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RESEARCH ARTICLE

Hoping for a normal life: Decision-making on hematopoietic stem cell transplantation by patients with a hemoglobinopathy and their caregivers

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Abstract

Background: To provide insight into the perspectives of children and young adults with transfusion-dependent thalassemia and sickle cell disease and their caregivers regarding the decision for hematopoietic stem cell transplantation (HSCT).

Procedure: A qualitative longitudinal multicenter study. Data collection consisted of 40 audio-recorded conversations between physicians and families and 77 interviews with patients and/or caregivers related to 27 unique cases, collected at different time points throughout the decision-making process.

Results: Conversations and interviews revealed "hoping for a normal life" as an overarching theme, consisting of four main topics: (i) "Building a frame of reference" refers to a process where patients or families try to obtain comprehensive information on HSCT and translate this to their situation to decide. (ii) "Balancing between loss and benefit" reports the process of considering the advantages and disadvantages of continuing with supportive care to treat their disease versus choosing HSCT. (iii) "Experiencing the impact of HSCT" describes the impactfull experience of the HSCT period by those who chose HSCT. (iv) "Balancing again" refers to reflecting on the decision made.

Conclusions: The hope for a normal life guided the decision-making process, described as a constant balance between the impact of the disease and HSCT. A structured approach to explore patients' and caregivers' perspectives on HSCT decision-making is needed, where specifically discussing the impact of the disease and hope for a normal life need to be integrated in the process.

KEYWORDS
caregiver, decision-making, hematopoietic stem cell transplantation, hemoglobinopathy, pediatric, young adult

Abbreviations: HSCT, hematopoietic stem cell transplantation; SCD, sickle cell disease; TDT, transfusion-dependent β-thalassemia.

1 | INTRODUCTION

Hemoglobinopathies are inherited red blood cell disorders, including transfusion-dependent β-thalassemia (TDT) and sickle cell disease (SCD). Both diseases are progressive and invalidating, demand lifelong adherence to treatment, and severely affect quality of life and life expectancy.[1,2] Currently, hematopoietic stem cell transplantation (HSCT) is the only established curative therapy option for patients with TDT and SCD.[3] Lately, gene therapy has emerged as a promising alternative[1,4]; however, its accessibility still hampers its widespread clinical use.[5]

A recent study showed that the appraisal of HSCT decision-making for patients with a hemoglobinopathy significantly varied among professionals in a scenario-based survey.[6] The decision to continue supportive care or perform HSCT for patients with a hemoglobinopathy is evidently not clear-cut, and therefore can be seen as a preference-sensitive decision. Preference-sensitive decisions refer to decisions with scientific uncertainty with no clear-cut answers, where the offered treatment options' advantages and disadvantages depend on personal values.[7] In such situations, shared decision-making is an appropriate approach. This approach supports individuals in making decisions that are right for them, considering and incorporating their values and perspectives.[8] Decision-making between long-term supportive care or HSCT is complex due to the difficult risk–benefit balance. This decision becomes even more complicated when considering the future potential of gene therapy. Previous qualitative research has shown that the professionals' perspectives and frame of reference, based on expert knowledge and experiences, had an important influence on decision-making for HSCT.[9,10] Knowledge of this influence on the professional emphasizes the importance of being aware of the patients' and caregivers' perspectives. These perspectives were explored in several American qualitative studies for patients with SCD and their caregivers.[11–13] Although these studies provide valuable insights into the process of HSCT decision-making, more insight is needed into the perspectives of European pediatric and young adult patients with TDT and SCD and their caregivers. The current study aims to offer novel insights into the process of decision-making from patients' and caregivers' perspectives to support future decision-making on HSCT and upcoming innovative therapies.

2 | METHODS

2.1 | Design

A qualitative, longitudinal multicenter study was performed to provide an indepth insight into the HSCT decision-making process from patients' and caregivers' perspectives. This study was part of a larger longitudinal study that separately reported on the consultation techniques[14] and the professionals' perspectives.[10] The COREQ[15] checklist was used as a guidance tool for reporting (Supporting Information).

2.2 | Population and recruitment

The population of the larger study consisted of patients with TDT or SCD and caregivers who were considering HSCT. Patients between 10 and 35 years old and caregivers of patients between 0 and 18 years of age who consented to participate were eligible for inclusion. A language barrier was only an exclusion criterion in case participation with the assistance of an interpreter interfered with adequate study participation. Patients were recruited from eight Dutch medical centers specialized in hemoglobinopathies, including two HSCT centers (one transplanting children with TDT and SCD and one transplanting adults with SCD). Local staff identified eligible participants and obtained written informed consent.

Indications for HSCT included children with transfusion-dependent β-thalassemia, children with HbSS or HbSβ^0 SCD with either severe sickle cell complications or a strong wish of the family for transplant. Indications in adults with SCD comprised recurrent crisis and/or high degree of hemolysis and/or an organ complication in case of human leukocyte antigen (HLA)-identical donor. The HSCT preparative regimen for children consisted of a preconditioning with fludarabine and dexamethasone (SCD patients with a haplo-donor and all TDT patients), ATG, thiotepa, treosulfan, and fludarabine. For adults with an HLA-identical donor, the preconditioning consisted of hydroxyurea and azathioprine and the nonmyeloablative conditioning regimen of alemtuzumab and total body irradiation (3 Gy). Fertility preservation was offered to females from 10 years of age and post-pubertal males, with the possibility to discuss cryopreservation at an earlier age or testis biopsy in pre-pubertal boys. Adults were offered fertility preservation, but the low risk of infertility with the used condition also was explained.

2.3 | Data collection

Data collection consisted of (i) audio-recorded conversations between a patient or family and a physician as part of regular care; and (ii) research-focused interviews at different time points throughout the decision-making process between June 2017 and October 2020. Data collection started when a conversation between a patient or family and a physician about HSCT as a treatment option was initiated. Conversations were held at the hospitals by the referring or referred-to physician. Semi-structured interviews were planned at a location of the participant's preference. The first interview was planned after the first conversation. In-person interviews were preferred to know about the personal perspectives, but the choice was left to participants. Repeated interviews were planned during the trajectory until 1 year after the decision to opt in or out of HSCT. A topic list, based on the existing literature[16–18] and experiences of the research team, guided the interviews. Topics included insight into the disease, health status, treatment (options), considerations, influencing factors, guidance, and information. The topic list was adjusted during the research process based on the first analysis steps. For example, the need for peer support was initially not a topic, but we added questions about

peer support because it appeared an important topic. Observational memos were written shortly after the conversations and interviews, reflecting on the setting, atmosphere, circumstances, and themes. An experienced interviewer and specialized pediatric HSCT nurse (Hilda Mekelenkamp) performed all interviews and was introduced to the families by the physicians. In case pediatric patients underwent an HSCT, the interviewer took care of the patients in her role as a nurse. Including 27 cases consisting of multiple participants and data sources, we evaluated our information power as adequate in relation to the study aim and gained knowledge.[19]

2.4 | Data analysis

Data were analyzed thematically. Patterns were developed inductively on the meaning of HSCT decision-making from the perspectives of patients with a hemoglobinopathy and/or their caregivers. All recorded conversations and interviews were transcribed verbatim. The scripts were read and re-read to become familiar with its content. Next, all scripts were open-coded, referring to labeling text fragments with a short description of its meaning while staying close to the data. Four team members were involved in the coding process, and 20 transcripts were coded by two researchers (Martine de Vries, Frans Smiers, Ineke Saalmink, Hilda Mekelenkamp), and the others by one (Hilda Mekelenkamp). Subsequently, codes were compared and categorized, defining and refining themes. Lastly, the data were interpreted and described by its meaning.[20] The program Atlas.ti22 supported the coding process. During all steps of the analysis, the themes were discussed with the research team consisting of HSCT experts (Frans Smiers, Arjan Lankester, Hilda Mekelenkamp), a hemoglobinopathy expert (Frans Smiers), an ethicist (Martine de Vries), and qualitative researchers (Martine de Vries, Hilda Mekelenkamp) until consensus was reached.

2.5 | Ethical considerations

This study was performed according to the Declaration of Helsinki. All participants consented to participation. The study was approved by the Medical Ethics Committee of the Leiden University Medical Center (P17.084).

3 | RESULTS

In total, 54 individuals were included in the study: 16 patients (age range: 9–31 years at inclusion), 17 fathers, and 21 mothers (Table 1). Eleven patients did not participate because of their young age; the median age of the total group of patients was 11 years at inclusion (age range: 1–31 years). Of the 30 invited families, 26 participated. The option of HSCT was discussed in 27 patients, including two children in one family. HSCT was eventually performed in 16 pediatric and five adult patients, whereas in six cases the families decided to continue with supportive care. Forty consultations and 77 interviews were analyzed. Six consultations took place with the referring physician and 34 with the HSCT physician, who also acted as referring hematologist in five cases. Individual and mixed interviews were held, following the patient's or family's preference. Of the 27 cases, most were interviewed throughout the decision-making process twice (n = 12) or thrice (n = 11). Two families were interviewed once, and one family four times. The mean time between the first and last interview was 19 months, and between the eventual HSCT and last interview 12 months. Of the patients, nine had β-thalassemia and were transfusion dependent. Eighteen patients had SCD with at least recurrent crisis or central nervous system involvement, and only one patient had not used hydroxyurea. Most patients with SCD face other complications like acute chest, nephropathy, osteonecrosis, or joint problems.

An overarching theme and four main themes with subthemes, mapped in Figure 1, were abstracted from the interviews and consultations. The subthemes are illustrated with quotes in Table 2. In case of differences between perspectives of patients with TDT or SCD, or other subgroups, this will be addressed.

3.1 | Hoping for a normal life

Patients or caregivers explained that *hoping for a normal life* was an important value in considering HSCT. A normal life points to a good quality of life and a favorable future perspective, being able to do what you want without limitations like peers and siblings. The possibility of a cure was important for patients and caregivers and provided hope of leading a normal life and having a positive future perspective.

3.2 | Theme 1: Building a frame of reference

3.2.1 | Getting informed about treatment options

Patients and families were informed stepwise by their referring physician, and subsequently by the HSCT specialist. Continuous supportive treatments, such as red cell (exchange) transfusions, were previously discussed with patients as a non-curative possibility. Gene therapy was often discussed as a possible future option that is however not yet available as regular treatment. To get a good understanding of the HSCT procedure, patients and families needed more information. Most families had an active information-searching strategy, initiating their searches on the internet. Patients and caregivers tried to get more insight by asking specific questions. Personal, stepwise, and objective information from a professional led to trust, because it provided answers to personal questions and more insight.

TABLE 1 Characteristics of included families, consultations, and interviews.

Participating families ($n = 26$); patients ($n = 27$)	
Involved family members	
Actively participating patients	16
<12 years	*4*
12–15 years	*6*
>16 years	*6*
Caregivers	38
Fathers	*17*
Mothers	*21*
Sex of the patients	
Female	17
Male	10
Patient's age category (at inclusion)	
<12 years	16
12–15 years	5
>16 years	6
Patient disease (HSCT performed)	
Transfusion-dependent β-thalassemia	9 (8)
Sickle cell disease	18 (13)
Consultations (40) and interviews (77)	
Number of consultations with a physician per case	
1 Recorded consultation	12
2 Recorded consultations	14
Location of consultation	
At the referring hospitals	6
At the HSCT hospitals	34
Language of consultations	
Dutch	29
English	1
Translation by an interpreter (in-person or by phone)	10
Duration of consultations and interviews	
Duration consultations	Median 54 minutes [range: 16–105]
Duration of interviews	Median 40 minutes [range: 5–106]
Number of interview (moments) per case	
1 Interview moment	3
2 Interviews moments	12
3 Interviews moments	11
4 Interviews moments	1
Location of interview	
At respondent's home	40
At the HSCT hospital	32
External place	3
By phone	2

(Continues)

TABLE 1 (Continued)

Language of interviews	
Dutch	67
English	4
Translation by interpreter (in-person or by phone)	6

Abbreviation: HSCT, hematopoietic stem cell transplantation.

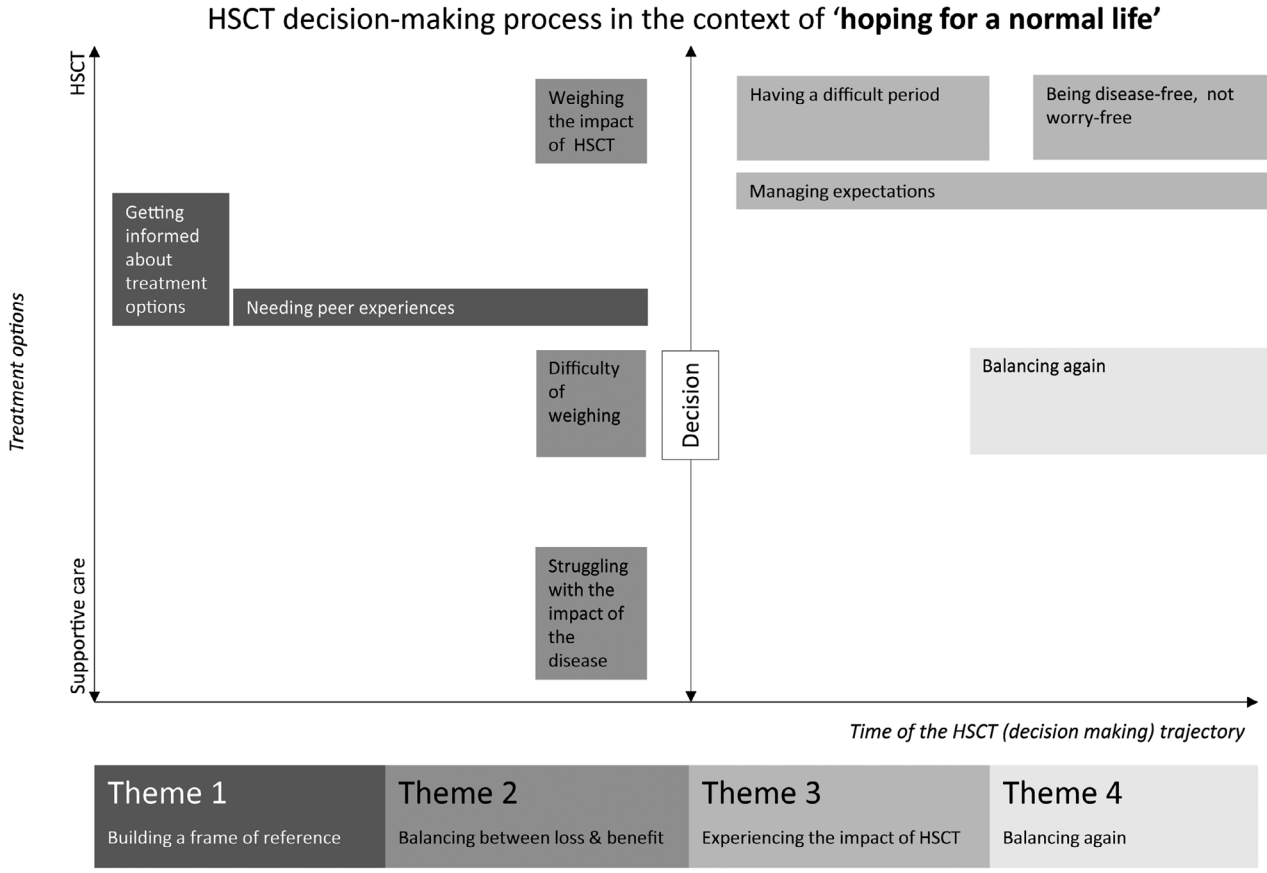

FIGURE 1 Themes described by patients and caregivers throughout the decision-making process on supportive care or HSCT, with overarching theme: hoping for a normal life. *HSCT=hematopoietic stem cell transplantation.*

3.2.2 | Needing peer experiences

During the consultations or interviews, almost all patients or parents mentioned their wish for peer contact with patients who had already undergone an HSCT, including all ins and outs. Patients and caregivers who experienced peer contact explained that this contact served to enrich their knowledge and to prepare for the HSCT process. Peer contact provided trust, hope, and worked as an incentive for HSCT. Peer contact embodied the positive and negative experiences. The possibility of being confronted with negative experiences may lead to avoiding peer contact, although this was only true for a few patients or caregivers.

3.3 | Theme 2: Balancing between loss and benefit

3.3.1 | Struggling with the impact of the disease

The experienced impact of the disease was an important consideration in decision-making. Almost all patients and caregivers understood very well the severity of the disease, because they all had experienced its impact directly as patient or as witness in their family. Sometimes, patients or caregivers needed more insight into the individual disease complications to realize its impact. A complicated course of the disease or fear of deteriorating was in most patients and caregivers the motivation to consider HSCT as option, hoping for a better life

TABLE 2 Illustrative quotes.

Overarching theme: Hoping for a normal life
A normal life points to a good quality of life and a future perspective, being able to do what you want without limitations
"I think an HSCT will be very tough for us. But even harder for her. She must go through it all. I think she is far too young to have to experience this. And yes, going bald, becoming infertile, no, I won't do that to her. I just want her to just have normal life. Just to go to school, and to do her own things." C2M-SCD
"My son loves football, he wants to play football so badly and you know, it's just not possible. He's too tired to do it and he's 10 years old, but he weighs less than 23 kg, and you know, you just want your child to be able to do everything normal kids do. And ….. when this is over, I think he will be able to do more normal things as well." C5F-SCD
Theme 1: Building a frame of reference
Refers to a process where patients or families hear about the possibility of a cure and try to get informed about the new treatment option and translate this to their situation to make a decision
1a. Getting informed about treatment options
"*So, it's very different for everyone, so the information I had read at the time was just really limited and focused more on children with leukemia. That's something very different from thalassemia*." C13M-TDT
"Well, we knew about HSCT as an option, but we did not know about the details. [….] But we did read about it, and we searched for additional information on the internet. But yes, when we had the conversation and got more details about the disease and treatment, yes then things changed a bit, it scared us." C3M-TDT
1b. Needing peer experiences
"*I had already decided beforehand, before I contacted her* [a patient who underwent HSCT previously], *that I was going to do it. But the conversation did help me to prepare for what was going to happen."* C16P-SCD
My son knew someone, and he was in the same situation [having the same disease], *and he also had a transplantation. But the transplantation led to many complications. My son had contact with this boy and when he spoke to him, he said I am never going to do that. But for the last 4–5 months, we have had no contact with this family. Therefore, it was easier to accept the transplantation."* C20F-TDT
Theme 2: Balancing between loss and benefit
At a certain point during the disease course, patients and caregivers need to weigh the advantages and disadvantages of continuation of supportive care or choosing HSCT. This process of consideration can be described as balancing between loss and benefit
2a. Struggling with the impact of the disease
"I don't think I will do the HSCT, because things are much better now than they were before, because if I was severely affected [experiencing more disease burden], *I would have immediately said, just do it. But now that I see myself like this, I think I'm fine with it."* C1P-SCD
"I think if she hadn't experienced that organ damage [renal failure], *I would not have opted for an HSCT. Then I would have thought, she has occasional pains and things, but her organs are still basically fine. And that's my biggest fear because I think she's quite young for such a complication."* C8M-SCD
"Yes, looking at the consequences for later life, I think that's important. If she doesn't do the transplant, that will have consequences for her later. Because of the accumulation of iron in her organs, damage. Yes, I feel I can prevent her from these complications." C17F-TDT
2b. Weighing the impact of HSCT
"Yes, I want my child to get better, but if my child gets better and then something else [an HSCT complication] *takes its place. That is life from frying pan to fire."* C18M-SCD
"I just find that whole infertility thing the worst. Look, that chemotherapy, the hair falls off, but that grows back again. So that's not really a disaster, but what I really care about is the infertility. So, I just don't want to be the one that takes that away from her." C2M-SCD
2c. Difficulty of decision-making
"But also, my feelings as a father, feelings as a parent, remain important to decide this. It's hard when I must decide for someone else. The HSCT is big and life-threatening. Maybe if it was for me, it would have been easier and I therefore wish I had the illness and that my children would have been healthy, but it's my son." C20F-TDT
"*On the one hand, I want you to get better, and on the other hand as a mother you know: if something happens* [an HSCT complication], *I will blame myself. It is difficult to decide. But on the other hand, I think yes, she has quite a few problems already, that others don't have at such a young age. Then I think, how old will she become, I really think like that. How old will she become if I do not choose HSCT? Then again, I will regret not trying all options."* C8M-SCD
"It's my doctor's explanation that matters most. What he explains to me, yes it helps me to worry less about the risks. But ultimately, I am the one who says, yes, we will do it." C27P-SCD

(Continues)

TABLE 2 (Continued)

Theme 3: Experiencing the impact of HSCT
Patients and families who decided on HSCT experienced its impact as a difficult period. The previously formed frame of reference required adjustment during this phase
3a. Having a difficult period
"It was tough to see how my son looked [while undergoing HSCT], *with hair loss. Thin, sickly, pain, a lot of pain, just pain, vomiting, not being able to walk properly."* C5M-SCD
"*Well, the period right after the transplant, the first 3 months after HSCT, was the worst period of my life. (…..) and I had little support at home as well."* C15P-SCD
3b. Being disease-free, not worry-free
I have to get used to a new feeling [after being transplanted], *because I feel very energetic. Which I'm not used to, I also have quite a lot of sleepless nights and after 5 hours of sleep I am already recharged for the whole day. Those are things I have to get used to, because I was always tired, I was always cold. And I was always very tired and now I don't have that at all."* C25P-SCD
"*The situation is not yet stable. For instance, when he has a cold, he is anxious, and he has to come to the hospital monthly for blood tests. We understand that he may not be able to have children in the future. We fret over these points, we worry about him." C20F*
"*Especially, new and increased loss was difficult to experience. I used to have pain attacks, like once in every 3–4 months, I was in pain and had to go to the hospital. And now it's basically pain almost every day as well as kidney disease. And no job and no social contacts and having trouble eating and things like that."* C15P-SCD
3c. Managing expectations
"It really is tougher than we think. At least for me. I thought way too easily about it." C11P-SCD
"What they had told me was okay, but there were things, which nobody had told me about. For example, yes, they had already told me that, that I might experience inflammation, but I didn't know that this might be so, so bad. But yes, it still differs with everybody, how bad you are affected by inflammation." C12P-SCD
"I guess I should have thought better about it [the HSCT and possible complications]. *And really kept asking about the disadvantages."* C15P-SCD
Theme 4: Balancing again
Following the choice for supportive care or HSCT, participants reflected on their decision, which could be referred to as balancing again
"It's going well, and we are quite happy that she hasn't had a crisis for a very long time. She just takes her medication [supportive care] *and just does everything that all children do, so in my opinion we see no difference, it's actually going just fine."* C2M-SCD
"I would choose it again. Better one period of pain than pain your whole life." C4P-TDT
"*Our life after the transplant is not like it was before. We have now been given life, and I see that my son can live like a normal person."* C12M-SCD

Note: Quotes were translated and somewhat adjusted for readability.
Abbreviations: C, case; F, father; M, mother; P, patient; SCD, sickle cell disease; TDT, transfusions dependent thalassemia; #, case number.

expectancy. A relatively stable course of the disease fed the hope of a continuous favorable course and made these patients not consider HSCT as an option. Patients with TDT and their parents explained that they knew that continuing with chronic blood transfusions would further deteriorate their health status and consequently limit life expectancy.

3.3.2 | Weighing the impact of HSCT

In their decision-making process, patients and caregivers not only weighed the impact of the disease but also the impact of HSCT. Realizing the possible HSCT risks, scared many patients and caregivers. Fear focused on the possible complications of the chemotherapy and on HSCT complications, particularly the mortality risk. Despite realizing the severity of the disease, the fear of losing their child during HSCT led a few families to the decision to stay provisionally on supportive care. The risk of long-term HSCT complications replacing the original chronic disease was an important consideration. Besides fear, some patients and caregivers explained that the possibility of HSCT brought hope and expectations of a cure for a chronic and deteriorating disease. Hearing the success rates supported trust in the decision for HSCT. In considering HSCT, caregivers explained they wanted to choose the option with the best possible outcome. For some parents, this included waiting for a fitting HLA-identical or matched unrelated donor (MUD). Infertility as a possible HSCT late effect was an important consideration. For caregivers, it was hard to decide on a treatment that could lead to infertility, and for some of them, this led to refraining from HSCT. Patients and parents who decided on HSCT did so because the chance of being cured was considered more important than the risk of infertility, even more with the current cryopreservation options.

3.3.3 | Difficulty of decision-making

Almost all patients and caregivers experienced the decision-making process as difficult. Deciding for supportive care or HSCT, both with

their unpredictable risks, led to doubts and fear. As the decision to go for HSCT or stick to supportive care never had to be taken acutely, it left participants with abundant time for questions and delay. Proxy decision-making seemed even more complicated, because parents felt responsible toward their child to consider all possibilities and make the right decision for their child. In deciding for their child, parents wanted to prevent anticipated decisional regret. Some parents explained that they wanted to prevent the regret of not taking the chance for an HSCT and being confronted with disease complications. Other parents explained that they did not want to regret choosing HSCT and finding out that this was unsuccessful. These two sides of possible regret were sometimes felt simultaneously. All parents decided with the best interest of their child in mind. Regardless of their decision and as a critical consideration, parents felt they needed to protect their child from more disease- or HSCT-related complications.

Most patients who were legally allowed to make their own decisions explained that they made the decision themselves, and it was felt important to have that control. Most of the parents stated that they made the decision together, and depending on the child's age, they involved the child to a greater or lesser extent. Most patients and caregivers discussed the options with close relatives or family members. Besides this support, patients and caregivers felt guided by information given by physician(s), which provided trust in the final decision-making. Furthermore, for a group of participants, religious beliefs provided strength in decision-making.

Most parents who decided for HSCT felt the importance of a timely start to prevent further disease complications. Reasons to perform HSCT at a young age were the relatively lower disease burden and concomitant favorable HSCT outcome, and the caregivers' perception that it was emotionally and physically easier for a younger child to undergo HSCT. In these cases, parents explained that they felt it was their responsibility to decide for their children and that they could not wait until their children will be able to decide for themselves. In contrast, parents who decided to the continuation of supportive care explained they wanted to give their children the possibility to decide for themselves.

3.4 | Theme 3: Experiencing the impact of HSCT

3.4.1 | Having a difficult period

Patients and caregivers perceived the HSCT as an impactful period associated with unknown and unexpected complications. Especially patients with SCD struggled with the experienced transient pain in the initial weeks post HSCT, as it was so different from SCD pain, harder to control, and thus tough to cope with. Furthermore, participants perceived the psycho-social impact of HSCT, including isolation, missing family and friends, feelings of powerlessness and hopelessness, fear of loss, the effect on school or work, and the difficulty to keep going. The HSCT care pathway was different for pediatric or adult patients, and so was its impact, which was also determined by the severity of complications.

3.4.2 | Being disease-free, not worry-free

From the narratives of patients and caregivers, the HSCT recovery period was characterized by mixed feelings. On one hand, the knowledge of a successful transplantation, being disease-free, having a new future perspective, a new identity without the disease, being able to do activities that were never possible, and dealing with a new energy balance after a lifetime having TDT or SCD. On the other hand, patients and caregivers need to cope with recovering from a difficult and impactful period, which did not only include HSCT but also all the fears from the initial disease trajectory, the uncertainty regarding remaining complications, the still necessary care, fears for a new loss like late HSCT effects or rejection of the graft, dealing with chronic pain, iron overload and chelation, or other chronic conditions. Especially, new and increased loss was difficult to experience.

3.4.3 | Managing expectations

In the pre-HSCT phase, participants built a frame of reference for HSCT. Most patients and caregivers explained that undergoing the HSCT was more complicated than expected. Participants remembered that they had been informed about possible complications and side effects. However, it was difficult to imagine what these complications would mean in practice, and running into complications was anticipated to be a limited risk. However, when facing complications, patients felt unprepared. At the same time, patients and caregivers understood that specific complications were hard to predict, specifically the impact in individual cases. Some patients expressed that they still struggled with the unexpected continuing or induced health issues caused by either the disease or the HSCT. Especially, young adults realized they were cured of SCD, but they had to cope with pre-existing damage for the rest of their lives. While most participants felt they had asked enough in the pre-HSCT phase, some patients explained that they should have asked more about specific side effects.

3.5 | Theme 4: Balancing again

Most patients and caregivers who chose supportive care, based their decision on the experienced impact of the disease and how they and their child could live a relatively normal life. They considered the HSCT impact too burdensome for the time being, but kept the option in mind as a future possibility, with a role for the child in the decision-making process. For some participants, the threat of loss due to HSCT was the primary consideration to stay on supportive care, and they hoped for less burdensome curative treatment options in the future. Patients and caregivers who decided for HSCT, balanced the HSCT's losses and benefits. For almost all transplanted patients, the HSCT and the recovery phase were tough, but respondents explained that it was worth it, and they did not regret their decision. The knowledge and experience that they no longer had TDT or SCD, and could think about a

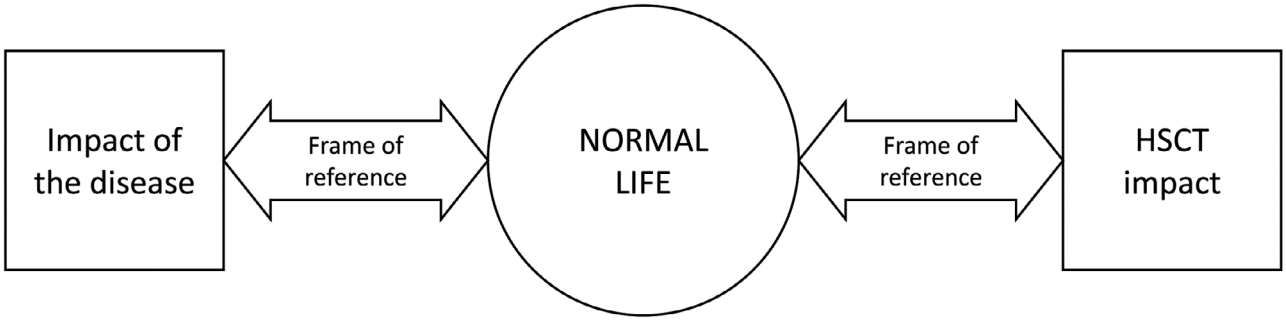

FIGURE 2 The four main decision-making concepts in the process of continuous balancing. "A normal life" was indicated as the central outcome or indicator of this balancing process. Considering the harms and benefits of the disease and HSCT were based on a built frame of reference. *HSCT = hematopoietic stem cell transplantation.*

positive future perspective outweighed the HSCT burden. In case substantial physical loss was experienced, patients could value the benefits the HSCT had brought them. This benefit protected them from feelings of disappointment regarding the HSCT process. Many patients and caregivers looked forward to a future cure for a longer period, and most believed that the impact of HSCT could also be overcome. Some patients still struggled with their decision due to the HSCT impact on physical and/or psycho-social levels, realizing this could fluctuate over time.

4 | DISCUSSION

This study identified "hoping for a normal life" as an overarching theme in the HSCT decision-making process. Four main themes with subthemes describe the decision-making process and reflect a continuous balancing between the expected impact of the disease and HSCT. Participants indicated "a normal life" as the central outcome of this balancing process. Hope for a normal life points to a good quality of life and a future perspective. To weigh the risks and benefits of the treatment options carefully, patients and caregivers needed to build a frame of reference. These four concepts can be identified as the main decision-making concepts in continuous balancing (Figure 2). In forming their frame of reference, participants expressed their need for peer experiences. In hindsight, patients and caregivers needed to adjust expectations regarding the HSCT process and its impact. For most participants, the HSCT impact was more complex than expected, still most participants did not regret their decision post HSCT, although some still struggled with the HSCT harms, as was recently also shown.[21] Earlier studies have described the concept of living a normal life as an important HSCT outcome, the burden of SCD as an influencing factor in deciding on HSCT, and the need for information as a relevant decision-making aspect.[11–13] We described the influence of these concepts in a broader multicenter sample, also including patients with TDT and young adults.

In this study, we described the difficulty of decision-making from the perspectives of patients and caregivers. The latter, proxy decision-makers, made decisions for their children, and they felt responsible for the decision, its risks, and outcomes. We observed underlying values in considering an HSCT or supportive care. Caregivers felt responsible for doing everything for a favorable future perspective for their child and preventing more harm. These parental values align with the concept "good-parent beliefs" in decision-making, as previously described.[22] The current study adds to this concept from a sample of caregivers of patients with a hemoglobinopathy, highlighting the hope for a future perspective.

From a medical ethics perspective, respect for autonomy is a core principle. Shared decision-making is a suitable model to engage patients' perspectives when preference-sensitive decisions need to be made. Four steps can be distinguished in shared decision-making as described by Stiggelbout et al.: (i) explaining the choice; (ii) informing about the options; (iii) exploring patients' preferences; and (iv) making the decision.[8] Based on the results of the current study, this shared decision-making model can be specified to optimize the HSCT shared decision-making process for patients with a hemoglobinopathy (see Table 3). The results showed the importance of personalizing point two with the frame of reference of patients and caregivers. We recommend exploring the impact of the disease from the experienced burden of the disease, supplemented with objective medical facts by the physician. Additionally, the provided information before HSCT could be enriched with patient-reported outcomes to support the decision-making process.[23] Furthermore, peer experience from those who already underwent HSCT is an important additional information source facilitating treatment and outcome expectation management. It is important to ensure a well-balanced and as unbiased as possible peer support by patients with different processes and outcomes. When exploring patient preferences, the hope for a normal life should be a specific topic. Professionals could elaborate to patients and/or caregivers what a normal life entails for them, their values, where their hopes are focused on, and whether they are realistic.

A strength of the current study is its longitudinal design, making it possible to eliminate the risk of recall bias and to follow the decision-making process over time. Another strength is the ability to include participants regardless of their language, as the population of patients with hemoglobinopathies is of multicultural and multilingual origin. Our study also has limitations: one is the possible selection bias because we included more patients who decided on an HSCT than patients who decided to continue with supportive care. We likely

TABLE 3 Suggestions to optimize the shared decision-making process in patients with a hemoglobinopathy considering HSCT.

Four-step model of shared decision-making described by Stiggelbout et al.[8]	Findings of the current study to specify and optimize the shared decision-making process in patients with a hemoglobinopathy considering HSCT
1. The professional informs the patient that a decision is to be made and that the patient's opinion is important	• A collaborative process between the referring and referred-to physicians
2. The professional explains the options and the pros and cons of each relevant option	• Providing objective medical facts about the disease severity • Supporting information with peer experiences from those who underwent an HSCT
3. The professional and patient discuss the patient's preferences; the professional supports the patient in deliberation	• Exploring the patients' and caregivers' frame of reference. What do they know about both options, what information is gained and where, what are previous experiences with the disease and/or HSCT • Exploring the impact and burden of the disease • Exploring the "hope for a normal life" for the individual patient and/or family. What does a normal life mean, what are important values, and where are hopes focused on. Discussing whether hopes are realistic • Exploring "good parent" values regarding the decision to stay on supportive care or to choose HSCT
4. The professional and patient discuss patient's decisional role preference, make or defer the decision, and discuss possible follow-up	• Considering the child's competence and participating role in decision-making

Abbreviation: HSCT, hematopoietic stem cell transplantation.

missed families who waived off the option HSCT from the first information they read or heard. Another limitation could be the interviewers' double role, which may have caused observer bias or role confusion. We paid attention to this double role by specifying it when the situation required, written reflections, and using investigators triangulation during analysis. An important limitation of qualitative research is its generalizability, partly by a small sample.[24] The current study was performed in a particular population with disease- and cultural-specific characteristics in a country with access to supportive care and curative therapy. That makes it difficult to generalize the results to other groups of patients or countries with different available healthcare.

With the current study, we described the experiences, hopes, and needs of patients with a hemoglobinopathy and caregivers regarding decision-making on HSCT. Within the decision-making process, which reflects continuous balancing between the impact of the disease and the HSCT impact, the hope for a normal life was guiding.

AUTHOR CONTRIBUTIONS

Conceptualization and design: Hilda Mekelenkamp, Martine de Vries, Arjan Lankester, and Frans Smiers. Data collection conversations: Marjon Cnossen, Harriët Heijboer, Jean-Louis Kerkhoffs, Erfan Nur, Frans Smiers, and Hilda Mekelenkamp. Data collection interviews: Hilda Mekelenkamp. Analysis and interpretation: Hilda Mekelenkamp, Martine de Vries, Frans Smiers, Arjan Lankester, and Ineke Saalmink. Supervision: Frans Smiers, Martine de Vries, and Arjan Lankester. Writing original draft: Hilda Mekelenkamp. Writing, review, and editing: Martine de Vries, Frans Smiers, and Arjan Lankester. All authors revised the manuscript and approved the final version for publication.

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CONFLICT OF INTEREST STATEMENT

The authors declare they have no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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