thalassemia reports

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Review

Bone Marrow Transplantation in Nonmalignant Haematological Diseases: What Have We Learned about Thalassemia?

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Abstract: Allogeneic stem cell transplantation remains the only therapy for congenital, severe haemoglobinopathies that is able to reverse the pathological phenotype. In the severe form of thalassemia, regular transfusions are needed early in life. This population of patients could benefit from allo-SCT. However, the great efficacy of transplantation must be counterbalanced by the mortality and morbidity related to the procedure. In this short review, we reviewed the most recent data in the field of transplantation in transfusion-dependent thalassemia (TDT), highlighting the factors that have a major impact on outcomes.

Keywords: Thalassemia; allogegeic stem cell transplantation; conditioning regimens

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1. Introduction

Allogeneic stem cell transplantation (allo-SCT) remains the only curative therapy for congenital, severe haemoglobinopathies. Nevertheless, post-transplant morbidity and mortality are of concern. Toxic mortality is more evident with increasing patient age, with the use of peripheral stem cells, with non-HLA-identical donors, and above all with iron overload, which in turn depends on adequate iron chelation. The subdivision of patients according to Pesaro risk classes (Table 1) remains significant in identifying patients with an increased risk of transplant mortality [1,2].

Table 1. Pesaro class risk factors and risk classes.

Cases	Hepatomegaly > 2 cm	Liver Fibrosis	Chelation History
Class 1	No	No	Regular
Class 2	No/Yes	No/Yes	Regular/irregular
Class 3	Yes	Yes	Irregular

In this paper, we will briefly review the results expected in 2022 after allo-SCT and the major achievements obtained in the last 10 years.

2. General Results

The clinical results from several experiences of allo-SCT in TDT are reported in Table 2. An extensive analysis of TDT patients receiving allo-SCT in Europe between 2000 and 2010 was reported by the EBMT. In this retrospective study, including 1493 patients, most were paediatric (91%, median age 6.6 years), and only 8% were aged more than 18 years (median age 22.9 years). Donors were HLA identical siblings (HLAid sib) in 71%, while only 14.1% were matched unrelated (MUD). The stem cell source was bone marrow in most cases (BM) (67%), peripheral blood stem cells (PBSCs) in 20%, and cord blood (CB) in 3.9%. The type of conditioning regimens was not reported. Overall, the 3-year OS and EFS were 88% and 81%, respectively. However, survival was improved in patients

with defined characteristics such as age less than 14 years, donor HLAid sib, and BM. The incidence of severe (grade 3–4) acute graft vs. host disease (aGVHD) was 9%, and the incidence of extensive chronic GVHD (cGVHD) was 6%. As expected, the incidences of aGVHD and cGVHD were lower when BM was used as the stem cell source and HLAid sib was used as the donor [3]. As reported in the recent Cochrane Review [4], randomized or near-randomized studies are lacking, and thus far, most clinical data and suggestions come from retrospective, frequently registry-based studies. Thus, selection bias should be considered when we are discussing allo-SCT in TDT.

Table 2. Clinical results from studies in patients receiving allo-SCT published after 2010. § This trial included 100 patients, and the analysis was limited to 82 patients classified as the intermediate-risk group based on the NF index.

Author	N	Median Age (y)	Pesaro Class III	Donor	CTX	T-Cell Depletion	BM	PBSCs	CB	OS	EFS	aGVHD II-IV	cGVHD	GF	TRM
7 Sabloff 2010	179	7 (<5–20)	36%	MRD 100%	BUCY	ATG 43%	100%	/	/	91%	88%	38%	13%	10%	19%
17 Bernardo 2012	60	7 (1–37)	7%	MRD 33% MUD 67%	TreoTTFLU	ATG MUD	79%	3%	18%	93%	84% TFS	21%	2%	9%	7%
24 Li 2012	82	6 (0.6–15)	§	MRD 36% MUD 64%	BUCYFLUTT 100%	ATG MUD	87% /	13% 100%	40% /	90% 92%	83% TFS 90%	3.6% 9.6%	/ /	3.5%	8.5%
18 Mathews 2013	50	11 (2–21)	100%	MRD 97%	TreoTTFLU	/	26%	74%	/	87%	78%	35%	11%	8%	12%
18 Mathews 2013	24	12 (3–21)	100% IIIHR	MRD 97%	TreoTTFLU	/	29%	71%		86%	77%	35%	11%	8%	13%
8 Galambrun 2013	108	6.2 (0.7–32)	45%	MRD 89% UD 6%	BUCY 88% BUTTFLU 7%	ATG 53%	89%	3%	9%	86%	69% TFS	22%	6%	23%	/
30 Anurathapan 2014	98	10–20	22%	MRD 65% MUD 33%	BUCY MRD BUCY MUD BUFLU *	/ ATG MUD ATG all pts	65%	33%	/	94%	MUD 82% MRD 88%	23%	9%	8% 0% *	7%
24 Shenoy 2018	33	1–17	/	MUD 51% CB 49%	TTFLUMel	CAMPATH	51%	/	49%	BM 82% CB 75%	BM 82% CB 81%	BM 24% CB 44%	BM 29% CB 21%	3%	18%
5 Li 2019	1110	6 (<1–25)	54%	MRD 61% MUD 23%	BUCY 22% BUCYFLU 23% BUCYFLUTT 34% TreoTTFLU 15% Others 5%	ATG 75%	29%	61%	10%	90% <6y 84% 7–15y 63% 16–25y	86% <6y 80% 7–15y 63% 16–25y	/	/	9%	/
22 Chiesa 2019	87	1.7	/	MRD 14% MUD 61% mMUD18% Other family D 7%	TreoTTFLU	CAMPATH 87% ATG 1%	26%	62%	12%	* 97% vs. 65%	/	31%	2%	1%	99% vs. 3%
20 Luftinger 2022	772	7 (0.5–17.9)	/	MRD 50% MUD 18% mMUD 8% Other family D 22%	BUFLU-based 410 TREOFLU-based 362	77%	80%	19%	/	BU-based 92% TREO-based 94%	/	15%	13%	4% vs. 9%	/

* The OS was extrapolated from the survival curve, based on an AUC of more or less than 6000 mg hour/L. The TRM in this study was different based on the PK values of Treo, which were higher when the AUC was >6000 mg hour/L.

Factors such as HLA-identical family donors, myeloablative conditioning regimens, bone marrow as a stem cell source, and early recipient age (see below) are considered of the utmost importance because of their impact on clinical outcomes.

The first point to address must be *recipient age*. Indeed, it is clear that the main outcome endpoints are jeopardized when the age of the recipient is increased. However, it is less clear what the age cut-off is that can help to separate patients with high vs. low risk. In the Cochrane Review [4], the cut-off age retrieved by the studies analysed was 14 years. The EBMT registry reported on TDT patients allografted between 2000 and 2010 (n = 1493) (3). Most patients were aged less than 18 years with a median age of 6.6 years, while only 9% were adults with a median age of 22.9 years. Clearly, overall survival (OS) and event-free survival (EFS) were better in patients aged less than 14 years. Indeed, in the group that was greater than 14-years-old, the OS was 82%, and the EFS was 74% (compared to more than 90% and 83%, respectively, in the younger groups). In another registry-based study from the CIBMTR, including 1110 patients, the impact of age on the clinical outcome was analysed. The median age of the whole population was 6 years (<1–25), but only 3% of them were aged between 16 and 25 years. EFS and OS were higher in the cohort aged less than 6 years, the intermediate group between 7–15 years, and the lower aged cohort aged 16–25 years (EFS 86% vs. 80% vs. 63%, and OS 90% vs. 84% vs. 63%, respectively) [5]. However, it should be noted that most patients were inadequately chelated (88%) with hepatomegaly, which could have an important bearing on the results observed. In both of these registry studies, the donors were matched related or unrelated. A similar impact of age was also reported in a cohort of patients transplanted with HLAid cord blood [6].

Sabloff et al. analysed patients from countries outside Italy, where clinical results were clearly improved over time. The authors included only patients receiving allo-SCT from HLAid siblings, aged less than 20 years, and MAC regimen (BuCy). The median age was 6 years, but again, age $\leq$7 years had an impact on survival (5-year OS 98% vs. 86%, respectively) [7]. In a French experience, even if only 11 adult patients received transplantation, the survival was lower than that of the young patients [8].

Many hypotheses can be proposed to explain the strong impact of age on outcomes. The most immediate could be that younger patients have a shorter duration of disease, with a lower exposure to transfusions and iron overload. This means that organ integrity can be preserved or is less affected, leading to better tolerance of intensive conditioning regimens. A second point related to fewer transfusions could be the low risk of allogeneic immunization. However, other factors, such as conditioning regimens, GVHD prophylaxis, ethnicity, and donor age, can contribute to or interact with recipient age.

The second point to discuss is the *stem cell source*. Bone marrow is considered the ideal stem cell source in non-malignant disease due to the reduced risk of both acute and chronic graft versus host disease, which are considered "not suitable" because of the nonneoplastic nature of the disease. In the EBMT study [3], BM was the most frequently used stem cell source (67.8%) compared to peripheral blood (20.3%) and cord blood (3.9%). The authors observed a significant negative impact of PBSCs and CB on EFS and OS compared to BM (76% vs. 85% vs. 82% and 81% vs. 93% vs. 90%, respectively). The lower survival with PBSCs was attributed to a higher incidence of severe aGVHD (8% vs. 3%). On the other hand, in the CIBMTR study [4], 61% of patients received PBSCs and 29% received BM. In their multivariate analysis on factors influencing survival, aGVHD and cGVHD, PBSCs did not enhance the risk of developing GVHD or reduce survival. When BM cannot be collected, regardless of the reason, and PBSCs are the stem cell source available for a definite patient, some parameters of transplantation should probably be modified. For example, GVHD prophylaxis should be reinforced with in vivo T-cell depletion or with ex vivo selective T-cell depletion, such as an $\alpha\beta$-depletion platform. This could reduce the risk of severe GVHD. On the other hand, the use of PBSCs could lower the risk of graft failure because of higher CD34+ cell count.

Another relevant variable on the outcome of TDT is the *conditioning regimen*. The condition regimen plays a different role in the outcome: it is useful because TDT patients

have hyperexpanded bone marrow, often with islets of extramedullary haematopoiesis, and ablation of this hyperplastic tissue is necessary to favour engraftment. Furthermore, myeloablative doses can help to eliminate immune-activated B cells/plasma cells and T cells induced by frequent transfusions. The net effect of MAC is an increased probability of avoiding graft failure, one of the most important causes of death. In the first reports from Pesaro, a myeloablative conditioning regimen based on oral busulfan and cyclophosphamide (osBUCY) was simply taken from what was used at that time as a total body irradiation-free conditioning regimen for malignant diseases [9]. This regimen allowed a low rate of graft failure and good survival [1,2]. On the other hand, the BUCY-based MAC regimen in TDT patients, with iron overload in the liver, heart, and endocrine organs and initially administered an oral formulation, can elicit veno-occlusive disease (VOD), lung toxicity, and severe mucositis, with a high risk of GVHD and infections. This scenario was more evident in patients with more severe organ damage from iron accumulation (Pesaro class 3). It is in this high-risk group of patients and in patients allografted with an unrelated donor that new or alternative conditioning regimens were developed, adding/replacing cyclophosphamide with other drugs such as thiotepa [10] or fludarabine [11]. In this group of patients, Gaziev et al. modified the previously published protocol 26 [12], characterized by pretransplant cytoreduction and immunosuppression. They added thiotepa to the conditioning regimen with the aim of reducing the incidence of graft failure. Thirty-seven patients (median age 9.9 years, range 5–16.6) were treated with the newer protocol, and the incidence of graft failure was 0% (compared to 15% in patients treated with p26), leading to a 5-year TFS of 92%. The 1-year TRM was 8%. All patients received bone marrow from a HLAid sibling [13].

In recent years, the definition of MAC based on the degree of haematopoietic toxicity [14] has been challenged by the introduction of an intravenous formulation of BU (ivBU), the adoption of a PK-based dosage of BU, and the development of more tolerant alkylating agents such as treosulfan (TREO). Overall, all of these changes define MAC with reduced toxicity (RTC). The use of ivBU has significantly improved its therapeutic index, reducing, but not eliminating, pharmacokinetic variability [15]. The use of PK-guided BU dosage further improved the clinical outcome in both malignant and non-malignant diseases in adult and paediatric settings. The data relative to the impact of PK-guided BU have been reviewed by van der Stoep et al., confirming that, at least in children, a correct BU dosage correlates with clinical outcomes [16]. The replacement of BU with another alkylating agent, such as TREO, has gained increasing interest. TREO is characterized by renal clearance as an unmodified product, but in general, clearance is variable in the paediatric setting. The results obtained with conditioning regimens including TREO were interesting because, at myeloablative doses, the tolerance was good with a low rate of graft failure and toxic deaths. Two seminal papers reported on these results. Bernardo et al. treated 60 TDT patients with a TREO-based conditioning regimen (associated with fludarabine and thiotepa). The median age was 7 years (1–37), and 70% of donors were unrelated. In vivo T-cell depletion by ATG was used only with UD. Few patients were classified as class 3 Pesaro (7%). The cumulative incidence (CI) of graft failure was 9%, the CI of grade 2–4 acute GVHD was 14%, and the CI of TRM was 7%. No cases of VOD were observed. The 5 y OS and TFS were 93% and 84%, respectively [17]. Mathews et al. observed a TREO-based RTC in the high-risk class 3 Pesaro group and very high-risk class 3 (defined by age more than 7 years and hepatomegaly more than 5 cm). TREO was administered with fludarabine and thiotepa, and 50 patients were included, with a median age of 11 years (1–21). Most patients received PBSCs (74%) from a HLAid sib. TREO-based RTC was associated with a clear improvement in all clinical outcomes compared to conventional BUCY, which was used in 139 patients previously treated. The CI of graft failure was 8% (vs. 12%), the TRM was 12% (vs. 28%), the CI of aGVHD was 35% (vs. 44%), and the CI of VOD was 22% (vs. 66%). The 3-year OS and EFS were 87% and 78%, respectively [18]. Similarly, Choudhary et al. treated 28 patients (21 class 3 Pesaro, and of these, 11 were class 3 HR) with TREOFLU and thiotepa before allo-SCT from HLAid donors. The median age was 9.6 years

(2–18). The CI of grade 2–4 aGVHD was 14.3%, the TRM was 21.4%, and 3 were severe VOD. The OS and TFS were 78.5% and 71.4%, respectively [19]. More recently, the EBMT compared the outcome of TDT patients reported in the Promise database receiving allo-SCT from a HLAid sib or UD and conditioned by BUFLU-based (n = 410) or TREOFLU-based RTC (n = 362) from 2010 to 2018. In the two groups, the median ages were 8.6 years (0.5–17.9) and 5.7 years (0.7–17.7), and in 50% of cases, the donor was a HLAid sibling. In the BUFLU-based group, CY and thiotepa were frequently added, and most patients in the TREOFLU-based group also received thiotepa. The 2-year OS was not different (92.7% vs. 94.7%), and the TRM was 5% and 6%, respectively. Although the incidence of graft failure was not reported, the CI of second allo-SCT was higher in the TREOFLU-based group (4.6% vs. 9%). Importantly, the CI of severe cGVHD was very low (4.3% and 5.8%, respectively), even if very few patients received in vivo T-cell depletion (overall 8.9%). Age and donors other than HLAid sibs were significant risk factors for mortality [20]. TREO clearance is highly variable, and several studies have tried to correlate TREO PK data to outcomes. Mohanan et al. analysed 87 TDT patients receiving TREOFLU plus thiotepa before allo-SCT, mostly from a HLAid sib (77%). The median age was 9 years (1.5–25), and 84% were classified as the class 3 Pesaro risk group. The incidence of graft failure was 6.2%, the 100-day TRM was 17%, and the incidence of liver VOD was 18.4%. The OS and EFS were 75.9% and 78%, respectively. When they tried to correlate PK parameters to outcomes, no significant correlation was found. However, in a multivariate analysis, low-TREO clearance correlated with low OS and EFS. Of note, the plasma levels were similar between 12 and 14 g/m^2 [21]. Chiesa et al. prospectively analysed 87 paediatric patients with different diseases (not including TDT). They found that the optional AUC for TREO was 4800 mg*h/L (range 3863–6037) and that there was a correlation between low AUC levels and poor engraftment and high AUC levels and toxic mortality [22]. In this study, TREO was associated only with fludarabine. Finally, van der Stoep et al. analysed 110 patients with non-malignant disease (50% haemoglobinopathies) conditioned with TREOFLU with (68%) or without thiotepa. The median age was 5.2 years (0.2–18.8), and the donors were HLAid sibs (30%), UD (45%), and haplo (25%). BM was infused in 66% of patients. The authors did not find a significant correlation with major clinical outcomes and different levels of exposure to TREO. Only skin toxicity was more frequently found with higher TREO AUC levels [23].

Every time the conditioning regimen is modified, mainly to reduce the toxicity and mortality, the engraftment rate can be affected, leading to a mixed donor chimerism (MC). The association between MC levels at day +28 (high when residual host cells were more than 25%) and the risk to reject donor marrow after MAC, BM, and HLAid sibling is well known [24,25]. Using less-intensive conditioning regimens, the MC rate could be different and theoretically higher. When treosulfan-based regimens were utilized before transplantation, the MC rate ranged from 8% to 50% [18,19,21]. On the other hand, in the paper from Shenoy et al. [26], MC was absent, while in another paper [27], the rate was 28%, but all MC patients reversed their pathological phenotype. Of note, three out of fifteen MC patients received donor lymphocyte infusions to convert MC in complete chimerism. The MC rate differences could be explained because under the umbrella of RIC regimens are included different protocols in terms of chemotherapeutic agents and GVHD prophylaxis. However, MC did not surely herald rejection, and stable MC is well described in at least 10% of patients in the Pesaro cohort [28]. Indeed, these patients with stable MC were independent from red cell transfusions, frequently with a residual donor chimerism around 20%.

Although a HLAid sib is considered the ideal *donor* for these patients, the probability of finding such a donor is at best 25%. Thus, alternative donors such as unrelated or nonidentical familial donors have been sought. Of course, with alternative donors, the risk of graft failure and TRM, with a reduction in survival, can be high. In a prospective trial from China, 82 patients with TDT (median age 6 years, range 0.6–12) received an adapted MAC consisting of PK-guided BU, Cy, fludarabine and thiotepa before MSD or MUD stem

cell infusion. In the MUD group (n = 52), all patients were infused with PBSCs. The overall survival was similar based on donor type (3-year OS and EFS 90% vs. 92% and 83% vs. 90%, respectively). Graft rejection was observed in three patients (CI 3.7%), and TRM was 8.5%. VOD was observed in 6%. Of note in this study, the authors classified patients using two parameters: age (<4 vs. >8 years, ferritin levels <3000 vs. >5000) and hepatomegaly (<2.5 under costal margin vs. >4 cm) due to the impossibility of performing liver biopsy to define Pesaro class risk [23]. In the studies from EBMT (3) and CIBMTR (5), 14% and 23% of patients received transplantation from UD donors, respectively. In the EBMT study, the 2 y OS and EFS were 77%, which was lower than that in the HLAid sibling group, while in the CIBMTR study, the 5 y OS and EFS were 93% and 89%, respectively, without a significant difference compared to the HLAid sibling group. In the French experience (8), the thalassemia-free survival (TFS) was poor when the donor was unrelated (n = 12). Shenoy et al. treated 33 TDT patients with UD or cord blood (CB) after a reduced-intensity immunoablative, alemtuzumab-based conditioning regimen in a prospective phase 2 trial. The median ages were 10 years (UD) and 3.5 years (for CB). They did not observe any graft failure in the UD patients and only one in the CB group. The 5-year OS and TFS were both 82% in the UD group and 81% and 75% in the CB group. The TRM was similar (18% and 19%, respectively) [26]. In a second EBMT study, 18% of patients received transplantation from UD, and major clinical outcomes were not different from the HLAid sibling group (20). In recent years, transplantation from a mismatched family donor, mainly from haploidentical donors, has become more appealing because of dedicated platforms, which have reduced the incidence of complications, with a consensual improvement in survival. Basically, two specific platforms have been employed when the donor is haploidentical: selective T-cell depletion and post-transplantation cyclophosphamide. Of course, the feasibility of transplantation from haploidentical donors drastically enhances the pool of donors available.

Gaziev et al. treated 14 patients (median age 7 years, range 3–15) with haemoglobinopathies (11 with TDT) with haploidentical donors and ex vivo αβ T cells after MAC. All patients received a CD34+ cell megadose, with immunosuppression after transplantation. The incidence of graft failure was 14%, and the 5 y OS and DFS were 78% and 39%, respectively. Despite ex vivo T-cell depletion and post-transplant immunosuppression, the patients developed grade 2–3 aGVHD (28%) and extensive cGVHD (21%). Viral infections were frequent due to delayed immunoreconstitution [29]). A similar transplant modality was applied to 70 children (median age 0.9 years) affected by different non-malignant diseases (10 with TDT) who received allo-SCT from haploidentical donors using ex vivo αβ T-cell and CD19 B-cell depletion and MAC, but without post-transplant immunosuppression. The clinical results are encouraging because the 5 y OS was 91% and the DFS was 86%. However, the incidence of graft failure (primary and secondary) was particularly high (55%) in high-risk patients because of disease, including TDT. Most of these patients were successfully retransplanted. The CI of acute and chronic GVHD was extremely low, and the main driver of mortality was viral infections linked to delayed immunological reconstitution [30].

GVHD prophylaxis with post-transplantation cyclophosphamide (PTCY) with T-cell-replete stem cell infusion from haploidentical donors quickly gained popularity in the field compared to previous systems based on ex vivo T-cell depletion. Mainly used in patients with haematological malignancies, the Baltimore group tested this modality in patients with haemoglobinopathies. Bolanos-Maede et al. first reported a prospective trial consisting of a non-myeloablative conditioning regimen and PTCY in 17 patients (5 TDT). Based on the data from a previous trial on sickle cell disease [31], the protocol was modified with a higher dose of total body irradiation (from 200 to 400 rads) to try to lower the incidence of graft failure (reported to be 50%). The median age was 16 years (6–31). The treatment was extremely well-tolerated, and only one patient developed graft failure, five had grade 2–3 aGVHD (incidence 29%), and only one had moderate cGVHD. No treatment-related mortality was reported, and all TDT patients became transfusion independent [32]. Anurathapan et al. used the PTCY platform, preceded by the MAC

regimen, and pretransplant pharmacological immunosuppression (PTIS). A total of 83 TDT patients were treated, with a median age of 12 years (1–28). The CI of grade 2–4 aGVHD was 42%, and that of grade 3–4 aGVHD was 7%. Only 4% of patients had extensive cGVHD. Graft failure was observed in two patients with high titres of donor-specific antibodies. VOD was observed in 18% of patients. Four patients died from complications (5%), and the 3-year OS and EFS were both 96% [33]. In a prospective trial from China, 54 TDT patients received haploidentical transplantation after MAC and modified PTCY-based GVHD prophylaxis using CSA and short-course low-dose methotrexate (days +1, +2, +5 and +10). The median age was 6 years (range 3–14), and all patients were infused with PBSCs. Graft failure was observed in three patients. The CI grade 2–4 aGVHD was 13.8%, and cGVHD (all limited) was 28.5%. The OS and EFS were 98% and 90%, respectively, which were better in the group of patients receiving an intensified conditioning regimen (CY 200 mg/kg instead of 120 mg/kg). No patients died from treatment-related toxicity [34].

3. Conclusions

Allogeneic stem cell transplantation, while waiting for gene therapy, remains the only curative option for TDT. Clearly, the scenarios are changing because few patients can receive what is considered the gold standard transplantation consisting of a young patient, HLAid sibling, myeloablative condition regimen, and BM as the stem cell source. On the other hand, changing one or more of these variables must be linked to adapting the others. For example, the same conditioning regimen cannot be used if the recipient's age is higher than 16 years or more, if the donor is unrelated or haploidentical, or if iron chelation is not optimal due to organ damage. Furthermore, specific prognostic scores have been recently developed for both transfusion-dependent and transfusion-independent thalassemia (31). In this analysis, seven variables were included; namely, heart and liver disease, ALT levels > 42, diabetes, sepsis, haemoglobin levels < 9 g/L, and serum ferritin $\geq$ 1850 ng/mL; and three categories were identified: low, intermediate, and high risk. The survival rate was significantly different among the three categories (59.8% vs. 26.4% vs. 13.8%). The development of risk scores, such as the Thalassemia International Prognostic Scoring System (TIPSS) [35], could help to counsel patients and families and to plan treatment, such as allo-SCT, based on objective information, even in patients with no TDT.

We think that the safety profile should guide every modification in the transplant procedure to maintain toxicity- and treatment-related mortality at levels as low as possible.

Finally, the place of allo-SCT in thalassemia will re-shaped with the advent of gene therapy. While this kind of therapy holds high promise and, at least by patients and their family, it is perceived as a definitive solution, many shadows need to be swept away. Affordability, wide diffusion, long term toxicities, and costs are all important points to address in the next future.

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