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Peripheral stem cell harvest using G-CSF in young sickle cell patients after erythrocyte exchange transfusion

Abstract

Gene therapy approaches for Sickle Cell Disease (SCD) are being introduced into routine clinical care in European countries. One major hurdle to successful gene therapy is the large amount of CD34+ hematopoietic stem cells required. The standard of care in preparation for gene therapy with Exagamglogen-autotemcel does not allow the use of G-CSF for patients with SCD. We present a series of ten SCD patients [1,2], in which we safely have been using G-CSF after erythrocyte exchange transfusion to obtain autologous back-ups before stem cell transplantation. G-CSF use for stem cell mobilization in SCD was tolerated well after HBS-reduction below <30% (Median 27.50%).

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Introduction

Sickle Cell Disease (SCD) is one of the most common inherited diseases worldwide [3]. Outcomes for allogeneic Stem Cell Transplantation (SCT) from an HLA-identical sibling donor are excellent. Unfortunately, a high percentage of patients lack a suitable sibling donor. This is why alternative (matched unrelated and haploidentical) donor SCT protocols have been established over the past years [4]. Due to higher incidences of graft rejection in these scenarios, it is recommended to harvest autologous stem cell back-ups prior to alternative donor SCT. Moreover, gene therapy approaches have been developed and are now introduced into routine clinical care in European countries. One major hurdle to successful gene therapy is the large amount of CD34+ hematopoietic stem cells required. Repetitive courses of apheresis with stem cell stimulation are needed to reach the necessary stem cell amounts. G-CSF is a growth factor commonly used to stimulate neutrophil regeneration after chemotherapy or during episodes of fever in neutropenia. It is also used for harvest of peripheral hematopoietic CD34+ stem cells in allogeneic SCT donors or recipients for autologous back-ups. Severe complications including pain crises and even fatalities had been reported after G-CSF use in SCD patients [5,6]. It had been recommended to avoid G-CSF use in SCD patients ever since. SCD is a chronic inflammatory disease with a constantly elevated number of activated erythrocytes and platelets. These processes are enhanced by G-CSF and are thought to be responsible for the intolerance of SCD patients to G-CSF stimulation. However, no clinical problems were seen in persons with HBS trait [7]. In preparation for gene therapy a combination of stem cell harvest and autologous back-up is needed [8]. The standard of care in preparation for gene therapy with Exagamglogen-Autotemcel does not allow the use of G-CSF for patients with SCD. It remains challenging to reach sufficient stem cell numbers by peripheral apheresis using plerixafor alone [1,2]. That is why we present our current experience in utilizing G-CSF for obtaining autologous back-ups in a series of paediatric SCD patients, that we have been using for the past eight years.

Patients and methods

Software: Existing medical records and digital files were used for data research. Microsoft Excel was used for data collection and statistical and descriptive analyses.

Patient cohort: The patient cohort consisted of 10 paediatric SCD patients, eight of them had a HBSS and two a compound-heterozygous HBS/ß^0-Thal subtype. Median patient age at the time of stem cell transplantation was 15 years (6-20 years). Five patients were male and five female patients. Five patients had undergone splenectomy. One patient was on chronic exchange transfusion due to retinal infarction, none of the other patients exhibited extensive cerebral vasculopathy. All patients were treated at the Department for paediatric oncology and haematology at the Charité- University Medicine Berlin. Genetic diagnosis was performed at our laboratory and all patients underwent allogeneic stem cell transplantation at our centre (Table 1) displays further patient details.

Protocol: In the preparation for HSCT patients underwent one complete blood exchange transfusion not more than 4 weeks prior to the start of the conditioning regimen. A central venous catheter was placed immediately prior to the exchange transfusion. Stem cell harvest was aimed to take place approximately 1-3 weeks after the exchange transfusion.

Erythrocyte exchange transfusion: All patients received a full erythrocyte exchange transfusion exchanging approximately the total blood volume. Extended blood group matching was used for the erythrocyte concentrates. Exchange transfusions were performed at our Stem Cell Facility using the TERUMO Electrooptical® system.

Stem cell collection: After erythrocyte exchange transfusion all patients underwent peripheral stem cell harvest using G-CSF +/- Plerixafor. G-CSF stimulation was started 5 days prior to stem cell apheresis with the standard daily dose of 2x5 µg/kg bodyweight. A CD34+ cell count was done on day 1. Based on the results of the CD34 cell count, patients received an additional stimulation with Plerixafor (Cut-off 10/µl). Stem Cell harvest was performed at our Stem Cell Facility using the TERUMO Electrooptical® system.

Results

After one complete blood volume erythrocyte exchange followed by stem cell mobilisation with G-CSF (2x5 µg/kg for 5 days), none of the ten patients with sickle cell disease experienced any G-CSF mobilization-related adverse events (Table 2). The HBS proportion after exchange transfusion was <40% for nine out of ten patients (Table 2). The median CD34+

Table 1: Details on SCD patients undergoing G-CSF stimulated stem cell apheresis for cryopreservation of autologous back-up prior to alloSCT.

Patient ID	Sex	Age at HSCT	Diagnosis	Subtype	Main complications	Bodyweight in kg	Donor	Stem cell source
1	f	20	SCD	HbS/ß^0-Thal	Bone necroses, recurrent pain crises	41	MMRD	PBSC
2	m	12	SCD	HbSS	Chronic hemolysis	49	MMRD	PBSC
3	f	9	SCD	HbSS	Pathological doppler ultrasound	23	MMRD	PBSC
4	m	22	SCD	HbSS	Retinal infarction	90	MMRD	PBSC
5	f	17	SCD	HbSS	HU non-responder, recurrent pain crises	66	MUD	BM
6	m	20	SCD	HbSS	HU non-responder, recurrent pain crises	60	MUD	BM
7	m	19	SCD	HbS/ß^0-Thal	Secondary hemosiderosis, recurrent pain crises	61	MMRD	PBSC
8	f	12	SCD	HbSS	Abdominal pain crisis, Acute chest sydrome	45	MMRD	PBSC
9	f	14	SCD	HbSS	Acute chest syndrome	53	MMRD	PBSC
10	m	7	SCD	HbSS	Acute chest syndrome, splenic sequestration	13	MMRD	PBSC

Abbreviations: f: female; m: male; alloSCT: allogeneic hematopoietic stem cell transplantation; SCD: sickle cell disease; HSCT: stem cell transplantation; HbSS: sickle cell disease.

Table 2: Details on stem cell collection and cell counts.

Patient ID	Day of apheresis	CD34+ cells /µl preapheresis	CD34+ cells/µl postapheresis	Collected CD34+ Cells/kg	Collected CD34+/ kg in total x 10^6	Plerixafor	Chronic exchange transfusions	HbS post exchange in %	Days between exchange and back-Up	HU stop
1	1 2	29,6 26,8	23,7 n.d.	1TE à 1,02x10^6 1TE à 1,70x10^6	2,72	yes	no	8.6	7	no
2	1 2	18,4 163,7	23,8 217,7	1TE à 0,7x10^6 1TE à 4,79x10^6	5,49	no	no	17.6	19	yes
3	1	100	45,9	2TE à 2,85x10^6	5,7	no	yes	29.5	28	no
4	1 2 3	40 123 294	15 130 483	1TE à 0,3x10^6 1TE à 0,47x10^6 1TE à 0,6x10^6	1,37	no	yes	19	5	yes
5	1	148	108	2TE à 2,8x10^6	5,6	no	yes	36	20	yes
6	1 2	60 120	64 60	1TE à 2,9x10^6 1TE à 5,6x10^6	8,5	no	yes	13.6	5	yes
7	1 2	76 50	50 14	2TE à 1,25x10^6 1TE à 0,8x10^6	3,05	no	no	19.1	15	no
8	1 2	22 13	9 8	1TE à 1,2x10^6 1TE à 1,12x10^6	2,32	no	no	28.8	5	no
9	1 2	8 78	8 n.d.	1TE à 0,72x10^6 1TE à 3,63x10^6	4,35	yes	no	38.3	5	no
10	1 2	10 42	10 n.d.	1TE à 0,52x10^6 1TE à 3,44x10^6	3,96	yes	no	n.d.	5	no

Abbreviations: HU: Hydroxyurea; HU stop: HU stop more than 2 weeks prior to autologous back-up, n.d.: not determined.

count in the peripheral blood after 5 days of G-CSF mobilisation was 76.5x10^6/µl. Three patients received in addition one dose of plerixafor (2.4 mg/kg subcutaneously) due to insufficient mobilization of CD 34+ cells (<10/µl). The first patient received plerixafor out of security reasons, although her cell count exceeded 10/µl CD34+ cells. Stem cell apheresis achieved more than 1x10^6/kg CD34+ cells in all ten patients, though CD34+ cell yields differed widely across the cohort (Table 1). Median CD34+ cell yield was 4.15x10^6 cells/kg (range 1.37x10^6 - 8.5x 10^6 cells/kg).

With one exception (patient 4) patients that did stop hydroxyurea at least two weeks prior to start of mobilisation (patients 2, 5 and 6) were among those with the highest CD34+ yield in our cohort (median 5,6x10^6 cells/kg). Patient 4 needed three apheresis cycles and had the lowest CD34+ yield of all patients (1.37x10^6 cells/µl in total) due to technical problems concerning leukocyte isolation (clotting and undistinguishable cell phase). This patient had not been on hydroxyurea for more than 12 months at the time of stem cell mobilisation.

Discussion

Our protocol of stem cell mobilisation with G-CSF proved to be feasible and tolerated well. None of the patients in this case series experienced any stimulation-related adverse event. This evidence encourages to re-open the discussion as G-CSF has been regarded as contraindicated in patients with SCD due to some reports of fatal events after G-CSF use in the past [5,9]. G-CSF increases the risk of sickling through neutrophil activation as well as endothelial and platelet activation. We hypothesize that through full erythrocyte exchange, next to the amount of HBS, hypercoagulability and hyperinflammation in patients with SCD can be reduced to a level that allows the use of G-CSF. Furthermore, exchange transfusions may re-establish bone marrow homeostasis in patients with SCD by reducing haemolysis and disease activity. This may enable physiological leukopoiesis and might contribute to better mobilisation results. Our protocol opens new possibilities for stem cell mobilisation in patients with hemoglobinopathies qualifying for curative therapies like allogeneic SCT or gene therapy. Harvesting sufficient amounts of CD34+ stem cells has been challenging using plerixafor alone. G-CSF (also in combination with plerixafor) can contribute to solve this issue especially in patients receiving gene therapy, which requires more than ten-fold higher CD34+ yields than autologous back-ups for SCT. One major limitation to our study are the insufficient cell numbers. This problem can be overcome by the integration of G-CSF use in the currently established mobilization protocol for gene therapy for Thalassemia patients, where sufficient cell numbers are regularly reached in one mobilization cycle using G-CSF and plerixafor in combination. Recently, Acrimony et al. reported an improved stem cell harvest in 5 patients with SCD receiving G-CSF in combination with plerixafor undergoing stem cell collection in preparation for gene therapy without any G-CSF related complications [10]. Moreover, a preparation phase of 8 weeks with regular blood exchange transfusions, as recommended in the current preparation phase for CRISPR/Cas9 therapy will be able to effectively reduce HBS to <25%. The median HBS proportion after one course of erythrocyte exchange transfusion in our cohort was 27.5% (8.6-38.3%), which reduces the risk of sickle cell related complications comparable to HBS-trait levels. G-CSF use had been shown to be save for people with HBS trait [7], Early cessation of hydroxycarbamide will most likely improve cell numbers further. In our patient cohort we observed higher CD34+ cell yields in patients that did stop medication with hydroxyurea at least two weeks prior to mobilisation. The use of hydroxyurea is associated with lower CD34+ counts in peripheral blood as well as in the bone marrow [11,8]. A recent phase 1 study examined the safety and efficacy of plerixafor for stem cell mobilisation in patients with SCD [8]. Here, patients stopped HU at least two weeks prior to start of mobilisation and received exchange transfusion before the start of mobilisation. The study reported a positive correlation of the

interval between HU cessation and apheresis and CD34+ cell yields. The study observed no plateau of this correlation after 35 days [11].

Conclusion

In conclusion, the presented case series shows the feasibility and safety using G-CSF for mobilizing CD34+ cells in children with SCD. It needs to be adjusted as suggested in order to reach sufficient cell numbers for utilization as starting material for autologous gene therapy.

Declarations

Data availability: The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Ethics statement: The analyses involving humans were approved by The Ethics Committee of Charité - University Medicine Berlin. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation in this study was provided by the participants' legal guardians/next of kin.

Authorship contributions: TM: Writing - Review & Editing, Writing - Original Draft, LO: Writing - Review & Editing, Writing - Original Draft, Supervision, Project Administration, Methodology, Conceptualization. GH: Data Collection, Writing - Review & Editing, Investigation. KM: Data Collection, Methodology, Writing - Review & Editing. JG: Visualization, Investigation, Data Curation, Writing - Original Draft. LA: Writing - Review & Editing, Formal Analysis. AE: Supervision, Writing - Review & Editing, Investigation. JS: Writing - Review & Editing, Investigation. RM: Investigation, Writing - Review & Editing, Supervision. AS: Investigation, Writing - Review & Editing, Supervision.

Conflict of interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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