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Safety and Efficacy of Prolonged Hydroxycarbamide Administration in Patients with Sickle Cell Disease in Northwestern Greece

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Authors' contributions

This work was carried out in collaboration between all authors. Author AM was the principal investigator, performed statistical analysis and wrote the paper; authors FK, NC and EK were responsible for the acquisition of the data and author EB co-ordinated the study. All authors read and approved the final manuscript.

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ABSTRACT

Hydroxycarbamide (HC) is a ribonucleotide reductase inhibitor which promotes fetal hemoglobin (HbF) induction and has proven efficacy in sickle cell disease (SCD) patients. Given its mechanism of action and prior reports of genotoxicity in animal models, concern exists regarding long-term safety in relation to its cytotoxic effects. The purpose of this study was to retrospectively analyze the long-term (range 3-20 years, median 11) HC-derived clinical and biological effects, in 30 SCD patients (age range 20-68 years) from one referral center. HC treatment resulted in significant reduction of painful crises and transfusions, increase of HbF and hemoglobin as well as drop of white blood cell count and lactate dehydrogenase values. During the long term follow up time the following disease complications were observed: pulmonary hypertension (2 patients), leg ulcers (1 patient) and renal impairment (1 patient). Seven patients discontinued HC therapy because of scheduled pregnancy (3), severe neutropenia (2) and non-compliance (2). One poor HC compliant

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patient died of pulmonary embolism. No case of malignancy was observed. This retrospective study of most prolonged administration of HC, provides data supporting the safety and the well-established usefulness of chronic administration of HC in SCD.

Keywords: Hydroxycarbamide; sickle cell disease.

1. INTRODUCTION

Hydroxycarbamide (HC) is a hemoglobin F (HbF) promoting agent which has been established as an effective treatment for sickle cells disease (SCD) patients who suffer from frequent pain crises, acute chest syndrome, severe vaso-occlusive episodes or severe anemia [1]. HC inhibits the enzyme ribonucleotide reductase and therefore the DNA synthesis with cytotoxic effects on the S-phase of the cell cycle [2]. It is assumed that HC causes a transient arrest in erythropoiesis followed by a recovery period, during which HbF-synthesizing immature progenitors are recruited. HC treatment decreases the incidence and severity of vaso-occlusive phenomena through several other mechanisms, such as mild reduction of neutrophil count, macrocytosis, reduced expression of adhesion molecules on sickle erythrocytes, increased erythrocyte hydration and induction of local nitric oxide release resulting in vasodilatation and reduced platelet aggregation [3].

However, there are concerns regarding the long-term safety of HC in relation to its mechanism of action through ribonucleotide reductase inhibition. There are sporadic reports of malignancy occurring in SCD patients receiving HC, which are probably explained by the background cancer risk as in the general population [4,5]. Large cohort studies over the last 20 years have not shown an increase in myelodysplasia or carcinogenicity [6-8]. Nevertheless, data on chronic use of HC in SCD are always needed for further documentation of long-term safety and efficacy of the drug. With this study we add our experience on the safety and clinical effects of prolonged use of HC in adult SCD patients treated in a referral academic center for hemoglobinopathies.

2. MATERIALS AND METHODS

The study included 30 SCD patients living on region of Northwestern Greece and followed over the last 20 years at the Thalassaemia Unit of the University Hospital of Ioannina. The diagnosis was based on the clinical, haematological, biosynthetic, and genetic studies. Eleven patients were male and 19 female; the age range was 20-68 with a median 39). Medical files of the patients were retrieved, comprehensive data were recorded and analyzed. Appropriate ethical approval was obtained.

3. RESULTS

The demographic, laboratory and clinical data are shown in Table 1. Four patients had the homozygous type of SCD and 26 the double heterozygous sickle cell/beta thalassemia (17 sickle beta zero, 9 sickle beta plus). The underlying mutations of beta gene were IVSI-110 (18 patients) and IVS1-6 (8 patients). The median time of follow up was 11 years (range 3-20 years). The total follow-up time was 322 patient-years whereas the total HC exposure period was 364 patient-years. The mean dose of HC was 29.2 mg/kg/day. The main clinical outcomes of HC therapy are shown in Table 1. In terms of efficacy, HC induced substantial increase of HbF and marked reduction of painful crises and transfusions needed. All these outcomes were designated as statistically significant. HC treatment was also associated with significant rise of hemoglobin (Hb) levels, as well as with reduction of serum lactate dehydrogenase (LDH) and white blood cell (WBC) count. The disease complications that were observed during the follow up time were: pulmonary hypertension (2 patients), leg ulcers (1 patient) and renal impairment (1 patient). Seven patients stopped HC therapy (mean therapy duration 8.4 years) because of non-compliance (2 patients), scheduled pregnancy (3 patients) and severe neutropenia (2 patients). One poor HC compliant patient died of pulmonary embolism. No patient developed cancer.

Before HC administration 3 men chose to store sperm samples and 1 was found to be oligospermic. Two male patients fathered a child (one while on HC) and 3 female patients managed to carry out a normal pregnancy and delivery after discontinuation of therapy for 4 months. No female patient continued HC through her pregnancy. None of the babies born to

Table 1. Demographic data and clinical/laboratory outcomes of chronic hydroxycarbamide treatment in 30 SCD patients

Demographic data			
Age, years (median, range)	39 (20-68)		
Male/female	11/19		
SS/Sβthal^0/Sβthal$^+$ (N)	4/17/9		
Follow-up, years (median, range)	11 (3-20)		
Dosage of HC, mg/kg/day(mean±SD)	29.2 ± 3.9		
Clinical and laboratory outcomes of HC treatment			
	Before (previous year before treatment)	**After (last year of follow-up)**	**P value***
Hb, g/dl	8.8±0.6	9.6±1.3	0.0007
WBC, K/μL	12.2±2.8	10.3±2.9	0.0004
HbF, %	5.6±2.1	12.4±7.1	< 0.0002
LDH (IU/L)	577±285	510±229	0.0079
Painful crises/year at home(N)	5.7±3.2	3.2±3.1	0.0002
Painful crises/year at hospital(N)	3.2±1.8	1.2±1.5	< 0.0001
Transfusions/year (N)	4.8±2.9	2.7±3.4	< 0.0001

*Values are presented as mean±SD; * Wilcoxon signed rank test*

patients who were under HC had birth defects or any other problems.

4. DISCUSSION

This prolonged retrospective study emphasizes that the chronic administration of HC in adult patients with SCD significantly reduces the incidence of painful crises and the number of transfusions, without major safety issues. The fact the gender ratio was female-predominant could be attributed to the fertility concerns mostly in male patients who did not consent to take HC. The harmful effect of HC on spermatogenesis has been suspected but never proved. Our findings and clinical data from large cohorts as well as expert panel reports did not support such a hypothesis [6-9].

Regarding the few complications that were observed during the follow up time, these could be attributed to the underlying disease. HC therapy is associated with skin ulceration in patients with myeloproliferative disorders [10]. When skin ulceration occurs in patients with SCD, it is unclear whether the ulceration is related to the underlying vasculopathy or the use of HC or both. The reasons for discontinuation of treatment in our patients (scheduled pregnancy, severe neutropenia, non-compliance) are in accordance with other studies [6-8].

The significantly fewer painful crises and the less frequent blood transfusions firmly support the efficacy of HC, as previously reported [6]. Many factors may contribute to those effects, including significantly increased HbF and MCV and significantly fewer WBC, as it was shown in our patients.

In our study no malignant disease (myelodysplasia and/or acute leukemia or other cancers) was recorded, although such cases have been reported in the literature [4,5]. This finding is very important taken into account that our 30 patients had a total of 364 patient-years of HC exposure.

5. CONCLUSION

In conclusion, this retrospective study, which valuated data of prolonged administration of HC, provides information supporting the safety and the well-established efficacy of chronic administration of HC in SCD adult patients as long as the treatment is taken regularly. The findings of the study add a favorable point for the use of HC in SCD and the better adherence of both physicians and patients to the treatment protocol.

CONSENT

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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