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Computer Algorithm-Based Hydroxyurea Dosing Facilitates Titration to Maximum Tolerated Dose in Sickle Cell Anemia

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Abstract

Adults with sickle cell disease (SCD) experience acute and chronic complications and die prematurely. When taken at maximum tolerated dose (MTD), hydroxyurea prolongs survival; however, it has not consistently reversed organ dysfunction. Patients also frequently do not take hydroxyurea, at least in part because of physician discomfort with prescribing hydroxyurea. We sought to develop a computer program that could easily titrate hydroxyurea to MTD. This was a single-arm, open-label pilot study. Fifteen patients with homozygous SCD were enrolled in the protocol, and 10 patients were followed at baseline and then for 1 year after hydroxyurea initiation or dose titration. Fetal hemoglobin significantly increased in all 10 patients from 8.3% to 25.1% ($P < .001$). Nine patients were titrated to MTD in an average of 7.9 months, and the tenth patient's hydroxyurea dose was increased to 33 mg/kg/day. Computer program dosing recommendations were the same as manual dosing decisions made using the same algorithm for all patients and at all times. We also evaluated markers of cardiopulmonary, liver and renal damage. Although cardiopulmonary function did not significantly improve, direct bilirubin and alanine aminotransferase levels significantly decreased ($P < .001$ and $P < .01$, respectively). Last, although kidney function did not improve, degree of proteinuria was significantly reduced ($P < .05$). We have developed a computer program that reliably titrates hydroxyurea to MTD. A larger study is indicated to test the program either as a computer program or a downloadable application.

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Conflicts of Interest

The authors declare no competing financial interests and no conflicts of interest.

Data Sharing

Data supporting the findings of this study will be shared on [ClinicalTrials.gov](https://clinicaltrials.gov).

Keywords

computer program; hydroxyurea; maximum tolerated dose; organ damage; sickle cell disease

Sickle cell disease (SCD) is a genetic disorder in which a missense mutation substitutes valine for glutamic acid in the 6th position of the beta-globin gene with polymerization of sickle hemoglobin on deoxygenation. Therefore, red blood cells (RBCs) transform from an easily deformable biconcave disc that moves freely through the microvasculature to a rigid sickled shape that occludes the microvasculature and prevents organs from receiving the oxygen needed to function properly. Subsequently, patients with SCD experience debilitating acute complications including painful crises and stroke as well as chronic manifestations such as pulmonary hypertension, renal failure, and liver disease. Despite its discovery more than 100 years ago, many patients are still dying by the fifth decade of life.^{1,2}

Hydroxyurea acts by increasing fetal hemoglobin (HbF), which reduces RBC sickling, decreasing adhesivity of reticulocytes and neutrophils to the endothelium and enlarging RBCs, reducing intracellular sickle hemoglobin concentration, decreasing neutrophil and reticulocyte counts, and releasing nitric oxide, which may lead to vasodilation.³⁻⁷ Hydroxyurea has been shown to decrease acute complications, reduce transfusion requirement, and prolong survival.⁸⁻¹¹ Despite the use of hydroxyurea, patients develop organ damage, which has been associated with premature mortality.¹²⁻²² Pediatric studies have shown that increased HbF reverses splenic dysfunction^{23,24} and protects patients from retinopathy.²⁵

Although hydroxyurea has been associated with improved survival, studies from the posthydroxyurea approval era found that patients continue to die early.^{15,18,19,22,26} However, hydroxyurea dosing was not considered by these studies, and only 7%-37% of patients were prescribed hydroxyurea at the time of death.^{15,18,19,26} Indeed, a recent study including data from a national registry reported the proportion of visits for adults with SCD that mentioned new or continued hydroxyurea prescriptions was only 11% between 2015 and 2017.²⁷ Common barriers to hydroxyurea use are inexperience with and discomfort of a number of adult SCD providers and primary care doctors with prescribing a chemotherapeutic agent. Further, many patients treated with hydroxyurea are not titrated to a maximum tolerated dose (MTD) or even a therapeutic effect. The aim of this study was to develop a computer program that would easily facilitate hydroxyurea dosing to MTD. We also sought to evaluate the effect of maximum tolerated dosing of hydroxyurea on markers of organ damage.

Methods

Study Population

The study was approved by the National Heart, Lung, and Blood Institute (NHLBI) Institutional Review Board at the National Institutes of Health (NIH), and all subjects signed informed consent. Patients with homozygous SCD (HbSS) were enrolled at the NIH Clinical Center in our Pilot Study to Assess Algorithm-Based Hydroxyurea Dosing in Patients With

SCD ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT02225132) identifier [NCT02225132](https://clinicaltrials.gov/ct2/show/study/NCT02225132)) between October 2014 and August 2016. They were eligible to enroll if they had HbSS, were at least 15 years of age, had an HbA < 15% if they had been recently transfused, and had sufficient blood counts (absolute neutrophil count [ANC] 2000/ μ L, platelets 150 000/ μ L, hemoglobin > 5.4 g/dL, and absolute reticulocyte count [ARC] 100 000/ μ L [unless the hemoglobin was >8 g/dL at baseline]). Patients on angiotensin-converting enzyme inhibitors and angiotensin receptor blockers had to be on a stable dose for at least 2 weeks prior to enrollment. Patients were excluded for reasons including pregnancy, chronic transfusion therapy, hydroxyurea dose of 20 mg/kg/day, or end stage renal disease.

Study Design

This single-arm, open-label, nonrandomized pilot study was designed to evaluate the effect of algorithm-based hydroxyurea dosing on HbF response, the ability to titrate each patient to the MTD of hydroxyurea, and organ function in patients with HbSS. The study followed a 2-month baseline period during which time 3 visits occurred and the following baseline data were gathered: complete blood count (CBC) with differential, ARC, hemoglobin electrophoresis, acute care panel, hepatic panel, gamma-glutamyl transpeptidase (GGT), cystatin C, lactate dehydrogenase, glomerular filtration rate (GFR), urine osmolality, and urine albumin-to-creatinine ratio. Patients were then treated with hydroxyurea for 1 year with dosing according to a dosing algorithm. Dosing decisions were made primarily by 2 investigators (A.C. and C.F.) employing the same algorithm used by the computer program; the investigators consistently adhered to the algorithm when making dosing decisions.

To ascertain more accurate values compared with isolated values, primary and secondary end-point laboratory values were calculated as the difference between the average of the 3 values obtained during the baseline period (at the first visit and then 1 and 2 months later) compared with the mean laboratory studies calculated from 3 values obtained in months 8, 10, and 12. Secondary end points included ejection fraction, tricuspid regurgitant velocity, and 6-minute walk distance 1 year after hydroxyurea compared with baseline. Mean laboratory parameters including total hemoglobin level, creatinine, GFR as calculated by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI),²⁸⁻³⁰ cystatin C, alkaline phosphatase, direct bilirubin, GGT, and urine albumin-to-creatinine ratio were compared in months 8, 10, and 12 with the values collected during the baseline period. The percentage of patients who reached MTD, concordance of the hydroxyurea dose as determined by the computer algorithm as compared with the dose derived manually, and frequency of nonadherence as determined by pill counts were also monitored.

The starting dose was 15 mg/kg/day (rounded to the nearest 200-, 300-, or 500-mg capsule) given as a single daily dose. Patients already taking hydroxyurea stayed on their current dose unless the dose was <15 mg/kg/day. The CBC with differential and ARC were checked 2 and 4 weeks after every hydroxyurea dose was adjusted (Figure 1). Hydroxyurea was held for any of the following based on NIH standard-of-care practice: ANC < 1500/ μ L, platelet count < 80 000/ μ L, hemoglobin < 5.4 g/dL, or ARC < 80 000/ μ L if hemoglobin was <8 g/dL (Table 1). If hydroxyurea was held, the CBC and ARC were repeated within 1-2 weeks. If counts were above toxicity parameters, hydroxyurea was restarted at the same dose. If

the blood counts were still abnormal, they were rechecked in 1-2 weeks, and if recovered hydroxyurea was restarted at the same dose. If toxicity recurred or persisted, hydroxyurea was held until blood counts recovered and then restarted at a dose reduced by 2.5 mg/kg/day, which defined MTD (Figure 1).

If tolerated for at least 8 weeks without toxicity and the patient was at least 70% compliant calculated by pill count and based on expected rates of adherence,^{31,32} the hydroxyurea dose was increased by 5 mg/kg/day up to a maximum of 35 mg/kg/day. The weight of the patient at the time of the hydroxyurea adjustment was used to calculate the next dose. MTD was defined as 2.5 mg/kg/day lower than the dose that led to significant myelosuppression (Table 1) after 2 different attempts or 2.5 mg/kg/day lower than the dose that took >2 weeks to recover blood counts or a dose of 35 mg/kg/day. Therefore, if a patient developed significant myelosuppression with 2 attempts at a specific dose or took >2 weeks to recover counts above the myelosuppression range (as defined in Table 1) at a specific dose, the computer program decreased the dose by 2.5 mg/kg/day and defined that dose as MTD. A dose of 35 mg/kg/day also defined MTD. After the patient finished the study, he or she was transferred back to the primary hematologist to continue hydroxyurea management.

Computer Program

Hydroxyurea doses were derived manually according to a written algorithm and were also determined by the internally developed computer program that used the same algorithm. The goal of the computer program was to titrate hydroxyurea doses to MTD. The software code was developed by and information technology support provided by the NHLBI Division of Intramural Research Scientific Information Office and Information Technology and Applications Center. The complete software package consists of a Php/HTML-built front end and a MySQL database in the background. The database is used to store historical data and could be queried to produce various statistics surrounding the stored information.

The computer program has options for normal kidney function where the starting dose is 15 mg/kg/day (Figure 2a) and abnormal kidney function (defined as a GFR of 10-60 mL/min/1.72 m²) where the starting dose is 7.5 mg/kg/day; all patients had normal kidney function. The computer program automatically calculated the initial dose based on patient weight (Figure 2A) and when the patient should return. On return, blood counts were manually entered into the computer program (Figure 2B), and the program would state whether hydroxyurea should be continued, at what dose the hydroxyurea should be administered, and when the patient should return. The program recorded blood counts, dates, and dosing calculations in the Patient Blood Counts History (Figure 2C), which could be exported to an Excel file. Once the patient had suitable blood counts for 8 consecutive weeks, the program would specify a dose increase (Figure 2C). If at any point, blood counts were insufficient, the program would recommend that hydroxyurea be held and when the patient should return (Figure 2D). The program would state when it was fine to restart hydroxyurea and if the dose needed to be decreased. The program would also inform when the patient reached MTD and at what dose (Figure 2E). After that time, the program would not make any other dosing recommendations, but blood counts could still be entered and saved.

Quality of Life

PROMIS quality-of-life questionnaires were administered at baseline and every 4 months during the hydroxyurea study period. The forms that were used were the Pain Interference - Short Form 8a, Fatigue-Short Form 8a, Ability to Participate in Social Roles and Activities - Short Form 8a, and Physical Function-Short Form 8b in paper-and-pencil format. The total raw scores for each subscale were derived by summing the individual item responses, and raw scores were converted to standardized *t* scores, with a mean of 50 and standard deviation of 10.

Statistical Considerations

Sample size was estimated based on a test of the mean change in HbF from baseline to 1 year in an earlier cohort of patients followed at the NIH, where dosing practice did not necessarily include titration of hydroxyurea to MTD. The mean absolute change in HbF in months 8, 10, and 12 from baseline was about 11% with a standard deviation change of 10% with standard hydroxyurea dosing. With the assumption that the HbF change for this study being of a similar magnitude and using a paired *t* test, a sample size of 9 would be needed to achieve 83% power at a significance level of 0.05 using 2-sided testing.

We assumed that up to 30% of patients would be nonadherent, defined as missing > 20% of pills within 1 month on at least 2 occasions.³³ We chose a higher adherence threshold of 80% rather than the 70% required to escalate hydroxyurea dose because adherence rate will affect the primary end point, HbF level, and because 80% was chosen as the threshold to evaluate hydroxyurea response in the Multi-Center Study of Hydroxyurea.³³ Further, because RBC transfusion may suppress HbF, frequent transfusions may interfere with hydroxyurea response. Based on our cohort of 71 patients, up to 20% of patients received >2 transfusions per year. Therefore, we assumed that up to 20% of patients would receive >2 transfusions during the study period. So the total dropout rate was expected to be up to 60%, and, therefore, a sample size of up to 24 patients would be needed. Any patients who received >2 transfusions per year or were noncompliant were removed from the protocol.

The statistical program R, version 3.6.1, was used to perform the analyses. The primary response variable, absolute change in HbF, was compared from the mean baseline level (calculated over 3 baseline visits) with the mean level achieved from months 8, 10, and 12 using a paired *t* test with 95% confidence interval. For secondary response variables that were compared with baseline, a paired *t* test was used for continuous variables. For secondary response variables not compared with their baseline, descriptive analysis was performed with mean, standard deviation, 95% confidence interval, and frequency, where appropriate. Subjects were only included in the final analyses if primary end-point data were collected 3 times during the baseline period and in months 8, 10, and 12 or at baseline and after 1 year of therapy, depending on the variable being evaluated. Per protocol, not all secondary end-point data were collected in month 10. Data collected at 9 or 11 months therefore may have been used in lieu of the 10-month data.

Results

Baseline Characteristics

A total of 15 subjects were enrolled to participate. Of that, 5 (33%) were male. Age at enrollment ranged from 19 to 60 years, with a mean of 33 years. Of the 15 enrolled, 5 subjects were removed from the study. Two were removed for reaching significant myelosuppression before dose escalation began, 2 for noncompliance, and 1 for receiving more than the 2 blood transfusions. Of the final 10 patients who completed the study, 2 (20%) were male (Table 2); mean age at enrollment was 33 years (range, 26-51 years). Only 1 subject was administering hydroxyurea at baseline at a dose of 15 mg/kg/day.

Computer Program Results

Of the 10 patients who completed the study, 9 were titrated to MTD at a mean of 7.9 ± 2.2 months. The median MTD for the 9 patients was 27.5 mg/kg/day (range, 17.2 to 35 mg/kg/day). The 10th patient's hydroxyurea dose was not titrated to the maximum dose of 35 mg/kg/day but instead to 33 mg/kg/day because of the limited duration of the study. Importantly, computer program dosing recommendations were the same as manual dosing decisions made using the same algorithm for all 10 patients and at all times. Table 3 lists the total hydroxyurea and weight-based daily dose for each subject at the 12-month point (median, 1700 mg; range, 1200-2500 mg; and median, 23 mg/kg/day; range, 12.5-35.0 mg/kg/day, respectively). The most common cytopenia that defined MTD was reticulocytopenia in 8 subjects, neutropenia in 6 subjects, and thrombocytopenia in 1 subject; 4 of the subjects experienced both neutropenia and reticulocytopenia. The mean ARC at the time of MTD was 53.4 ± 20.4 K/ μ L, mean ANC was 1.3 ± 0.2 K/ μ L, and platelet count in the 1 subject was 54 K/ μ L.

Hematologic Findings

HbF levels increased significantly in the 10 patients, from a mean of $8.3\% \pm 5.9$ to $25.1\% \pm 6.2$ ($P < .001$, Figure 3A and Table 3). As expected, ANC significantly decreased (6.3 ± 2.4 to 2.6 ± 1.0 K/ μ L; $P < .001$), mean corpuscular volume significantly increased (93.6 ± 8.2 to 118.0 ± 4.0 fL; $P < .001$), and platelet count significantly decreased (388.0 ± 111.7 to 293.9 ± 120.1 K/ μ L; $P = .03$). Total hemoglobin did not change (8.1 ± 1.4 to 8.8 ± 1.0 g/dL; $P > .05$). There was evidence of decreased hemolysis with significantly decreased indirect bilirubin (3.2 ± 2.0 to 0.89 ± 0.46 mg/dL; $P = .001$) and reduced ARC (396.5 ± 97.0 to 102.8 ± 55.6 K/ μ L; $P < .001$).

Laboratory and Cardiopulmonary Markers of Organ Damage

To evaluate markers of liver damage, we serially collected GGT, direct bilirubin, and alanine aminotransferase (ALT) at baseline and after titrating hydroxyurea dosing. GGT levels did not significantly differ ($P > .05$). However, direct bilirubin (0.4 ± 0.08 to 0.2 ± 0.10 mg/dL; $P < .001$) and ALT (32.6 ± 13.5 to 21.4 ± 9.4 ; $P < .01$) significantly decreased when comparing baseline values with those values collected after MTD dosing of hydroxyurea (Figure 3B,C). Therefore, some markers of liver damage were improved.

In contrast, we did not find any significant differences in cardiopulmonary parameters including ejection fraction, tricuspid regurgitant velocity, or 6-minute walk distance. Last, to evaluate markers of kidney function, creatinine, urine osmolality, estimated GFR, and urine albumin/creatinine ratio were monitored at baseline and at prespecified times after titrating hydroxyurea. There was no significant difference in creatinine, urine osmolality, cystatin C, or CKD-EPI at baseline compared with posthydroxyurea titration ($P > .05$). Albumin/creatinine ratio also did not significantly decrease before and after hydroxyurea titration (226.7 ± 309.5 to 148.3 ± 303.4 ; $P = .16$). However, 2 of the 10 subjects had much higher albumin/creatinine ratios with levels >300 before and/or after hydroxyurea titration compared with the other subjects (Figure 3D). We therefore performed log transformation and found that the log albumin/creatinine ratio significantly decreased after hydroxyurea titration, from 4.3 ± 1.6 to 3.2 ± 1.8 ; $P < .05$ (Figure 3E).

Quality of Life

No significant changes from baseline to 12 months posttreatment initiation were found on any of the PROMIS subscales (all $P > .05$).

Discussion

We previously found that among 383 patients with homozygous SCD screened at the NIH over a 9-year period, only 65% were treated with hydroxyurea despite the vast majority meeting disease criteria severe enough to warrant initiating hydroxyurea.² Further, the median hydroxyurea dose was only 19.4 mg/kg/day, and mean ANC at the time of enrollment was $5600/\mu\text{L}$, intimating that patients taking hydroxyurea were not on an MTD. In the Multi-Center Study of Hydroxyurea, only 33% of patients in the hydroxyurea group were administering hydroxyurea at MTD or had received a higher dose that was later decreased within 6 months of initiating hydroxyurea.³⁴ By the end of the study, 51% of the patients were on an MTD or close to maximal dose. Controversy exists in high-resource settings regarding whether hydroxyurea should be dosed at MTD or titrated solely to a therapeutic effect. However, our retrospective analysis suggested that hydroxyurea dose and hydroxyurea-induced HbF were associated with survival.² Further, larger prospective analyses that reported improvement in survival also titrated hydroxyurea to MTD.^{20,21,35}

At least in part because of the complexity involved in managing adults with severe SCD, the focus has typically not been to push hydroxyurea to MTD. Ideally, a computer program would make the hydroxyurea dose titration process easier, more effective, and less intimidating for primary providers who frequently manage adults with SCD. Proof of principle is evidenced by multiple computer-based warfarin dosing studies which increased confidence regarding warfarin dosing for doctors and nurses, decreased the number of venipunctures, and either produced dosing results that were equal to or superior to manual dosing recommendations.³⁶⁻³⁸ Our simple computer program facilitated dosing of hydroxyurea to MTD in 9 of the 10 patients and titration to a dose close to MTD in the 10th patient. Importantly, the computer program recommendations matched the manual dosing decisions in all the patients at all times. Therefore, the computer program was effective at meeting our goals. We sought to enroll patients who were not on hydroxyurea or on a low

dose so that multiple dosing recommendations would be made by the computer program for each participant. However, a patient on a higher hydroxyurea dose (ie, 20-25 mg/kg/day) could be enrolled, with the current dose being entered into the computer program and the computer program following the algorithm to increase the dose to MTD.

As expected, titration of hydroxyurea to MTD led to a significant increase in HbF for all 10 patients and also a significant decrease in ANC and platelet count and reduction in markers of hemolysis. We did not see a significant change in hemoglobin, possibly because of the profound decrease in reticulocytes. We also found for the first time that hydroxyurea dosing at MTD led to a significant decrease in direct bilirubin and ALT, suggesting that liver damage may have improved. This finding is noteworthy because an elevated direct bilirubin has been associated with early mortality in adults with SCD.³⁹ Previous studies regarding hydroxyurea's effect on markers of cardiopulmonary function are conflicting.^{40,41} Although 1 analysis reported no difference in measures of systolic function between children on and off hydroxyurea, the authors noted improved diastolic function in the hydroxyurea group.⁴² An adult study found no difference in systolic or diastolic function in patients receiving hydroxyurea or transfusions compared with untreated adults with SCD.⁴³ Our study did not find a significant difference in ejection fraction, tricuspid regurgitant velocity, or 6-minute walk distance. Therefore, hydroxyurea dosing for 1 year was not associated with significant improvement in cardiopulmonary function.

Hydroxyurea has been reported to decrease cortical iron kidney deposits in a patient with SCD.⁴⁴ Further, hydroxyurea has been shown to prospectively decrease proteinuria in adults and children with SCD^{45,46} and was associated with a lower prevalence of albuminuria in adults with SCD.⁴⁷ Although hydroxyurea dosed at MTD significantly decreased GFR in children with SCD, there was no significant change in cystatin C levels, and a randomized, placebo-controlled trial of fixed dose hydroxyurea (20 mg/kg/day) in infants did not show improvement in GFR between those receiving hydroxyurea versus placebo¹¹; however, infants receiving hydroxyurea had significantly higher urine osmolality and decreased kidney enlargement, implying some benefit to the kidneys.⁴⁸ We did not find significant differences in creatinine, urine osmolality, cystatin C, or estimated GFR, suggesting that renal pathology may have been too far advanced or that 1 year was not sufficient to reverse these kidney parameters. However, similar to other studies, hydroxyurea significantly decreased albuminuria in our patients.^{45,46,49,50} In fact, of 3 patients with macroalbuminuria at baseline, protein levels decreased to the microalbuminuria range in 1 patient and no albuminuria range in 1 patient.

Multiple studies, primarily involving children and young adults, and most retrospective analyses suggest that hydroxyurea is associated with improved quality of life for patients with SCD.^{51,52} Not surprisingly, quality of life improves with hydroxyurea and HbF response.⁵³ Ours is the first prospective study using PROMIS to evaluate the effects of hydroxyurea on adults with SCD. We did not find improvement in quality of life, likely because of the limited sample size.

The main limitation of our study was small sample size, which limited our ability to evaluate our secondary end points. Our sample size was calculated based on expected HbF

response as our primary end point. This study was primarily a pilot analysis to evaluate our newly developed computer program and its ability to titrate patients with SCD to MTD of hydroxyurea. Further, only patients with normal kidney function were included in this study. Therefore, we did not assess whether this computer program can be used in patients with renal dysfunction in whom dosing challenges are common.

Conclusions

We have designed a novel computer program that successfully titrated hydroxyurea to MTD in 9 of 10 adults and is available for public use. The computer program's dosing recommendations were the same as manual dosing decisions made using the same algorithm for all 10 subjects. We have also shown for the first time that hydroxyurea improved some markers of liver damage. A larger multicenter study is indicated to test the program either via the computer or as an application that can be easily downloaded to providers' phones. Our goal is for the program to help physicians, particularly those who are not sickle cell providers, to feel comfortable prescribing hydroxyurea and titrating the drug to MTD to improve patient accessibility and decrease morbidity and possibly mortality for patients with SCD.

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Figure 1.

Hydroxyurea dosing algorithm. This algorithm was incorporated into the computer program and was also followed for manual calculations. ANC, absolute neutrophil count; ARC, absolute reticulocyte count; BID, twice daily; CBC, complete blood count; diff, differential; GI, gastrointestinal; Hb, hemoglobin; HU, hydroxyurea; MTD, maximum tolerated dose; Plt, platelet count.

A

Edit Patient Correct recent entry Generate Excel File

Patient 5454, Normal Kidney Function

* Start Dose (15 mg/kg/day)

1350 mg

Next

Phlebotomy

10 records per page Search:

Date Volume Patient HB

No data available in table

Showing 0 to 0 of 0 entries Previous Next

Patient Blood Counts History

10 records per page Search:

Study Date	Dose	Weight	ARC	ANC	HB	Platelets	Comment
No data available in table							

Showing 0 to 0 of 0 entries Previous Next

B

Patient 5454, Normal Kidney Function

Please enter ARC, ANC, and Platelets in cells/uL. The values should be > 1000.

* ARC * ANC * HB * Platelets

86750 /uL 1755 /uL 10 g/dl 85123 /uL

Date * Weight

05/30/2018 90 kg

(+) Add comment

Reset Next

Phlebotomy

10 records per page Search:

Date Volume Patient HB

No data available in table

Showing 0 to 0 of 0 entries Previous Next

Patient Blood Counts History

10 records per page Search:

Study Date	Dose	Weight	ARC	ANC	HB	Platelets	Comment
No data available in table							

Showing 0 to 0 of 0 entries Previous Next

C Patient 5454, Normal Kidney Function

Check the blood counts again in 14 days.

* Dose (20 mg/kg/day)
1800 mg

Continue

Phlebotomy

10 records per page Search:

Date Volume Patient HB

No data available in table

Showing 0 to 0 of 0 entries Previous Next

Patient Blood Counts History

10 records per page Search:

Study Date	Dose	Weight	ARC	ANC	HB	Platelets	Co
05/30/2018 12:00 AM (0 days) ago	1350	90	86750	1755	10	85123	
05/30/2018 12:00 AM (0 days) ago	1350	90	65850	1250	10	82000	
05/30/2018 12:00 AM (0 days) ago	1350	90	85000	1600	10	85000	
05/30/2018 12:00 AM (0 days) ago	1350	90	85000	1600	10	85000	
05/30/2018 12:00 AM (0 days) ago	1350	90	85000	1600	10	85000	
05/30/2018 12:00 AM (0 days) ago	1350	90	85000	1600	10	85000	

Showing 1 to 6 of 6 entries Previous 1 Next

D

Edit Patient
Correct recent entry

Generate Excel File

Patient 5454, Normal Kidney Function

Hold HU and check the blood counts again in 7 days.

Continue

Phlebotomy

10 records per page Search:

Date
Volume
Patient HB

No data available in table

Showing 0 to 0 of 0 entries

Previous
Next

Patient Blood Counts History

10 records per page Search:

Study Date	Dose	Weight	ARC	ANC	HB	Platelets	Co
05/30/2018 12:00 AM (0 days) ago	1350	90	86750	1755	10	85123	
05/30/2018 12:00 AM (0 days) ago	1350	90	65850	1250	10	62000	

Showing 1 to 2 of 2 entries

Previous
1
Next

E

Patient 5454, Normal Kidney Function

The study is finished and the MTD for the Patient is 1575 mg.

Click [here](#) if you want to add more Patient data.

Phlebotomy

10 records per page Search:

Date
Volume
Patient HB

No data available in table

Showing 0 to 0 of 0 entries

Previous
Next

Patient Blood Counts History

10 records per page Search:

Study Date	Dose	Weight	ARC	ANC	HB	Platelets	Co
05/30/2018 12:00 AM (0 days) ago	1350	90	86750	1755	10	85123	
05/30/2018 12:00 AM (0 days) ago	1800	90	1000	10	10	1000	
05/30/2018 12:00 AM (0 days) ago	1800	90	85000	1600	10	85000	

Figure 2.

Computer program. (A) Recommended initial dosing based on weight and kidney function. (B) Blood count entry. (C) Blood count history and recommendation for dose increase. (D) Hold hydroxyurea recommendation for toxicity, in this case excessive myelosuppression. (E) Maximum tolerated dose of hydroxyurea reached. ANC, absolute neutrophil count; ARC, absolute reticulocyte count; HB, hemoglobin; MTD, maximum tolerated dose.

Figure 3. Selected laboratory parameters in study patients measured at baseline (mean of the 3 values obtained during the run-in period) and after hydroxyurea dose titration (mean of the 3 values obtained in months 8, 9-11, and 12). (A) Fetal hemoglobin. (B) Direct bilirubin. (C) Alanine aminotransferase (ALT). (D) Albumin-to-creatinine ratio. (E) Log albumin-to-creatinine ratio.

Table 1.

Hydroxyurea Dosing Parameters as per the Computer and Manual Dosing Algorithms

	Holding Parameters	Dose-Escalation Parameters
Absolute neutrophil count	<1500/ μ L	1500/ μ L
Hemoglobin	<5.4 g/dL	5.4 g/dL
Absolute reticulocyte count	<80 000/ μ L <i>if</i> hemoglobin < 8 g/dL	80 000/ μ L and/or hemoglobin 8 g/dL
Platelet count	<80 000/ μ L	80 000/ μ L

Table 2.

Baseline Characteristics

Patient	Type of SCD	Age at Enrollment	Sex	On Hydroxyurea?
1	HbSS	39	Female	No
2	HbSS	34	Female	No
3	HbSS	28	Male	Yes (15 mg/kg/day)
4	HbSS	30	Female	No
5	HbSS	32	Female	No
6	HbSS	28	Female	No
7	HbSS	51	Female	No
8	HbSS	27	Female	No
9	HbSS	26	Female	No
10	HbSS	35	Male	No

Table 3.

Hematologic Findings at Baseline and After Hydroxyurea Dose Titration

Patient	ANC		Hgb		MCV		Pit		ARC		HbF		HU Dose at 12 Months (mg/kg/day)	
	BL	FU	BL	FU	BL	FU	BL	FU	BL	FU	BL	FU		
1	4.2	2.6	7.5	9.6	86.8	116.7	335.0	279.0	343.3	104.9	7.8	24.9	2200 (35.0)	
2	8.1	4.6	7.5	9.4	90.6	113.3	445.3	354.3	455.7	109.5	6.0	25.5	1300 (19.8)	
3	4.7	1.6	11.5	9.1	114.7	123.9	273.0	146.0	251.5	47.0	20.4	32.1	1600 (19.0)	
4	7.4	3.6	9.1	9.0	92.5	121.7	291.7	92.7	355.1	57.8	17.3	33.4	2200 (12.5)	
5	6.1	2.2	7.4	6.7	91.4	120.7	243.3	263.0	412.8	74.0	6.7	24.5	1600 (20.9)	
6	9.2	2.7	7.2	7.7	86.4	115.6	440.7	198.0	344.9	34.9	7.5	30.8	1600 (30.2)	
7	9.7	2.7	8.7	9.7	98.4	117.0	548.0	357.0	591.4	139.8	6.8	27.7	2500 (33.0)	
8	3.5	1.3	7.3	8.3	88.3	123.1	497.7	370.0	388.9	90.4	1.9	20.0	1800 (24.6)	
9	6.6	2.1	6.6	8.3	94.5	112.6	507.3	412.3	326.0	151.4	3.8	14.9	2400 (35.0)	
10	3.1	3.2	8.1	10.1	92.6	115.6	297.7	466.3	495.1	218.0	5.2	17.5	1200 (16.4)	

ANC, absolute neutrophil count; ARC, absolute reticulocyte count; BL, baseline; FU, follow-up; HbF, fetal hemoglobin; Hgb, hemoglobin; HU, hydroxyurea; MCV, mean corpuscular volume; Plt, platelet count.