit as well as reduction in mortality [14–17]. In addition, the initial concerns on HU effects on fertility and carcinogenic potential have not been fully established in patients with SCD and require a long-term follow-up on large cohorts of SCD patients [7–13]. Despite such substantial body of evidence, hydroxyurea is considered an underutilized medication in SCD [1,13,18]. Thus, data from real-life experiences with hydroxyurea remain essential to further illustrate the role of this intervention to practicing clinicians.

Until the last decade, SCD was endemic in Southern Italy (Sicily and Calabria) with limited number of patients spread all over the country due to internal migration. Thus, data on the epidemiology and clinical profile of SCD in Italy, as Southern European country exposed to intense migration fluxes from areas endemic for SCD, such as the Sub-Saharian countries [19], have been deeply changed. Such current and future mobility and migration flows, pose considerable new challenges that have to be taken into consideration by member states and EU authorities primarily through collection of data from existing patients.

With this background, the aim of this study was to report the first, real-life experience with the use of hydroxyurea in a large cohort of SCD patients with heterogeneous descent and different compound state.

2. Methods

This was a retrospective cohort study of SCD patients attending treatment centers across Italy. All Italian Hematology Centers part of the Italian Society of Thalassemia and Hemoglobinopathies (SITE) and all Pediatric Hematology Oncology Units part of the Italian Association of Pediatric Hematology Oncology (AIEOP) were invited to participate in the study. Invitation was expressed during two meetings of the Working Groups and by a letter. All large Regional Reference Centers (pediatric and adult) for therapy of SCD participate to study. Out of 1638 patients registered at 33 participating centers, 652 (39,8%) patients had received hydroxyurea therapy for some period throughout their disease course and were included in this analysis. The indication for hydroxyurea initiation was 2–3 vaso-occlusive crisis and/or acute chest syndrome in the year prior. Hydroxyurea was initiated at a starting dose of 10 mg/kg/day, and adjusted or escalated according to tolerance. For each patient, retrieved data included demographics (age and gender), origin, genotype, and folic acid use. The duration of treatment (until discontinuation or death) and average hydroxyurea dose throughout therapy were also recorded. We also retrieved average of all available laboratory values up to three years pre-hydroxyurea and for the period on-hydroxyurea therapy including total hemoglobin level, fetal hemoglobin level, hemoglobin S level, white blood count, platelet count, lactate dehydrogenase level, total and direct bilirubin levels, aspartate and alanine aminotransferase levels, and serum creatinine level. The incidence of new complications pre- and on-hydroxyurea therapy was also retrieved as available from medical records and as defined by internationally recognized criteria [20], including: stroke, silent cerebral infraction, acute chest syndrome, vaso-occlusive crisis, hospitalization, leg ulcers, pulmonary hypertension defined as patients with a tricuspid-valve regurgitant jet velocity ≥ 3.2 m/s (3.6%) on transthoracic echocardiography further underwent right heart catheterization to confirm the diagnosis of PAH (mean pulmonary arterial pressure ≥ 25 mm Hg and pulmonary capillary wedge pressure ≤ 15 mm Hg) [21,33,34,35], AVN defined as bone necrosis confirmed by radiographs and in some cases MRI and chronic kidney disease was defined according to the National Kidney Foundation, Kidney Disease Outcomes Quality Initiatives (K/DOQI) guidelines [22]. For silent cerebral infarction, only patients with magnetic resonance imaging performed within the last ten years were considered to limit the chance of varying imaging methodology. In such patients screening scans were repeated every two years. For acute chest syndrome, vaso-occlusive crisis and hospitalization, aside from incidence the average number of episodes per year (to the nearest integer) were collected up to three years pre-hydroxyurea and for the period on-hydroxyurea. Safety data included adverse events as reported by the treating physician and the incidence of malignancy or death. Pregnancy incidents and their outcomes were also collected.

The study was approved by the ethical committee of Palermo 2 and the study was registered at clinical trials.gov (NCT02709681).

2.1. Statistical analysis

Descriptive data were reported as mean ± standard deviation, median (range), or percentages. Bivariate comparisons of laboratory and clinical data pre- and on-hydroxyurea were done using the paired-samples *t*-test for means, Wilcoxon matched-pair single-rank test for medians, and McNemar's test for percentages. Spearman's correlation (r) coefficient was used to evaluate correlations between hydroxyurea dose and changes in laboratory parameters. A Kaplan Meier curve was drawn to illustrate survival with and without hydroxyurea therapy. The Cox proportional-hazards regression model was used to estimate the hazard ratio and the 95% confidence interval (CI); the proportional hazards (PH) was checked (test and graphical diagnostics) by means of the scaled *Schoenfeld residuals*. The comparison between HU-treated and non-treated patients was done with the unpaired Wilcoxon test. In the Cox model the group of non-treated patients was compared with a subset of HU-treated patients with the age in the range of 25th and 75th percentile of the age of no treated subjects. All p-values were two-sided with the level of significance set at < 0.05.

3. Results

3.1. Patients' characteristics

A total of 652 SCD patients who had received hydroxyurea were included in this analysis. The mean age at the time of hydroxyurea initiation was 24.5 ± 15.0 years (range: 1.0–67.0), with 32.7% of patients being in the pediatric age group (< 18 years). There was an equal gender distribution with 51.4% of patients being men. The majority of patients were of Caucasian (64.4%) or African (35.6%) origin; Supplementary Fig. 1 illustrates the origins of patients analyzed in this study. Around half of the patients (46.6%) had a βS/βS genotype while the remaining patients had β^0/βS (28.1%), β^+/βS (22.1%), or other genotypes including βS/βC (3.2%). Patients' characteristics are summarized in Table 1.

3.2. Hydroxyurea therapy

The median duration of hydroxyurea therapy in the study sample was 7 years (range: < 1 year to 29 years). The wide range of treatment duration is related to the retrospective characteristic of this study. In fact, the large part of Caucasian patients started treatment many years ago since 1995. Whereas, pediatric subjects were placed under HU therapy after Baby HUG study [10,13]. The mean therapeutic dose was 18.0 ± 4.7 mg/kg/day (range: 6.0–32.0). The distribution of dose categories was: < 10 mg/kg/day (n/N = 14/598, 3.2%), 10–20 mg/kg/day (n/N = 434/598, 72.6%), and > 20 mg/kg/day (n/N = 150/598, 25.1%). Folic acid was concomitantly used in 71.3% of patients (n/N = 388/448).

3.3. Changes in laboratory parameters following hydroxyurea therapy

Changes in laboratory parameters pre- and on-hydroxyurea therapy are summarized in Table 2. Hydroxyurea therapy was associated with a significant increase in mean total hemoglobin level (+0.5 g/dL, $p < 0.001$). Hemoglobin increase was ≥ 1.0 g/dL in 44.5% (n/N = 125/490) of patients and was ≥ 2.0 g/dL in 19.0% (n/N = 218/490) of patients. Hydroxyurea therapy was also associated with a significant increase in mean fetal hemoglobin level (+8.0%, $p < 0.001$),