



Case Series

Myelotoxicity Under Hydroxyurea/Siklos In Sickle Cell Patients: Experience of the University Hospital of Guadeloupe Regarding 4 Clinical Cases

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Abstract

Background: Hydroxyurea (Siklos) is the cornerstone disease-modifying therapy for sickle cell disease (SCD). By increasing fetal hemoglobin levels, it reduces vaso-occlusive crises, acute chest syndrome, and hospitalizations. However, its use may be associated with hematological toxicity, including severe bone marrow suppression leading to aregenerative anemia.

Objective: To describe the clinical presentation, management, and outcomes of hydroxyurea-induced myelotoxicity in sickle cell patients followed at the University Hospital of Guadeloupe.

Methods: We conducted a retrospective descriptive case series study including sickle cell patients who developed hematological toxicity attributed to hydroxyurea between 2023 and 2026. Clinical, laboratory, therapeutic, and outcome data were extracted from medical records.

Results: Four patients with sickle cell disease (three HbSS and one HbS β 0-thalassemia), aged 28 to 75 years, were identified. All patients presented with symptomatic severe aregenerative anemia characterized by a marked decrease in hemoglobin levels associated with reticulocytopenia and macrocytosis. One patient also developed bicytopenia with neutropenia. Risk factors for toxicity included advanced age, renal impairment, previous episodes of hydroxyurea-related anemia, and multiple comorbidities. Management consisted of temporary discontinuation of hydroxyurea, administration of erythropoietin, blood transfusion when indicated, and subsequent dose reduction. Hematological recovery was observed in all patients after treatment adjustment, allowing reintroduction of hydroxyurea at lower doses.

Conclusion: Hydroxyurea-induced myelotoxicity is an uncommon but potentially severe complication in patients with sickle cell disease. Early recognition, regular hematological monitoring, and individualized dose adjustment are essential to prevent serious adverse outcomes while maintaining the therapeutic benefits of hydroxyurea.

Keywords: Sick cell disease; Hydroxyurea; Siklos; Myelotoxicity; Aregenerative anemia; Macrocytosis.

Introduction

Sickle cell disease is the most common genetic disorder in the world and constitutes a significant public health problem, particularly in populations of African and Afro-Caribbean origin [1]. It is characterized by the presence of an abnormal hemoglobin, hemoglobin S (HbS), which causes chronic hemolysis and vaso-occlusive complications that can considerably impair the quality of life and prognosis of patients [2].

Hydroxyurea (Siklos) is currently the main disease-modifying therapy for sickle cell disease. Its efficacy is based in particular on increasing fetal hemoglobin (HbF), reducing vaso-occlusive crises, and decreasing hospitalizations [3].

However, despite its well-established therapeutic benefits, hydroxyurea can cause hematological adverse effects, primarily myelotoxicity, which can manifest as severe aregenerative anemia, neutropenia, and/or thrombocytopenia [4].

Managing these complications can be complex, particularly in patients with comorbidities or pre-existing bone marrow failure. In the French overseas territories, especially Guadeloupe, where the prevalence of sickle cell disease is high, data on Siklos-induced anemias remain limited [5].

Through this series of clinical cases observed at the University Hospital of Guadeloupe, we report the diagnostic, therapeutic and evolutionary aspects of sickle cell patients who presented with severe anemia under hydroxyurea.

General Objective

To describe the diagnostic aspects and management of hydroxyurea-induced myelotoxicity in sickle cell patients followed at the University Hospital of Guadeloupe.

Specific Objectives

To describe the clinical and biological characteristics of patients with anemia while taking Siklos.

To identify factors that may contribute to the development of hematological toxicity.

To describe the therapeutic approaches used in the management of these complications.

To analyze the clinical and biological evolution after treatment adjustment.

Methodology

This is a retrospective descriptive case series study conducted at

the University Hospital of Guadeloupe. We included sickle cell patients followed in the sickle cell care unit who experienced hematological toxicity attributed to hydroxyurea (Siklos) during the period from 2023 to 2026. Clinical, biological and therapeutic data were collected from medical records

Observation

Clinical Case 1

A 28-year-old female patient with sickle cell disease (SS), with a baseline hemoglobin of 8-9 g/dL and a hemoglobin of 10.5-11 g/dL while on Siklos, had two previous blood transfusions and two previous episodes of acute chest syndrome. She was taking Siklos 1750 mg (26 mg/kg) daily, which she had started one year prior, and Speciafoldine 5 mg daily. All her vaccinations were up to date.

She consulted us in December 2025 for shortness of breath, physical asthenia, and lower back and right leg pain, rated 5/10, which had been present for 5 days. She had been treated at home with Acupan 30 mg and paracetamol 1 gram. Further medical history showed no fever, cough, or myotonic pain.

At our examination, she weighed 66 kg with a BMI of 26.11 kg/m², her blood pressure was normal (102/55 mmHg), her heart rate was normal (75 beats per minute), her oxygen saturation was 100%, and her temperature was 37°C.

She was lucid and coherent, her palpebral conjunctivae were slightly pigmented, and her bulbar conjunctivae were subicteric. Her superficial cervical lymph nodes were not enlarged. Chest: The chest was symmetrical and ample, with no signs of respiratory distress. The first and second heart sounds were audible and regular. Vocal fremitus was well transmitted, lung sounds were preserved, and there was a pure bilateral breath sound.

Her abdomen was not distended; it was soft and compressible, without organomegaly, and non-tender.

The ENT examination was unremarkable. We considered the possibility of anemia due to Siklos, given the normochromic, non-regenerative macrocytic anemia and iron deficiency.

We treated her as follows:

immediate discontinuation of Siklos for 15 days;

Tardyferon 80 mg: 1 tablet every other day;

Aranesp: two 150 µg injections 48 hours apart;

Acupan 30 mg tablets: 1 tablet every 6 hours;

Paracetamol 1 g: 1 tablet every six hours.

The patient returned on day 5 with persistent shortness of breath despite taking erythropoietin.

The patient returned on day 5 with persistent shortness of breath despite taking erythropoietin. At our examination, vital signs were normal: BP 144/51 mmHg, HR 89 bpm, oxygen saturation 99%, respiratory rate 15 breaths per minute.

We considered the possibility of poorly tolerated anemia and ordered a follow-up blood test. We then prepared two units of red blood cell concentrates compatible with extended phenotyping and scheduled a blood transfusion for day 7. We continued with Tardyferon tablets; Siklos was reintroduced 15 days later at a dose of 750 mg with laboratory monitoring every 15 days for two months.

Clinical Case 2

A 65-year-old woman with sickle cell disease (SS), weighing 63 kg, with a baseline hemoglobin level between 7-8 g/dL, experienced numerous vaso-occlusive crises in childhood, hearing loss, bilateral osteonecrosis of the femoral head, and a history of anemia while taking Siklos six years prior, requiring several transfusions with iron overload. She also presented with microalbuminuria and an ACR of 12. She has been taking Siklos 1000 mg (15 mg/kg) for four years, along with Speciafoldine, Twystan, and Aranesp 300 µg every 15 days.

She presented to the emergency department in November 2025 with physical asthenia and dyspnea on minimal exertion. On examination, she was asthenic, tachycardic at 120 bpm, and had conjunctival pallor. The rest of the examination was unremarkable. We initially suspected severe anemia and set aside three phenotyped and compatible packed red blood cells (PRBCs).

Ultimately, she was transfused with two PRBCs and the Siklos was immediately discontinued. We reintroduced it weeks later. She continued taking Aranesp and Spiafoldine. On day 22, we observed an increase in hemoglobin and reticulocyte count.

The patient then presented to the emergency department three months later in 2026 with severe anemia and was transfused with two PRBCs. Siklos was discontinued and later reintroduced at a dose of 750 mg, then increased to 1000 mg one month later. Aranesp was administered subcutaneously at a dose of 150 µg, twice weekly.

Clinical Case 3

A 62-year-old patient with sickle cell disease (SB0), weighing 65 kg, with a baseline hemoglobin of 8/dL and an alpha mutation, a history of transfusion, centrilobular emphysema, IgA gammopathy, nephropathy, and a smoking habit (5-6 cigarettes per day), was taking Triatec, Speciafoldine 5 mg, and Siklos 1250 mg (19 mg/kg), which was started in 2020 due to worsening proteinuria.

He consulted us in 2025 for physical asthenia and exertional dyspnea that had appeared two days prior, without any signs of infection or other complaints.

On examination, we noted primarily mild pallor of the skin and mucous membranes. Given his non-regenerative macrocytic anemia while taking Siklos, along with mild thrombocytopenia, we considered the possibility of myelotoxicity. We stopped the Siklos and gave Aranesp 300 mg in two doses per week and checked 20 days later and resumed the Siklos, decreasing to 1000 then 250 mg per day.

Clinical Case 4

75-year-old female with sickle cell disease (SS), weighing 68kg, with a baseline hemoglobin of 8-9g/dl, with proteinuria nephropathy, sickle cell retinopathy, hypertension, bilateral osteonecrosis of the humeral head, myocardial infarction with worsening of her anemia, the reason for her being put on Siklos + Aranesp since 2022; Severe OSA, treated with oxygen therapy, Siklos 500 mg daily (8 mg/kg), Aranesp 150µg daily, Speciafoldine, Corvasal 2M 3 times daily (1 tablet), and Kardegic 1 sachet daily.

The patient consulted us in June 2024 for physical asthenia. Clinical examination revealed a normal oxygen saturation (100%), normal blood pressure (133/66 mmHg), a normal heart rate (85 bpm), and slightly discolored eyelid conjunctivae.

Laboratory tests showed normochromic, normocytic, non-regenerative anemia with neutropenia, indicating bicytopenia, likely due to Siklos.

The patient received a transfusion of one unit of packed red blood cells, Siklos was temporarily discontinued, and the Aranesp dose was increased to 300 µg per week. Siklos was reintroduced one month later at a dose of 250mg per day.

Discussion

Our work highlights the occurrence of severe, aregenerative anemias associated with myelotoxicity under hydroxyurea (Siklos) in sickle cell patients followed at the University Hospital of Guadeloupe. Although hydroxyurea is currently the standard disease-modifying therapy for sickle cell disease, its use remains limited by the occurrence of hematological adverse effects, primarily dose-dependent myelosuppression [2].

In our observations, all four patients presented with macrocytic, aregenerative anemia with a decreased reticulocyte count, consistent with bone marrow toxicity induced by hydroxyurea/Siklos. This macrocytosis is a classic biological effect of the treatment, secondary to the inhibition of DNA synthesis of erythroid precursors [4]. However, in our cases, the significant

drop in hemoglobin associated with the decrease in reticulocytes indicated clinically significant bone marrow toxicity requiring therapeutic adjustment.

The first clinical case illustrates severe anemia in a young patient with a significant decrease in hemoglobin to 6 g/dL and reticulocytopenia, despite an inflammatory profile not suggestive of an acute infectious or hemolytic complication. The progressive correction after temporary discontinuation of Siklos, administration of erythropoietin, and blood transfusion strongly supports a drug-induced toxicity. This observation is consistent with data in the literature showing that the myelotoxicity of hydroxyurea is generally reversible after discontinuation of treatment [3].

Furthermore, this first case highlights the diagnostic difficulty associated with iron metabolism abnormalities in sickle cell patients. Despite elevated ferritin, the decreased transferrin level, coupled with severe anemia, led to the consideration of functional iron deficiency. In sickle cell patients, the interpretation of iron markers remains complex due to the chronic inflammatory context, transfusion episodes, and hemolysis [1].

The second clinical case is particularly remarkable due to the extreme severity of the anemia, with a hemoglobin level of 2.9 g/dL associated with a significant drop in reticulocytes. This patient presented several factors likely to increase the toxicity of hydroxyurea: advanced age, a history of hematological toxicity with Siklos, early renal failure, and post-transfusion iron overload. Advanced age is recognized as a vulnerability factor to drug-induced myelosuppression due to decreased bone marrow reserve and pharmacokinetic changes [6]. Moreover, the presence of moderate chronic kidney disease may have contributed to drug accumulation. Since Siklos is partially eliminated renally, reduced clearance exposes patients to an increased risk of hematological toxicity [7]. This observation underscores the importance of close monitoring in elderly patients or those with renal insufficiency.

The third case illustrates the difficulty of therapeutic management in patients with multiple comorbidities. In this S β 0-thalassemia

sickle cell patient, the presence of nephropathy, pulmonary emphysema, and chronic active smoking could also contribute to impaired erythropoiesis. Nevertheless, the biological improvement after temporary discontinuation of Siklos and dose reduction reinforces the hypothesis of drug toxicity.

In all our observations, several biological elements were consistently observed: marked macrocytosis, reticulocytopenia, and improvement after treatment interruption. These characteristics are consistent with the hematological toxicity criteria described in international recommendations [5].

One of the key findings of this series highlights the importance of regular biological monitoring in patients receiving hydroxyurea/Siklos. Current guidelines recommend frequent complete blood counts, particularly during the initiation and dose titration phases [8]. Insufficient monitoring could lead to serious, life-threatening hematological complications.

Our cases also underscore the value of individualized treatment. In some patients, especially the elderly or frail, the maximum tolerated dose may be significantly lower than the standard doses usually used. In our observations, the gradual resumption of low-dose treatment after hematological recovery allowed us to maintain the therapeutic benefit of Siklos while limiting the recurrence of toxicity.

Finally, this series serves as a reminder of the complexity of managing sickle cell patients on hydroxyurea. In cases of severe anemia, it remains essential to rule out other common causes such as aplastic crisis, hyperhemolysis, vitamin deficiency, infection, or splenic sequestration before concluding that drug toxicity is the cause [9].

Despite the small sample size, this study is valuable because it describes real-life clinical situations observed in a sickle cell disease expert center in an overseas territory. It highlights the need for rigorous multidisciplinary monitoring and personalized adjustment of hydroxyurea treatment (Tables 1-5).

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Leucocytes	Valeur j1	J2	J5	J7(TS)	J21
Hématie	1,51 Tera(3,8-5,8)	1,810 Tera/l	1,44Tera/l	2,2 Tera/l	2,43T/l
Leucocyte	2,7 Giga/l(4-10)	2,95Giga	3,1Giga	3,7Giga	4,72Giga
Hémoglobine	6,4 g/dl(11,5-16,5)	7,7g/dl	6g/dl	8,2g/dl	9,4g/dl
Hématocrite	18,8% (37-47%)	22,6%	18,5%	24,5%	28,5%
VGM	124,5fl (80 -100)	124,9fl	128,5fl	Double population	117,3fl
TCMH	42,4 pg(27-32)	42,5pg	41,7pg	37,3pg	38,7pg
CCMH	34 g/dl(32-36)	34,1 g/dl	32,4g/dl	33,5g/dl	33g/dl
Plaquette	200Giga/l(150-500)	193 Giga/l	177Giga/l	145Giga/l	224G/l
Réticulocytes	33 Giga/l(50-150)	45 Giga/l	54Giga/l	84 Giga/l	123G/l
Folate sérique	40 nanogramme/ml (3,1-20,5)	38nanogramme/ml	34nanogramme/ml	19nanogramme/ml	17,7ng/ml
Ferritine	440nanogramme/ml (20-200)	438nanogramme/ml	412nanogramme/ml	398nanogramme/ml	390nanogramme/ml
Vitamine B12	246 pg/ml(189-883)	250pg/ml	270picog/ml	280pg/ml	300pg/ml
Transferrine	1,9 g/l(2-3,6)	1,9g/l	1,8g/l	1,9g/l	1,6g/l
Fer sérique	28,1 micromole /l (5,83-34,5)	28micromole/l	25micromol/l	17,7micromol/l	29microl/l
Coefficient de saturation de T	59 %(20-40)	58%	50%	48%	42%
LDH	395 UI/l(135-214)	367UI/l	328Ui/l	315Ui/l	529Ui/l
Bilirubine totale	10micromol/l	9,5Microl/l	5micromol/l	15micromol/l	17micromol/l
Bilirubine conjuguée	2,6mg/l	2,5mg/l	4mg/l	5micromol/l	6micromol/l
CKD -EPI	112ml/'	110ml/'	115ml/'	120ml/'	117ml/'

Table 1: Biological assessment of the first observation.

Paramètres biologiques	Valeur J1 nov 2025	J22 nov 2025	J1 2026	J2 post TS	J10 post TS
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Leucocytes	5,45 Giga/l(4-10)	7,5G	7,78G	8,39G	7,31G/l
Hématie	1,04Tera(3,8-5,8)	1,99 Tera/l	0,66Tera/l	1,94Tera/l	2,87T/l
Hémoglobine	4 g/dl(11,5-16,5)	8g/dl	2,9g/dl	6,8g/dl	10g/dl
Hématocrite	14,2% (37-47%)	23,4%	8,9%	20%	30,4%
VGM	136,5fl (80 -100)	double population	134fl	double population	105,9fl
TCMH	46,2pg(27-32)	40,2pg	47pg	35,1pg	33,6pg
CCMH	33,8g/dl(32-36)	34,2 g/dl	34,8g/dl	34g/dl	35,2g/dl
Plaquette	208Giga/l(150-500)	247Giga/l	180Giga/l	166Giga/l	294G/l
Réticulocytes	68 Giga/l(50-150)	166Giga/l	15Giga/l	66Giga/l	233G/l
LDH	329 UI/l(135-214)	358UI/l	352Ui	370Ui	481Ui
Bilirubine totale	12,4micromol/l	10Microl/l	15micromol/l	26micromol/l	6micromol/l
Bilirubine conjuguée	6,5micromol/l	5micromol/l	6mg/l	7micromol/l	4micromol/l
transferrine	2,3g/dl	2g/dl	2g/dl	2g/dl	1,9g/dl
fer sérique	13,9micromol/l	42,5micro/l	20micro/l	16,9micro/l	17micromol/l
ferritine	426 ng/l	869ng/l	810ng/l	789ng/l	714ng/l
CST	24%	85%	70%	36%	35,6%
CKD EPI	65,46ml/'	64,41ml/'	56,55ml/m2	68ml/m2	73,6ml/m2

Table 2: Biological assessment of the second observation.

Paramètres biologiques	Valeur J1	J20	4 mois après
Leucocytes	4,4 Giga/l(4-10)	5,5G	8,2G
Hématie	1,56 Tera(3,8-5,8)	2,3 Tera/l	3,22Tera/l
Hémoglobine	5,8g/dl(11,5-16,5)	7,8g/dl	8,5g/dl
Hématocrite	17,4% (37-47%)	25,1%	26,5%
VGM	101,3fl (80 -100)	109fl	82fl
TCMH	37,2pg(27-32)	33,9pg	26,5pg
CCMH	36,7g/dl(32-36)	31 g/dl	32,2g/dl
Plaquette	126Giga/l(150-500)	317 Giga/l	224Giga/l

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Réticulocytes	23Giga/l(50-150)	185Giga/l	186Giga/l
Folate sérique	16,8 nanogramme/ml (3,1-20,5)	non dosé	38,5
Ferritine	405nanogramme/ml (20-200)	non dosée	463
Vitamine B12	385picogramme/ml(189-883)	non dosée	440
Transferrine	1,6gramme/l(2-3,6)	non dosée	1,7
Fer sérique	35,6 micromole /l(5,83-34,5)	non dosée	29,3
Coefficient de saturation de T	89(20-40)	72%	68,9%
LDH	315 UI/l(135-214)	UI/l	Ui/l
Bilirubine totale	10micromol/l	20Microl/l	micromol/l
Bilirubine conjuguée	6mg/l	9mg/l	mg/l
CKD EPI	85ml/°	80ml/°	82ml/°

Table 3: Biological assessment of the third observation.

Paramètres biologiques	20 jours avant la consultation	J1 de consultation + Ts	J30 post transfusion
Hématie	2,24 Tera (3,8-5,8)	1,67 Tera/l	2,8Tera/l
leucocytes	7Giga/l (4-10)	5000G/l	9,4
Neutrophile	3498/mm3	1865/mm3	48,5
Hémoglobine	8,5 g/dl (11,5-16,5)	6,7g/dl	8,8g/dl
Hématocrite	25,8% (37-47%)	20,1%	23,6%
VGM	115,2fl (80 -100)	120fl	114fl
TCMH	37,5pg(27-32)	40,1pg	39,8pg
CCMH	33g/dl(32-36)	33 g/dl	32,4g/dl
Plaquette	292Giga/l(150-500)	407 Giga/l	305Giga/l
Réticulocytes	162Giga/l(50-150)	47Giga/l	104Giga/l
LDH	382UI/l	291UI/l	447UI/l
Ferritine	1006nanogramme/ml (20-200)	1081nanog/ml	1010nanog/ml
Transferrine	2,4g/l(2-3,6)	2,33g/l	2g/dl
Fer sérique	155micromole /l(5,83-34,5)	50,8	12,7

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Coefficient de saturation de T	45%(20-40)	87%	23%
Bilirubine totale	37 micromol/l	21,7Microl/l	24micromol/l
Bilirubine conjuguée	15,5micromol/l	10,7micromol/l	11micromol/l
CKD EPI	88ml/min	74ml/min	87,2ml/min

Table 4: Biological assessment of the fourth observation.

Variable	patient A	patient B	patient C	patient D
Âge	28A	65A	62A	75A
Sexe	F	F	M	F
Génotype	SS	SS	Sbeta0	SS
Traitement de fond	Siklos 1000mg, acide folique	Siklos 1000mg, aranesp 150, acide folique	siklos 1250mg, iec, acide folique	Siklos, aranesp,150, speciafoldine, corvasal, kardegic
Antécédent	STA, TS	Anémie sous siklos il ya 6ans, IR	protéinurie, tabagique	HTA, IR, IM
Hb de basse	8-9g/dl	7-8g/dl	8g/dl	8-9g/dl
clinique	asthénie physique, essoufflement	asthénie physique, tachycardie	asthénie physique, paleur	asthénie physique
GR	1,44 tera/l	0,66tera/l	1,56tera/l	1,67tera/l
Hg	6g/dl	2,9g/dl	5,8g/d	6,7g/dl
VGM	128fl	134fl	101,3fl	120fl
TCMH	41,7pg	47pg	37,2pg	40,1pg
Réticulocytes	45giga/l	15giga/l	23giga/l	33 giga/l
Plaquettes	177giga/l	180giga/l	126giga/l	407giga/l
Globule blanc	3,1giga/l	7,78giga/l	4,5giga/l	3,9giga/l
LDH	328Ui/l	325Ui/l	315Ui	291Ui
Bilirubine totale	9,5 micromol/l	10micromol/l	10micromol/l	21micromol/l
Bilirubine conjuguée	2,5micromol/l	5micromol/l	6micromol/l	10,7micromol/l
fer sérique	28,1micromol/l	25micromol/l	35,6micromol/l	50,8micromol/l

ferritine	250nanog	810nanog	510nanogram	1081nanogram
transferrine	1,9 g/l	2g/l	2g/l	2,33g/l
CST	59%	35%	40%	87%
CKD -EPI	112ml/’	56,55ml/’	80ml/’	74ml/’
Diagnostic	Myélotoxicité	Myélotoxicité	myélotoxicité	myélotoxicité
Prise en charge	arrêt siklos, ts 2 cgr, aranesp 150 mg j1 et j3 + tardyferon	Arrêt siklos, ts 2cgr, aranesp 300,	arrêt siklos, aranesp 300	Arrêt siklos, TS 1cgr, aranesp 300
Evolution	bonne évolution	bonne évolution	bonne évolution	bonne évolution
Reprise siklos	15 jours après à la dose de 500 mg	15 jours après à faible dose 500mg	reprise 20 jours après à 250mg par jour	un mois après à 250mg/jr

Table 5: Summary biological assessment of four clinical cases.

Conclusion

Hydroxyurea (Siklos) remains the cornerstone disease-modifying therapy for sickle cell disease and significantly reduces vaso-occlusive complications. However, its use may be associated with clinically significant hematological toxicity, particularly severe aregenerative anemia secondary to bone marrow suppression.

This case series highlights the heterogeneous presentation of hydroxyurea-induced myelotoxicity, ranging from isolated severe anemia to bicytopenia, particularly in elderly patients and those with multiple comorbidities. Temporary discontinuation of treatment, supportive care including erythropoietin and blood transfusion when indicated, and subsequent dose adjustment resulted in favorable clinical and hematological outcomes in all patients.

These observations emphasize the importance of regular hematological monitoring, individualized dose titration, and early recognition of toxicity signs. In patients presenting with severe anemia while receiving hydroxyurea, alternative causes must be carefully excluded before attributing the event to drug toxicity.

Further studies involving larger cohorts are needed to better identify risk factors for hydroxyurea-induced myelotoxicity and to optimize monitoring strategies in patients with sickle cell disease.

Limitations of the Study

This study has some limitations. First, it is a series of clinical cases with a small sample size, limiting the generalizability of the results. Second, its retrospective nature exposes the study to a risk of missing data and heterogeneity in biological monitoring.

Furthermore, the absence of pharmacological measurement of hydroxyurea prevents formal confirmation of drug accumulation. Certain associated comorbidities, particularly renal insufficiency or chronic inflammatory conditions, may also have contributed to the occurrence of the observed cytopenias.

Nevertheless, this series has several strengths. It describes situations rarely reported in the Caribbean literature and highlights important practical issues concerning the monitoring of Siklos in real-world settings. It also underscores the need for an individualized approach in frail sickle cell patients.

Lessons Learned From The Three Clinical Cases

Hydroxyurea can cause potentially serious, severe, non-regenerative anemia in patients with sickle cell disease.

Macrocytosis associated with reticulocytopenia is a major indicator of drug-induced myelotoxicity in the context of good adherence to treatment.

The hematological toxicity of Siklos is generally reversible after temporary discontinuation and dose adjustment.

Elderly patients, patients with renal insufficiency, or those with a history of hematological toxicity require close monitoring regardless of the time elapsed since the start of treatment.

Regular monitoring of complete blood counts (CBC) and reticulocyte counts is essential during hydroxyurea treatment.

Management should be individualized to maintain therapeutic benefit while minimizing toxicity.

In the event of severe anemia during Siklos treatment, other causes of anemia in sickle cell patients must be systematically ruled out.

Algorithm for the management of anemia under hydroxyurea in sickle cell patients.

1. Clinical suspicion

Sickle cell patient on Siklos presenting with: asthenia, pallor, worsening anemia, dyspnea.

2. Initial laboratory workup

Complete blood count (CBC).

Reticulocytes, Bilirubin, LDH, CRP.

Ferritin, Serum creatinine, Hemoglobin electrophoresis.

3. Look for signs of hematological toxicity

Consider myelotoxicity if:

Macrocytosis, Reticulocytopenia, Possible neutropenia, Possible thrombocytopenia.

4. Rule out differential diagnoses

Viral aplastic crisis, Hyperhemolysis, Splenic sequestration Severe infection, Vitamin deficiency, Renal failure.

5. Therapeutic management

If moderate toxicity, Reduce Siklos dose.

Close monitoring, If severe toxicity Temporarily discontinue Siklos, Blood transfusion if Necessary hydration, vitamin supplementation, erythropoietin as indicated.

6. Monitoring

Complete blood count (CBC) reticulocytes, renal function, clinical progress.

7. Resumption of therapy

Gradual resumption of Siklos, dose adjusted to the patient's profile, regular monitoring.

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Ethical Statement

This study was conducted in accordance with the ethical principles of the Declaration of Helsinki. Clinical data were collected anonymously and confidentially. Information that could identify patients was removed to preserve their confidentiality. Access to

medical data was limited to the investigators involved in the study, and no personal information was disclosed. Informed consent was obtained from the patient before the use of clinical data.

Conflicts of Interest

The authors declare no conflicts of interest.

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Author Contributions

All authors participated in patient care, data collection, and the writing and revision of the manuscript. All authors read and approved the final version of the manuscript.

Declaration of the use of artificial intelligence

Artificial intelligence (ChatGPT, OpenAI) was used as a writing assistance tool for grammar and language correction, sentence rephrasing, improvement of the scientific writing style, manuscript structuring, and abstract preparation. All outputs generated by the artificial intelligence tool were carefully reviewed and validated by the authors. The authors retain full responsibility for the accuracy, integrity, and scientific content of the manuscript, as well as for the conclusions presented in this work.

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