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ARTICLE

Late effects after hematopoietic stem cell transplantation for β-thalassemia major: the French national experience

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ABSTRACT

In this retrospective study, we evaluate long-term complications in nearly all β-thalassemia-major patients who successfully received allogeneic hematopoietic stem cell transplantation in France. Ninety-nine patients were analyzed with a median age of 5.9 years at transplantation. The median duration of clinical follow up was 12 years. All conditioning regimens were myeloablative, most were based on busulfan combined with cyclophosphamide, and more than 90% of patients underwent a transplant from a matched sibling donor. After transplantation, 11% of patients developed thyroid dysfunction, 5% diabetes, and 2% heart failure. Hypogonadism was present in 56% of females and 14% of males. Female patients who went on to normal puberty after transplant were significantly younger at transplantation than those who experienced delayed puberty (median age 2.5 *vs*. 8.7 years). Fertility was preserved in 9 of 27 females aged 20 years or older and 2 other patients became pregnant following oocyte donation. In addition to patient's age and higher serum ferritin levels at transplantation, time elapsed since transplant was significantly associated with decreased height growth in multivariate analysis. Weight growth increased after transplantation particularly in females, 36% of adults being overweight at last evaluation. A comprehensive long-term monitoring, especially of endocrine late effects, is required after hematopoietic stem cell transplantation for thalassemia.

Introduction

In β-thalassemia, absent or reduced synthesis of the β-globin chain results in ineffective erythropoiesis and peripheral hemolysis. Anemia of the most severe form of the disease, known as β-thalassemia major (β-TM) or transfusion-dependent thalassemia, is treated with lifelong red blood cell transfusions associated with chelation therapy in order to limit chronic complications and premature deaths related to iron overload. If this conventional therapy has dramatically improved survival and quality of life of patients,[1,2] allogeneic hematopoietic stem cell transplantation (HSCT) is, in clinical practice, the only curative treatment. Only recently, patients were treated with β-globin gene therapy using autologous hematopoietic stem cells (HSCs) modified by lentiviral vectors.[3]

Hematopoietic stem cell transplantation has been successfully performed over the last 30 years[4-7] with current thalassemia-free survival rates of 80-90% in children transplanted with HLA-matched sibling donor (MSD) before the onset of complications related to their disease or to the supportive treatment.[8,9]

Thalassemia is a rare disease in France. HSCT results from 1985 to 2007 were reported for 108 β-TM patients with 87% survival rate and, for patients treated after 2004, 85% thalassemia-free survival.[10]

Hematopoietic stem cell transplantation potentially results in a better long-term quality of life than that observed in patients treated with regular transfusion and chelation therapy.[11,12] However, β-TM patients are exposed to late transplant-related complications particularly when transplant is performed in older children, adolescents or adults and in patients who have received inadequate chelation therapy before HSCT.[12-14] Occurrence of late hepatic, endocrine and cardiovascular complications have been described, related to past and residual iron overload (IO) as well as conditioning toxicity, viral infections and chronic graft-*versus*-host disease (GvHD). Few studies have analyzed the long-term health status after HSCT including fertility in thalassemia patients.

The present report includes almost all patients with β-TM who successfully received an allogeneic HSCT in France between 1985 and 2012 and were alive at least two years after HSCT. The aim of this national retrospective study was to evaluate over time the long-term outcomes in β-TM patients after allogeneic HSCT using post-transplant medical examination data, long-term treatment records, and laboratory test results.

Methods

This retrospective non-interventional study was approved by the national regulatory authorities (CCTIRS ref. 13.425 / CNIL n. 2009-674) and was partly based on data collected in the national registry of β-TM patients.[15] Between December 1985 and December 2012, 134 patients had received an allogeneic HSCT for β-TM in 21 French transplantation centers. Fifteen patients died within two years post transplant. Twelve patients resumed regular transfusions after graft failure and 107 of 134 patients were alive at least two years after successful HSCT. Six were not analyzed in the long-term study (e.g. because they had returned to their home country or were lost to follow up) and 2 died of chronic GvHD early in the third year post transplant. Finally, 99 patients were studied for transplant-related long-term effects. Neither graft failure nor death occurred after two years post transplant.

Patients' characteristics at HSCT

The clinical characteristics of the 99 patients analyzed are reported in Table 1. Age at HSCT ranged from 8 months to 26 years old (median age 5.9 years). No patient had diabetes or thyroid dysfunction. Only one patient who was transplanted at 19 years of age had pre-existing IO-related cardiomyopathy. One male and 2 females were treated for hypogonadism. The median duration of clinical follow up after transplantation was 11.9 years (range 2-30 years).

Transplantation procedure

All conditioning regimens were myeloablative, for the most part based on busulfan combined with cyclophosphamide (BuCy). In the first years of the program, 3 patients received irradiation (Table 1). Six patients underwent a second allogeneic HSCT after a median time of 2.8 years after the first transplantation due to graft failure. Ninety-one percent of transplants were from HLA-MSD. Sixty-seven patients received anti-thymocyte globulin as part of conditioning. All patients received cyclosporine A as GvHD prophylaxis, combined with methotrexate in 58 patients. Grade II-IV acute GvHD occurred in 22 patients. Chronic GvHD occurred within two years post transplant in 14 patients (limited in 9, extensive in 5). Within two years after successful HSCT, immunosuppressive treatment was stopped in 94 patients (median time dura-

Table 1. Patients' and HSCT characteristics.

Number of patients	99
Male/female	45/ 54
Age at transplantation, years, median (IQR)	5.9 (3.1-11.2)
Age at last assessment, years, median (IQR)	20 (14.2-28.3)
Follow-up duration, years, median (IQR)	11.9 (7-19.3)
Serum ferritin level before HSCT µg/L, median (IQR)	1400 (835-2250)
Splenectomy	30
Height SDS at transplantation, median (IQR)	-0.2 (-1.66, 0.29)
Weight SDS at transplantation, median (IQR)	- 0.18 (-1.62, 0.88)
Pesaro classification (<18 years)	
- Class 1/Class 1 or 2/Class 2	30/15/39
- Class 2 or 3/ Class 3	4/3
Puberty at transplantation in female patients, n	**54**
- Ongoing puberty or post-pubertal	6
- Delayed puberty and aged ≥ 13 years	2+2*
- Pre-pubertal	44
Type of donors, n	
- MSD/matched other related	91/5
- URD	3
Source of stem cells, n	
- Bone marrow	84
- Cord blood/cord blood + bone marrow	11/3
- Peripheral blood stem cells	1
Conditioning regimen (MAC = 100%), n	
- Busulfan + cyclophosphamide	86 (oral=52)
- Busulfan + fludarabine ± thiotepa	10
- Others including irradiation (5 or 6 Gy thoracoabdominal or total body irradiation).	3

HSCT: hematopoietic stem cell transplantation; IQR: interquartile range; SDS: standard deviation scores; MSD: matched sibling donor; URD: unrelated donor; MAC: myeloablative conditioning; n: number. *Sex hormone replacement for hypogonadism.

tion of 9 months). Forty-four patients underwent phlebotomy and/or received chelation therapy after transplant.

Definition of methods and end points

Late effects data documented by physicians were collected through visits to reference or transplant centers. Collected data included medical examination results, long-term treatment, and laboratory tests (serum ferritin, creatinine and hormone levels). Measurements of height and weight were converted to standard deviation scores (SDS) using French references.[16] Delay of puberty, hypogonadism, being overweight, hypothyroidism, heart failure, and diabetes were defined using standard criteria (see *Online Supplementary Methods*).

Statistical analysis

Continuous variables were reported as mean±Standard Deviation (SD) or as median and interquartile range (IQR) for non-normal distribution. Wilcoxon signed rank test was used to compare sample median. As repeated measurements were made on the same statistical units (several measurements for each patient), univariate and multivariate linear mixed-effects models were used.[17] Those variables significantly associated with outcome and those that were marginally significant ($P<0.10$) in univariate analysis were included into multivariate analysis. For all analysis, a two-tailed test was used; $P<0.05$ was considered significant. All statistical analysis was performed using IBM SPSS Statistics v.20 (IBM SPSS Inc., Chicago, IL, USA).

Results

Thyroid, diabetes and heart

Eleven patients (11%) developed thyroid complications after HSCT (Table 2). The spectrum of thyroid complications was broad. Seven of 11 patients with a median serum ferritin level at transplant of 1560 μg/L had subclinical or overt hypothyroidism; this was transient in 2 cases. Two patients developed nodules or cysts without biological abnormalities and 2 other patients an autoimmune thyroid disease. Only 3 of 90 patients who received a single transplant with no irradiation developed permanent hypothyroidism. No patient experienced thyroid carcinoma.

Five patients (5%) had diabetes mellitus after transplantation; their median age at HSCT was 13.7 years (range 1.8-26) and median serum ferritin level 1085 μg/L. Two patients were treated with corticosteroids for GvHD (Table 2).

One patient, with arrhythmia and cardiomyopathy before transplant, regained normal heart rhythm and function after HSCT. Two patients who received a single conditioning with BuCy (200 mg/Kg) at the age of 13 and 4 years developed cardiac insufficiency 84 and 116 months, respectively, after HSCT. The first patient, now aged 39 years, has a moderate cardiac insufficiency whereas the other, who experienced a more severe disease course, is still undergoing treatment at the age of 20 years (Table 2). Their serum ferritin levels at HSCT were 370 and 1510 μg/L, respectively. No cardiac MRI was available at onset of cardiac symptoms to allow investigation of a possible cardiac iron overload.

Growth

In multivariate analysis, older age at the time of transplantation and, to a lesser extent, higher serum ferritin levels inversely correlated to height SD scores after transplant (*Online Supplementary Table S1*). Patient's sex was not found to affect height SDS evolution after transplantation. Height SDS also decreased with time ($P<0.001$). Forty-nine patients (30 females and 19 males) had reached their full-grown height at last follow up. The median SDS for final height was of -1.4 (range -3 to 1.3) in males and -1.1 (range -3 to 3) in females.

The multivariate analysis revealed that, unlike height, weight SDS increased with time ($P<0.001$). This increase was more prominent in females compared to males ($P=0.003$) (*Online Supplementary Table S1*). At last follow up, 36% of the 49 adult patients (11 females and 7 males) were overweight [Body Mass Inedx (BMI) >25 kg/m^2]. Four adult females were obese with a BMI of over 30 kg/ m^2.

Pubertal development in females

At last evaluation, 43 of 54 females were assessable for puberty. For 6 of 43 patients, puberty was reached or ongoing at HSCT: all had secondary amenorrhea after transplant and 5 had hypogonadism (hypergonadotropic in 4 patients). Four of 43 females had delayed puberty at HSCT: all of them subsequently developed hypogonadism.

Thirty-three of 43 females were pre-pubertal at transplant. One third (12 of 33) experienced spontaneous and normal puberty after one HSCT performed at a median age of 2.5 years. Only one patient had hypergonadotropic

Table 2. Thyroid complications, diabetes and impaired cardiac function.

	Number of patients	Median time HSCT-disease (months, range)	Conditioning	a/c GvHD	Treatment
Thyroid complications	11			0/0	
Hypothyroidism	7**	68 [11-164]	Bu-Cy, TLI (n=1)		L-Thyroxin (n=7)
Hashimoto disease	1*	102	Bu-Cy		L-Thyroxin + Surgery (n=1)
Hyperthyroidism (Grave disease)	1	30	Bu-Cy		Carbimazole and L-Thyroxin
Hemorrhagic pseudocysts /nodules	2	n=1, 226; n=1, 276	TBI/Bu-Cy		Surgery (n=2)
Diabetes	5*	78 [3-249]	Bu-Cy (n=4)° TBI (n=1)	2/1	Insulin (n=4) OAD (n=1)
Impaired LVEF (≤ 50%)	2	n=1, 84; n=1, 116	Bu-Cy	0	ACEI (n=1) Diuretics (n=2)

HSCT: hematopoietic stem cell transplantation; a/cGvHD: acute/chronic graft-*versus*-host disease; Bu-Cy: busulfan and cyclophosphamide; TBI: total body irradiation; TLI: total lymphocyte irradiation; LVEF: left ventricular ejection fraction; OAD: oral anti-diabetic; irr: irradiation; ACEI: angiotensin-converting enzyme inhibitor. *Second transplant for one patient. °One patient had received irradiation for extra medullary hematopoiesis before HSCT. **Second transplant for 2 patients.

hypogonadism. Delayed puberty was observed in 21 of 33 patients; most of these cases presented hypergonadotropic hypogonadism (Table 3). The patients who spontaneously started their puberty were significantly younger at transplant compared to those who had delayed puberty [median age 2.5 years (range 1.6-5.9) *vs*. 8.7 years (range 1.7-12), respectively; $P<10^{-3}$].

Pubertal development in males

Twenty-nine of 45 males were assessed for puberty. Five of 29 males were post-pubertal at HSCT: one patient who had required hormonal replacement therapy before HSCT remained on treatment after HSCT for hypergonadotropic hypogonadism.

The 2 of 29 males with ongoing puberty at transplant completed normal puberty. Among the 22 males who were pre-pubertal at transplant, only 4 (18%) had delayed puberty and 3 developed hypogonadism after transplant (hypogonadotropic in 2 cases). Eighteen of 22 patients (82%) transplanted at a median age of 5.9 years started puberty spontaneously.

Fertility and pregnancy

Among the 27 females aged 20 years and over at last evaluation, 11 (40%) had had at least one successful pregnancy after transplant. Sixteen successful pregnancies were recorded with a median age of 26 years (22-33 years) at delivery. Two patients had benefited from oocyte donation; both had had delayed puberty and post-HSCT hypogonadism. Among the 9 remaining patients, 3 experienced normal puberty after HSCT and 6 had delayed puberty. It is worthy of note that 5 of 9 patients were diagnosed with hypergonadotropic hypogonadism.

Among the 21 males aged over 20 years at last visit and evaluable for fatherhood, 4 (19%) fathered at least one child; 3 had experienced normal puberty and one patient had delayed puberty, hypergonadotropic hypogonadism and oligoasthenozoospermia. He and his partner had benefited from *in vitro* fertilization, which had resulted in a full-term pregnancy and delivery.

Other complications

Other relevant long-term late effects were encountered. Eleven patients had acquired hepatitis C virus (HCV) infection before transplant and had a positive HCV-RNA after HSCT. At last evaluation, 3 of 11 patients remained positive (2 of 3 did not require antiviral treatment), 7 of 11 became HCV-RNA negative after an antiviral treatment, and one recovered spontaneously. Five patients developed liver complications: 3 had liver fibrosis, one nodular regenerative hyperplasia, and one focal nodular hyperplasia; none of them developed hepatocellular carcinoma. At last visit, only 3 patients still had limited chronic GvHD that did not require any treatment, but another patient developed severe bronchiolitis obliterans. Two patients presented psychiatric disorders (one schizophrenia, one paranoia). No secondary malignancy was recorded. Creatinine levels (n=99) at a median time of 11 years after transplant were within the normal range for sex and age groups in all patients except for one 14-year old male patient with a chronic kidney disease stage 2 (96 μmoles/L). Another patient with diabetes developed a chronic proteinuria (2 gr/L) without renal insufficiency. Proteinuria was not routinely investigated after transplant in the study population.

Ongoing medication

Half of the patients were on long-term treatment at last evaluation. Hormonal therapy (sex hormone replacement, thyroid hormone or insulin therapy) was prescribed for 34 patients, antibiotic therapy for 17, and cardiac treatment for 2. One patient with mixed chimerism was receiving long-term treatment with erythropoietin. The only patient receiving systemic immunosuppressive therapy at last evaluation was treated for auto-inflammatory arthritis.

Serum ferritin and hemoglobin levels

Mean serum ferritin level at last evaluation was 405 μg/L±295. Thirty-seven patients were treated with phlebotomy, 7 with chelation therapy, and 11 with both. In multivariate analysis, serum ferritin levels after transplant significantly decreased with time and with the use of phlebotomy/iron chelation therapy. Serum ferritin levels after transplant were higher in older patients and/or in patients with high serum ferritin levels at HSCT (*Online Supplementary Table S2*).

Median hemoglobin value at last evaluation was 125 g/L (range 86-170 g/L). All patients were free of transfusion, and only one patient received erythropoietin therapy.

Discussion

Nearly all β-TM patients successfully treated in France with allogeneic HSCT were assessed for late effects with a long follow up after transplantation (median duration of follow up 12 years). The vast majority of patients were trans-

Table 3. Gonadal dysfunction after hematopoietic stem cell transplantation (HSCT) in female patients.

	Number of patients	Median age at HSCT (years)	Median age at assessment (years)	Spontaneous menarche	Secondary amenorrhea	Hypogonadism	Pregnancy (≥20 years)
Ongoing puberty or post-pubertal at HSCT	6	19	31	-	6	4+1*	1 /6
Delayed puberty and aged ≥ 13 years at HSCT	4	13.6	26.5	0	-	2+2*	1°/2
Pre-pubertal and aged < 13 years at HSCT	33						
Normal puberty	12	2.5	18.5	12	3**	1	3 /5
Delayed puberty	21	8.7	21	5	4	15	5 + 1° /14

*Hypogonadotropic hypogonadism. °Oocyte donation. **Transient in 2 cases.

planted early in childhood from MSD and all received myeloablative conditioning regimen (MAC), most often BuCy.

At last evaluation, hypogonadism, defined as low estradiol levels or need for long-term sex hormone replacement therapy, was observed in 58% of female patients. Hypogonadism was hypergonadotropic in 84% of cases, the few cases of hypogonadotropic hypogonadism being observed in female patients who were post-pubertal or over 13 years at transplant. After transplant for thalassemia, ovarian failure has been reported with a frequency ranging from 50% to 100% (Table 4).[18-25] Here, we report that gonadal dysfunction generally resulted from the busulfan-related ovarian toxicity rather than IO which would lead to hypogonadotropic hypogonadism. In several studies of β-TM patients, older age at HSCT (>7 years) has been associated with more frequent post-transplant hypogonadism.[14,20,22,24,25] This observation can be explained by the fact that the older the patient at HSCT, the higher the pre-transplant exposure to IO, but also by a possible reduced gonadal toxicity to busulfan in very young children. The pool of oocytes is limited and decreases from birth,[26] and pre-pubertal gonadal quiescence is gonadal-protective in children receiving chemotherapy.[27] High-dose busulfan-based conditioning regimens are known to induce amenorrhea and elevated gonadotropin levels in almost all post-menarcheal women and at least 50% of pre-pubertal

Table 4. Review of the literature on long-term complications in β-thalassemia major (β-TM) transplanted patients.

Study reference	Uni/multicentric (number of patients)	Follow up, years [range]	End points	Results
Santarone[39] 2018	Unicentric (122)	24 [4-34]	Cancer	8 cases
Santarone[31] 2017	Unicentric (75)	24 [10-33]	Pregnancy	40% women (n=15 including 2 after oocyte donation) 21% partners of male patients (n=8)
Caocci[38] 2017	Multicentric (258)	11 [1-30]	Cancer Pregnancy	3 cases 6 women and 6 partners of male patients
See[25] 2017	Unicentric (40)	Cumulative incidence at 10 years	Diabetes Growth Gonadal dysfunction Thyroid Pregnancy	2 cases Mean decrease in height SDS of -0.84* ° 55% gonadal dysfunction° 7.5% hypothyroidism One female patient
Chaudhury[24] 2017	Multicentric (176)	7 [1-20]	Cancer Growth Cardiac, renal Gonadal dysfunction Pregnancy Thyroid	No case Similar mean height and weight z-score > 4 years post HSCT/BL No cardiac complications, 20% renal complications (proteinuria/ elevated serum creatinine) 37% abnormal FSH or LH or testosterone level No case No case
Aldemir-Kocabas[22] 2014	Unicentric (41)	5.4 [2-10]	Growth Gonadal dysfunction Thyroid	Similar mean height SDS after HSCT and at BL° +0.6 mean increase in weight SDS * 14.6% low FSH, LH, testosterone or estradiol ° 10% hypothyroidism
La Nasa[12] 2013	Multicentric (109)	22.8 [11-30]	Cancer Kidney Organ transplant Pregnancy	4 cases 5 cases of chronic renal failure 2 (liver and kidney) 14% women (n=6), 17% partners of male patients (n=11)
Poomthavorn[23] 2013	Unicentric (47)	6 [1-10.6]	Gonadal dysfunction	77% females and 48% males: raised basal FSH (+/- raised LH) or low estradiol/ testosterone response to hCG
Khalil[21] 2012	Unicentric (47)	7 [2-11.6]	Diabetes Growth Heart Gonadal dysfunction Thyroid	9% diabetes 52% final height SDS < -2 11% cardiac events 80% females and 36% males (absence of pubertal development and elevated FSH/LH level) ° 11% hypothyroidism
Di Bartolomeo[11] 2008	Unicentric (90)	15 [1-24]	Cancer Pregnancy	2 cases 4 women and 2 partners of male patients
Li[19] 2004	Unicentric (32)	5 [2-8.8]	Growth Gonadal dysfunction Diabetes	Mean decrease in height SDS of 0.59* 100% females and 50% males (abnormal puberty) 1 case
De Sanctis[18] 2002	Unicentric (68)	3	Growth Gonadal dysfunction Pregnancy	Growth rate deceleration after transplant. Median final height around -0.5 in females and -1 SDS in males 66% females and 37% males (abnormal puberty) One female patient

SDS: standard deviation scores; FSH: follicle stimulating hormone; LH: luteinizing hormone; hCG: human chorionic gonadotropin. *After hematopoietic stem cell transplantation (HSCT) compared to baseline at HSCT (BL). °Young age at HSCT is protective.

females.[28-30] In our study, females who spontaneously started their puberty after transplant were significantly younger at transplant than those who experienced delayed puberty.

In this report, the frequency of hypogonadism in male patients (low testosterone levels or long-term hormone replacement therapy) was 14%, less than that usually reported in transplanted thalassemia patients (Table 4). This could be underestimated since more sensitive criteria such as inhibin levels, gonadotrophin-releasing hormone tests or semen analysis were not available.

A few pregnancies after HSCT for thalassemia have been reported but recently Santarone *et al.*[31] described in a monocentric study 15 women who became pregnant after HSCT. We also observed that fertility was preserved in at least one-third of female patients aged 20 years and over. The proportions of females requiring ovarian stimulation or who tried to conceive without success are not known. Surprisingly, in our study, several females with delayed puberty and hypogonadism became pregnant. All women who became pregnant received oral busulfan (median dose 14-16 mg/kg), which is known to have a wide intra- and inter-patient pharmacokinetic variability. Consequently, fertility should be re-assessed according to the more recent procedure of use, *i.e.* intravenous busulfan. Fertility in male patients (n=4) was also partially preserved.

We found that the rate of growth of β-TM patients was impaired after HSCT; height was influenced both by age and by serum ferritin levels at the time of transplant. These 2 variables reflect the impact of IO. This result is in agreement with most studies (Table 4),[14,32] although others reported patients catching up in the first years following HSCT.[5,19] Time elapsed after transplant also negatively influences the rate of growth, suggesting that a long-term follow up is necessary to assess the impact on height growth. We report a median loss from transplant of approximately one SD for patients reaching their full-grown height. Conditioning may contribute to growth delay in β-TM transplanted patients since a moderate decrease in height growth has also been observed in patients with hematologic malignancies receiving busulfan-based conditioning.[33]

Few data are available about weight development after HSCT in β-TM patients. In our study, weight SDS increased with time after transplant, especially in women. Being overweight appeared to be more frequent in thalassemia adult patients treated with HSCT (36% of patients at last evaluation) compared to those receiving conventional therapy (14.6% of adult patients; *data from the French β-thalassemia registry, personal communication, 2017*) or those receiving Bu-based conditioning for childhood leukemia.[34] This result leads us to propose accurate investigation of the metabolic syndrome after HSCT in thalassemia patients.

The frequency of hypothyroidism after HSCT ranged from 0% to 11% in thalassemia patients (Table 4). In this study, thyroid complications affected 11% of patients. It appeared to be mainly related to the cytotoxic effect of conditioning as half of these patients had received irradiation or a second transplant. Their age and serum ferritin levels at transplant were similar to those in the whole study population. It should be noted that hypothyroidism has been reported after treatment with BuCy.[35,36]

We found a 5% rate of diabetes mellitus after transplant compared to 0-9% in previous studies on transplanted β-TM patients.[19,21,25] Potential risk factors for diabetes mellitus are: IO (because patients developing diabetes tended to be older at HSCT), conditioning therapy administration, use of corticosteroids for GvHD management.

Cardiac complications have rarely been reported after a standard BuCy conditioning and are usually related to residual IO in β-TM patients.[21,37] The presence of cardiac IO could not be ruled out in the 2 patients who developed cardiac dysfunction as cardiac MRI T2* was not then routinely used in France. Nonetheless, one patient transplanted at just four years of age with low serum ferritin values at and after HSCT developed cardiac failure.

Three studies have reported several cases of cancer 10-25 years after HSCT for thalassemia, mostly cancer of the oral cavity and thyroid carcinoma.[12,38,39] Recently, 8 cases of secondary solid cancer (SSC) have been reported among 112 patients, mostly children transplanted from an MSD.[39] SSC occurred at a median time of 18 years after HSCT, stressing the need for a very long-term monitoring of TM survivors after HSCT. The length of follow up after HSCT may be too short in our study to record such cases. In addition, chronic GvHD, reported as an independent risk factor for secondary solid tumor,[39] in our study affected only 3 patients with untreated limited disease at last evaluation. Monitoring of thyroid through regular ultrasound, treatment of HCV infection, and of residual IO may also contribute to the lack of secondary malignancy.

Hepatic, psychiatric, or pulmonary complications were also observed in few patients. It is worth noting that HCV was successfully treated after transplant in nearly all patients with active infection.

In summary, long-term complications were mainly related to the conditioning regimen in our study population where most patients were transplanted in the early phase of their disease. Pre-transplant ferritin levels were not elevated, and only few patients had IO-related clinical complications. Moreover residual IO was treated in 44% of cases by phlebotomy and/or iron chelation, these 2 modalities of treatment being efficient after HSCT.[40-42] Reduced intensity or reduced toxicity conditioning based on treosulfan,[43] fludarabine, and/or use of low doses of busulfan were investigated in β-TM patients.[23,44] Long-term toxicity results of these studies are not yet available. In our report, Bu-based conditioning was myeloablative in all cases. Indeed, in our national experience, MAC was required in order to limit graft failure.[8] In current gene therapy trials, conditioning with high doses of Bu also appeared necessary to allow corrected autologous cells to graft.

Although not usually severe or life threatening, long-term effects after HSCT are frequent and diverse in TM patients, half of them undergoing long-term treatment, especially hormonal replacement. National and international guidelines describing comprehensive long-term monitoring should be established for thalassemia patients treated with HSCT.

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