Clinical Rheumatology (2019) 38:1501–1511
https://doi.org/10.1007/s10067-019-04435-2

ORIGINAL ARTICLE

Autologous haematopoietic stem cell transplantation (AHSCT) in autoimmune disease adult patients in France: analysis of the long-term outcome from the French Society for Bone Marrow Transplantation and Cellular Therapy (SFGM-TC)

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Received: 2 August 2018 / Revised: 22 December 2018 / Accepted: 4 January 2019 / Published online: 21 January 2019

Abstract

Introduction The use of autologous haematopoietic stem cell transplantation (AHSCT) in autoimmune disease (AD) patients has increased progressively worldwide. We retrospectively analysed the long-term outcome of AHSCT for AD reported to the French Society for Bone Marrow Transplantation and Cellular Therapy (SFGM-TC).

Method All French AD patients (≥ 18 years at transplant) with a first AHSCT between 1997 and 2013 were included. Primary data were derived from the European Society for Blood and Marrow Transplantation (EBMT) registry, and additional data were obtained through a specific questionnaire designed for the study. Primary end-point was overall survival (OS). Secondary end points were progression-free survival (PFS) and non-relapse mortality (NRM).

Results Ninety-four AD patients were included, of whom 71% suffered from rheumatologic diseases ($n = 67$, including 56 systemic sclerosis (SSc)), 16% from neurological disease ($n = 15$, including 14 multiple sclerosis (MS)) and 13% from various other AD ($n = 12$). After a median (interquartile range, IQR) follow-up of 83 months (38–130), OS at 5 and 10 years were 77% (95% CI 68.5–86.2) and 64% (95% CI 51.7–76.3), and for PFS 51% (95% CI 40.4–61.6) and 44% (95% CI 32.8–55.3), respectively. Overall, NRM was 8.7% (95% CI 4.0–15.5) at day 100, 9.8% (95% CI 4.8–16.9) at 5 years and 13.6% (95% CI 6.9–22.5) at 10 years.

Conclusions This first SFGM-TC retrospective report shows long-term benefit of AHSCT in AD patients with acceptable toxicity.

Keywords Adult patients · Autoimmune disease · Autologous · Haematopoietic stem cell transplantation

Introduction

Autologous haematopoietic stem cell transplantation (AHSCT) was first proposed in Europe in 1994 for treating severe autoimmune diseases (AD) refractory to conventional therapies [1, 2]. The rationale for AHSCT is based on its capacity to induce "immune resetting" after eradication of the autoreactive immune system with high immunosuppressive or myeloablative conditioning regimen and to allow the reappearance of tolerance with a "de novo" immune repertoire during the immune reconstitution process [3, 4]. Over the past 20 years, it was progressively shown [5–10] that AHSCT allows disease stabilisation for several types of severe or refractory AD with combined safety and efficacy, and a grade 1 level of evidence according to EBMT guidelines for scleroderma (SSc) and multiple sclerosis (MS) [11, 12]. With better patient selection and improved conditioning regimen, the AHSCT procedure has become safer over the years and more AD patients have been treated, with various developments according to the regions of the world and at each

This paper was presented in part at the ASH meeting 2015
Guillaume-Jugnot P, Marjanovic Z, Labopin M, et al. Autologous hematopoietic stem cell transplantation (AHSCT) in severe auto-immune disease adult patients: analysis of outcomes from the French Society for Bone Marrow Transplantation and Cellular Therapy (SFGMT-TC) in light of the European Society for Blood and Marrow Transplantation (EBMT) activity [abstract]. Blood 2015;126(23). Abstract 1985.

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country level [13]. In 2018, around 4000 AHSCT for AD patients worldwide have been performed with more than 2500 patients registered in the European Society for Blood and Marrow Transplantation (EBMT) registry [13], 1300 in the Centre for International Bone Marrow Transplant Registry (CIBMTR) and around 500 in the Asian registry.

In France, since the first AHSCT in a woman with severe refractory systemic lupus erythematosus (SLE) in 1997 (*EBMT registry data*), less than 10 AHSCT in adults patients were yearly reported to the EBMT registry [14]. Nonetheless, after the publication of early clinical studies in Europe [15, 16], and in the USA [17], several French transplant centres working in close collaboration with AD experts were involved in pivotal randomised trials, which successively demonstrated the efficacy of AHSCT in SSc [5, 6, 10, 18], in MS [7, 9] and in Crohn's diseases (CD) [8]. Other French patients with various types of AD have also undergone an AHSCT outside these specific trials and, as mandatory for any haematopoietic stem cell transplant in France, were reported to the French Society for Bone Marrow Transplantation and Cellular Therapy (SFGM-TC) registry. In the meantime, European [2, 12, 19, 20] and more specifically French written guidelines under the auspices of the SFGM-TC [14, 21] have informed both the patients and the clinicians, as well as the healthcare providers about the use and the results of AHSCT for AD, but the overall French activity for AHSCT in AD had not been yet analysed. We therefore designed the present retrospective study. The aim of this study was to analyse the long-term outcomes of all adult patients treated by AHSCT in France for AD.

Materials and methods

Population

We identified all adult patients treated with a first AHSCT performed in France for a diagnosis of AD, as reported to the SFGM-TC, using ProMISe database coordinated by the EBMT (*EBMT registry*) between 1997 and December 2013. Paediatric patients (below 18 years at time of first transplant) and AD patients treated with an allogeneic transplant were excluded. The SFGM-TC is a non-profit working group of French-speaking transplant specialists working in various centres and countries, including Belgium, Canada, Libanon and North Africa, who agree to report all consecutive stem cell transplantations performed in their centre with yearly follow-up thereafter. Informed consent in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines was obtained from all patients before AHSCT, and all SFGM-TC participating centres were requested to report all consecutive transplants for AD. The design of this retrospective study was validated by the scientific council of the SFGM-TC on 8 January 2015.

Study parameters and endpoints

Primary data were derived from the EBMT registry database after extracting the corresponding SFGM-TC data subset. Additional data were obtained through a questionnaire designed for this SFGM-TC study to assess baseline patient's clinical and biological status (within 3 months before mobilisation), including patient's clinical features (gender, age at diagnosis and AHSCT, median time from AD diagnosis to AHSCT, previous therapies before AHSCT) and specific disease characteristics based on modified Rodnan skin score (mRSS) [22], performance status (PS), Scleroderma Health Assessment Questionnaire (SHAQ), forced vital capacity (FVC), diffusing capacity of the lungs for carbon monoxide (DLCO), pulmonary arterial pressure (PAP), left ventricular ejection fraction (LVEF), presence of gastrointestinal involvement, antinuclear antibodies (ANA) and anti-topoisomerase 1 antibodies (Scl 70) positivity for SSc patients; and Expanded Disability Status Scale (EDSS) [23] for MS patients. According to EBMT guidelines [12], patients were to be assessed at least yearly by their referring physicians. The conditioning regimens were defined as "high intensity" including any busulfan or total body irradiation (TBI) containing regimens; "low intensity" including melphalan alone, cyclophosphamide alone, or fludarabine-based regimens; or "intermediate intensity" which contains all the other regimens, including the combined use of anti-thymocytes globulins (ATG) with high-dose cyclophosphamide as described previously [12, 15]. The following data were collected yearly up to last follow-up: non-relapse mortality (NRM); severe transplant related toxicities defined as any toxicity occurring in the 100 days after AHSCT, classified as grade III (requiring hospitalisation) or grade IV (life-threatening, requiring hospitalisation in intensive care); use of maintenance immunosuppressive therapies; onset of viral infections requiring hospitalisation, defined as either primary infection or reactivation [24]; secondary AD; or malignancies. Patient's AD evolution was classified as in "remission", "stabilisation", "improvement" or "relapse/progression". Primary end-point was the overall survival (OS), defined as time since day of transplant to death, irrespective of the cause. Secondary end points were the progression-free survival (PFS) defined as survival without evidence of relapse or progression according to local referring physicians; the NRM defined as any death following transplant, not attributed to progression or relapse of the disease according to local referring physicians.

Statistical methods

Categorical data were presented as number (percentage) and continuous data as median (interquartile range, IQR). The OS and PFS probabilities were estimated using Kaplan-Meier estimator, cumulative incidence for NRM, relapse/progression

being the competing event. All tests were two-sided. Statistical analyses were performed with IBM SPSS Statistics 22.0 and R version 3.1.2 (R Development Core Team, Vienna, Austria) software packages.

Results

Transplant population and activity

Ninety-nine patients, who underwent a first AHSCT for AD, were reported by 19 SFGM-TC centres to the EBMT registry from 1997 to December 2013. Five cases were excluded from the study due to other diagnosis (two cryoglobulinemia associated with hemopathies, one autoimmune haemolytic anaemia (AIHA) revealing a myeloma, one myositis finally classified as genetic dysferlinopathy) or death before transplant but after conditioning (1 patient), and 94 AD patients remained eligible for the study. Patient's clinical features are detailed in Table 1. Most of the AD patients were treated for SSc (59.6%, $n = 56$) including one with mixed connective tissue disease and two with coexisting rheumatoid arthritis (RA). The second indication was MS (14.9%, $n = 14$), while the other patients were referred for various types of AD (25.5%, $n = 24$), namely immune thrombocytopenic purpura (ITP) ($n = 5$), CD ($n = 5$), polychondritis ($n = 4$), polymyositis dermatomyositis ($n = 3$), SLE ($n = 2$), rheumatoid arthritis ($n = 1$), POEMS syndrome (acronym for Polyneuropathy, Organomegaly, Endocrinopathy, M proteins, and Skin changes syndrome) ($n = 1$), IgM neuropathy ($n = 1$), AIHA ($n = 1$), and ankylosing spondylitis ($n = 1$).

AHSCT procedure

Among 82 patients with full data concerning the transplant modalities, 89% ($n = 73$) were mobilised with cyclophosphamide and granulocyte-colony stimulating factor (G-CSF) and 11% ($n = 9$) with G-CSF alone. Graft selection (CD34+) was performed for 57 patients, and the median (IQR) dose of CD34 infused was 5.24×10^6/kg (2.83–7.88). Conditioning was based on using either low ($n = 17$; 19%), intermediate ($n = 64$, 71%), or high (n = 9; 10%) intensity chemotherapy regimens ($n = 90$). Sixty-three patients received additional rabbit ATG and another one unspecified additional serotherapy. Median (IQR) time to engraftment (neutrophils $\geq 0.5 \times 10^9$/L) was 11 days (10–13). AHSCT regimen details are summarised in Table 2. Forty-seven out of the 80 patients (58.7%) with available data developed severe grade III ($n = 37$) or IV ($n = 7$) transplant-related toxicities, and 3 patients died within 100 days after AHSCT. One 51-year-old SSc male, with a mean PAP at 75 mmHg at baseline, developed acute renal failure after high-dose corticosteroid during conditioning, both contributing to death "related to the procedure". Another 56-year-old female with POEMS syndrome and severe pulmonary restrictive syndrome was found eligible, although necessitating continuous positive airway pressure ventilation before transplant, and eventually died from respiratory failure 3 months after AHSCT. The third died from a cardiac toxicity at day 0.

Patient follow-up

After AHSCT, patients were followed for a median (IQR) duration of 83 months (38–130). Table 3 summarises clinical adverse events reported during patients follow-up. Thirty-four (46.6%) out of the 73 patients with available data had maintenance therapy following AHSCT. During the follow-up, 18 patients (19.1%) required 28 hospitalisations for viral infections, as described in Table 3. Some patients developed several viral infections. Among the nine patients with EBV reactivations, seven were treated with rituximab, whereas the two others were closely monitored. Among 86 patients with available data, 50 patients (58.1%) were in AD remission, improvement or stabilisation at last follow-up. Thirty-nine patients (45.3%) were considered as having AD relapse or progression by their referring physician during follow-up, and 26 patients (30.3%) received specific treatment for relapse/progression. Five SSc patients treated with rituximab for EBV reactivation after AHSCT showed either stabilisation ($n = 1$) or sustained remission ($n = 4$) after a median (IQR) follow-up of 5.8 years (1.6–8.8).

New onset of a secondary AD disease during post-transplant follow-up was reported in seven patients (9.2%) including five secondary AD among the 56 patients transplanted for SSc, and two among the 14 MS patients, as detailed in Table 3. A diagnosis of cancer was reported in five patients (6.6%), four among the SSc patients: one oesophagus epidermoid carcinoma, one lung epidermoid carcinoma, one undifferentiated carcinoma, which were the respective causes of death at 6, 11, and 13 years after AHSCT, and one patient with spino-cellular carcinoma in full remission after 2 years follow-up. The SSc patient who developed oesophagus cancer had a long-standing chronic alcoholic consumption. The SSc patient, who had developed de novo myasthenia gravis after full remission during 3 years after AHSCT, required further immunosuppression with mycophenolate mofetil and eventually died from lung cancer 12 years after AHSCT. The patient transplanted for an IgM neuropathy, who developed prostate adenocarcinoma, remained in AD remission 7 years after cancer diagnosis.

Outcomes OS, PFS and NRM

After a median (IQR) follow-up of 83 months (38–130) for the all cohort, the 5- and 10-year OS were 77.4% (95% CI 68.5–86.2) and 64% (95% CI 51.7–76.3), respectively (Fig. 1). The 5- and 10-year PFS were 51% (95% CI 40.4–61.6) and 44.1%

Table 1 Patients clinical features at baseline

Characteristics	Overall population (n = 94)	SSc patients (n = 56)	MS patients (n = 14)
Demographic characteristics			
Female, n (%)	51 (54.3)	33 (59)	3 (21.4)
Age at diagnosis, years, median (IQR)	38 (25–50)	45 (31–54)	25 (21–38)
Age at AHSCT, years, median (IQR)	45 (32–54))	48 (35–55)	38 (30–43)
Disease duration, months, median (IQR)	42 (18–95)	25 (14–48)	126 (71–164)
Follow-up, months, median (IQR)	83 (38–130)	84 (13–118)	57 (37–156)
First line therapies			
Treatments prior AHSCT, n (%)	73 (89)	44 (83.0)	9 (64.3)
Steroids, n (%)	48 (65.8)	32 (72.7)	2 (22.2)
Cyclophosphamide, n (%)	26 (35.6)	12 (27.3)	5 (55.6)
Methotrexate, n (%)	22 (30.1)	11 (25.0)	–
Azathioprine, n (%)	13 (17.8)	2 (4.5)	1 (11.1)
Mycophenolate mofetil, n (%)	9 (12.3)	4 (9.1)	2 (22.2)
Interferon, n (%)	9 (12.3)	–	8 (88.9)
Mitoxantrone, n (%)	4 (5.5)	1 (2.3)	3 (33.3)
Missing	12	–	5
Clinical features			
Performance status, median (IQR), 18 missing	–	1 (1–2)	–
mRSS, median (IQR), 12 missing	–	25 (20–35)	–
SHAQ, median (IQR), 22 missing	–	1.55 (0.8–2))	–
Gastro intestinal involvement, n (%), 14 missing	–	30 (71.4)	–
EDSS, 4 missing	–	–	6.5 (6–7)
Paraclinical data			
FCV (%), median (IQR), 10 missing	–	75 (61–89)	–
DLCO (%), median (IQR), 9 missing	–	52 (42–69)	–
PAP (mmHg), median (IQR), 8 missing	–	32 (27–35)	–
LVEF (%), median (IQR), 8 missing	–	65 (60–72)	–
ANA positivity, n (%), 9 missing	–	44 (93.6)	–
Scl 70 positivity, n (%), 10 missing	–	28 (60.9)	–

Within 3 months before mobilisation

SSc systemic sclerosis, MS multiple sclerosis, IQR interquartile range, AHSCT autologous haematopoietic stem cell transplantation, mRSS modified Rodnan Skin Score, SHAQ scleroderma health assessment questionnaire, EDSS expended disability status scale, FCV forced vital capacity, DLCO diffusing capacity of the lungs for carbon monoxide, PAP pulmonary arterial pressure, LVEF left ventricular ejection fraction, ANA antinuclear antibodies, Scl70 anti-topoisomerase 1

(95% CI 32.8–55.3), respectively (Fig. 2). Among SSc patients, the 5-year and 10-year OS were 73.7% (95% CI 61.8–85.7) and 55.4% (95% CI 38.5–72.3), respectively, and the 5- and 10-year PFS were 44.2% (95% CI 30.2–58.1) and 44.1% (95% CI 32.8–55.3), respectively. At last follow-up, 62 out of the 94 patients were alive (66%). The cause of death was AD relapse or progression in 16 patients (13 SSc, 1 ITP, 1 MS and 1 AIHA), AHSCT related cause in six patients (five SSc, one POEMS syndrome) including infections ($n = 3$), cardiac ($n = 1$), renal ($n = 1$) or respiratory ($n = 1$) failure. Other causes of death in five patients were malignancies ($n = 3$), inhalation pneumonia in a polychondritis patient ($n = 1$), and trauma ($n = 1$). In five patients, the cause of death was unknown. For the all cohort, the 100-day NRM was 8.7% (95% CI 4.0–15.5) and the 5- and 10-year NRM were 9.8% (4.8–16.9) and 13.6% (95% CI 6.9–22.5), respectively. Among SSc transplanted patients, the 100-day and the 5-year NRM were both 8.9% (95% CI 3.25–18.2), and the 10 years NRM was 11.4% (4.5–21.8).

Discussion

Since the first positive clinical results after AHSCT were reported 20 years ago in severe SSc [1], SLE [25] and CD [26]

Table 2 AHSCT procedure

AHSCT details	N (%)
Mobilisation, 12 missing	
Cyclophosphamide and G-CSF	73 (89)
G-CSF alone	9 (11)
Source of haematopoietic stem cells, 1 missing	
PBSC	92 (99)
Bone marrow	1 (1)
Ex-vivo manipulation, 6 missing	
No	31 (35.2)
Yes (CD34+)	57 (64.8)
Conditioning regimen	
Cyclophosphamide	64 (68)
BEAM	12 (12.7)
Melphalan	4 (4.3)
Busulfan + melphalan	4 (4.3)
BCNU + melphalan	4 (4.3)
Cyclophosphamide and TBI	3 (3.2)
TBI	2 (2.1)
Fludarabine + melphalan	1 (1.1)
Serotherapy, 9 missing	
Yes (with ATG except for 1)	64 (75.3)
No	21 (24.7)
Growth factors G-CSF, 9 missing	
Yes	57 (67)
No	28 (33)
Maintenance IT[a], 21 missing	
Yes	34 (46.6)
No	39 (53.4)
Steroids, n	32
Cyclophosphamide, n	1
Methotrexate, n	2
Azathioprine, n	1
Mycophenolate mofetil, n	3
Plasmapheresis, n	1

AHSCT autologous haematopoietic stem cell transplantation; G-CSF granulocyte colony stimulating factor; PBSC peripheral blood stem cells; BEAM carmustine/BCNU; BCNU etoposide, aracytin, melphalan; TBI total body irradiation; ATG anti-thymocytes globulins; IT immunosuppressive therapy

[a] One patient can have several immunosuppressive therapies

patients, who were previously resistant to standard therapies or biologics, early clinical studies in Europe [15, 16] and in the USA [17] followed by pivotal randomised clinical trials in SSc [5, 6, 10], MS [7, 9] and CD [8] have established the feasibility and the efficacy of AHSCT in specific AD. Important variations were observed in transplant rates according to countries, both overall and per head of population, and in relation to the type of AD [13]. At each country level, regular publication of transplant activity reports with updated patient follow-ups are required by the health authorities to improve knowledge of physicians, health providers, and patients about the uptake of AHSCT as a potential treatment for AD and to deliver more information by disease-specific national societies. The present retrospective study reports outcomes of all patients treated with AHSCT for AD in France until 2013.

As opposed to the rest of Europe, where MS is the first indication for AHSCT in AD [13], France has mainly transplanted SSc patients and very few with MS.

Other AD diseases were poorly represented in this national activity report. In France, as in other European countries, indications for AHSCT have become exceptional for RA or ITP, where other treat-to-target therapies have dramatically improved the patient prognosis over the past 15 years [27, 28]. Other indications remained very rare, such as for SLE, where the risk of AHSCT in highly immunosuppressed patients has to be balanced with the AD severity and available therapies [29].

The median (IQR) duration between AD diagnosis and AHSCT in this SFGM-TC study was 42 months (18–95). AD duration prior to AHSCT is an important determinant of the PFS and OS after AHSCT as previously shown in SSc, MS or CD patients [13]. AD specialists have progressively learnt the delicate balance to consider so as to refer patients to AHSCT early enough, when they are effectively resistant to first- and second-line standard therapies, and not too late, once advanced or irreversible organ damage—especially cardiac, lung and kidney function—increase the risk of adverse outcomes, or eventually contraindicate AHSCT [12, 14, 20, 21].

Consistent with the European guidelines [12, 20], patients were mostly mobilised with G-CSF plus cyclophosphamide (89%) in order to prevent an AD flare and to increase the yields of peripheral blood stem cells. Intermediate-intensity conditioning regimens, which carry a better safety profile, were mostly used (71%), possibly related to the number of SSc-treated patients in this SFGM-TC cohort. Nonetheless, 47 patients underwent severe transplant-related toxicities, of which three died, but two had been transplanted despite severe cardiac or pulmonary involvement, which today are considered as contraindication for AHSCT in SSc [20]. The retrospective analysis of these two NRM cases illustrates the importance of careful evaluation and patient selection in accordance with Good Clinical Practice (GCP) Guidelines [12, 14, 20, 21]. Careful adherence to GCP, which are easily accessible in English and in French on the MATHEC website (https://www.mathec.com), may improve the OS and PFS, and decrease the 100-day NRM after AHSCT in AD in the future, as shown for allogenic bone marrow transplant in haematological malignancies [30]. While gaining knowledge over the years, several clinical parameters specific to the AD per se and treatment-related factors have been well-recognised as carrying an unacceptable risk for the AHSCT procedure [31–34]. Careful cardiac and pulmonary assessment—including electrocardiography (ECG) plus 24-h holter ECG if abnormal standard ECG or presence of

Table 3 Clinical adverse events reported in AD patients during follow-up after AHSCT

Patients[a] with severe transplant-related toxicities in the 100 days following AHSCT, *n* (%), *14 missing*	47 (58.8)	
Infectious toxicities, *n* (%)	32 (68.1)	
Cardiac toxicities, *n* (%)	5 (10.7)	
Renal or urogenital toxicities, *n* (%)	5 (10.7)	
Digestive toxicities, *n* (%)	3 (6.3)	
Pulmonary toxicities, *n* (%)	1 (2.1)	
Reaction to ATG, *n* (%)	1 (2.1)	
Patients[a] with viral infections requiring hospitalisation during follow-up, *n* (%), *28 missing*	18 (26.1)	
	Hospitalisations (*n*)	Treatment (*n*)
VZV primary infection, *n*	1	Aciclovir (*n* = 1)
VZV reactivation, *n*	5	Valaciclovir alone (*n* = 3)
		Aciclovir + valaciclovir (*n* = 2)
VZV reactivation/HSV reactivation, *n*	1	Aciclovir + valaciclovir (*n* = 1)
CMV reactivation, *n*	4	Ganciclovir (*n* = 3)
EBV reactivation, *n*	9	Rituximab (*n* = 7)
		No treatment (*n* = 2)
EBV reactivation/CMV reactivation, *n*	2	Rituximab + ganciclovir (*n* = 2)
HBV reactivation, *n*	1	Entecavir (*n* = 1)
Influenza, *n*	3	None
Gastroenteritis, *n*	1	None
Dengue/HSV reactivation, *n*	1	*Missing data*
Primary diagnosis → secondary AD, *18 missing*, *n* (%)	7 (9.2)	
SSc → thyroiditis, *n*	1	Levothyrox
SSc → AIHA, *n*	1	Increased prednisone
SSc → myasthenia gravis, *n*	1	Neostigmin, azathioprine
		Immunoglobulins
		Plasmapheresis, MMF
SSc → sarcoidosis, *n*	1	Increased prednisone, MMF
SSc → anti-phospholipid syndrome, *n*	1	
MS → pelade, *n*	1	
MS → granulomatosis, *n*	1	
Primary diagnosis → secondary malignancy, *18 missing*, *n* (%)	5 (6.6)	
SSc → oesophagus epidermoid carcinoma, *n*	1	
SSc → unspecified carcinoma, *n*	1	
SSc → lung epidermoid carcinoma, *n*	1	
SSc → spinocellular carcinoma, *n*	1	
Neuropathy IgM → prostate adenocarcinoma, *n*	1	

AD autoimmune disease, *AHSCT* autologous haematopoietic stem cell transplantation, *ATG* anti-thymocytes globulins, *VZV* varicella zoster virus, *HSV* herpes simplex virus, *CMV* cytomegalovirus, *EBV* Ebstein-Barr virus, *HBV* hepatitis B virus, *SSc* systemic sclerosis, *AIHA* autoimmune haemolytic anaemia, *MMF* mycophenolate mofetil, *MS* multiple sclerosis

[a] One patient can have several events

palpitation, Doppler-echocardiography, cardiac MRI with contrast, cardiac catheterisation with fluid challenge, high-resolution chest CT and lung functions tests—is recommended prior to patient selection [20] in addition to infectious assessment and vaccinations as for any haematopoietic stem cell transplantation procedure. Multidisciplinary evaluation bringing together the autoimmune and auto-inflammatory diseases specialists and the transplant team haematologists to assess each patient condition prior to AHSCT referral is important to discuss the different therapeutic strategies available according to

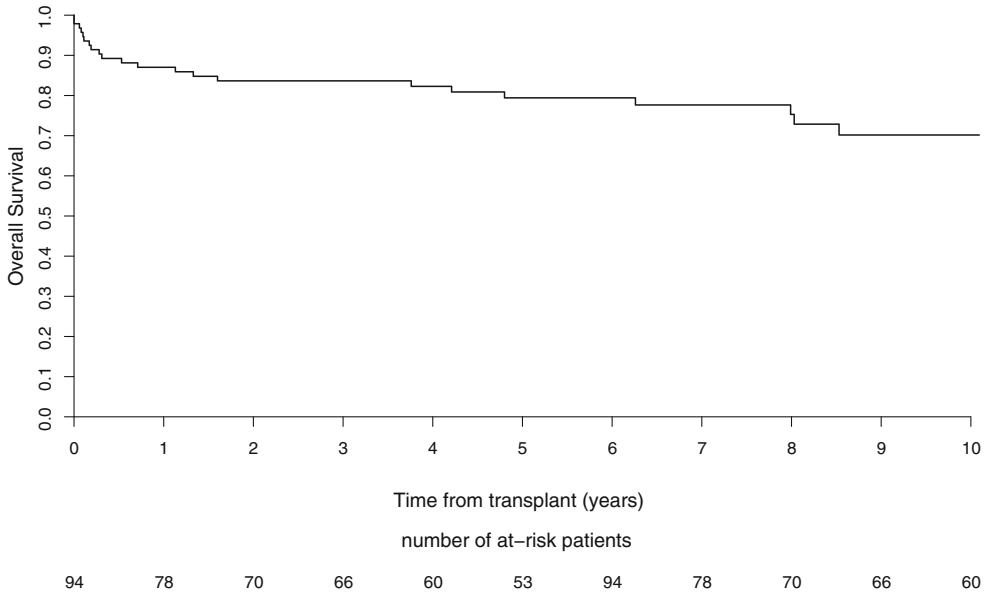

Fig. 1 Long-term incidence of OS

individual patient profile. In France, The Centre of Reference for Rare auto-immune Diseases d'Ile-de-France at St-Louis Hospital is hosting the National MATHEC platform multidisciplinary Consultation Meeting (RCP MATHEC) for pre-transplant evaluation of the AD patient to validate the indication and the ad hoc procedure for stem cell therapy by health care AD specialists and haematologists working together according to GCP guidelines (www.mathec.com).

During their follow-up after AHSCT, 18 patients (19.1%) required hospitalisation for viral infections and 3 of them developed simultaneous viral infections, illustrating that a viral infection may trigger another one [24]. Of interest, the five SSc patients treated with rituximab for post-AHSCT EBV reactivation showed AD improvement or sustained remission after AHSCT. These patients had received more intense immunosuppression with the use of rituximab for EBV reactivation during their post-transplant course. Rituximab, as a monoclonal antibody aiming at enhanced B depletion, in addition to standard conditioning regimen—in these SSc patients—may be beneficial in terms of clinical response in the long-term, as it is currently studied by Burt in SLE-transplanted patients [35] (NCT00278538).

During post-transplant follow-up, seven patients (9.2%) developed secondary AD, consistent with a larger previous EBMT retrospective study, where the cumulative incidence of secondary AD after AHSCT for AD was 7.7% after 3 years and 9.8% after 5 years [36]. The incidence of cancer is known to be increased in SSc patients compared to the general population [37], irrespectively of AHSCT. In addition, in two SSc

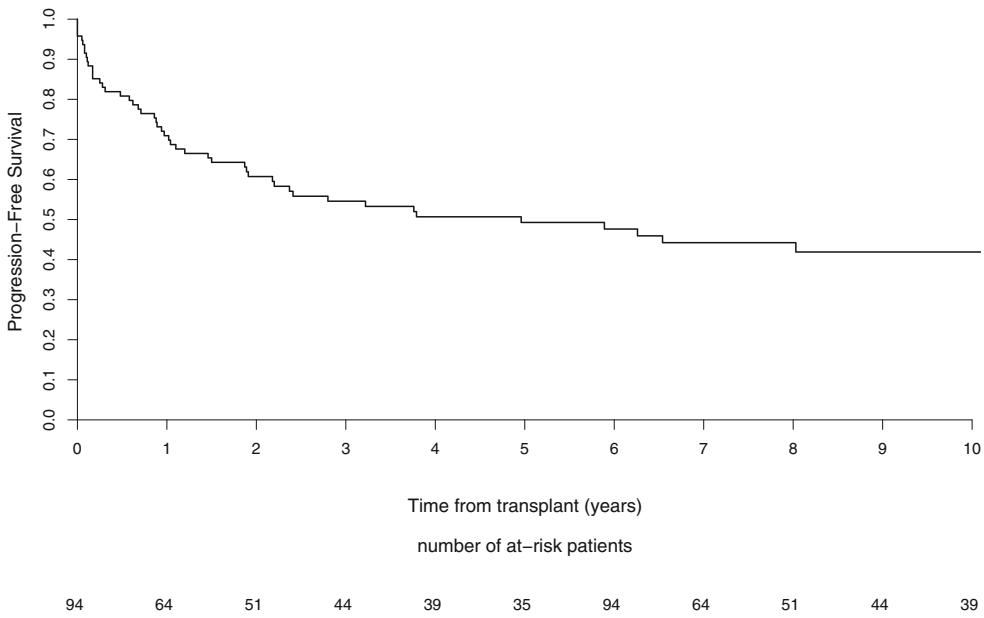

Fig. 2 Long-term incidence of PFS

patients reported and analysed in the cohort, chronic alcoholic consumption and need for enhanced immunosuppression for secondary onset of myasthenia gravis—as previously published [38]—were additional risk factors for neoplasia. The onset of spino-cellular carcinoma is a well-known complication after immunosuppression, underlying the need for regular and close post-transplant monitoring in accredited centre, to allow early diagnosis and treatment without relapse, as in the present case. Prostate adenocarcinoma, as successfully treated in the patient transplanted for an IgM neuropathy, is one of the most common cancer in the male population [39].

The 5-year OS was 77.4% for the all cohort, consistent with results previously described in UK [40] and at the European state level [15], where the 5-year OS were 78% and 85%, respectively. In this SFGM-TC cohort, the 5-year PFS at 51% appeared higher than 5-year PFS previously reported in UK at 33% or in Europe at 43% [15, 40]. Consistent with this trend, the 100-day NRM was 8.7% lower than 100-day NRM in UK (13%), but higher than 100-day NRM in Europe (5%). A recent EBMT study, with the contribution of several non-European countries (Australia, China, Canada, Lebanon, Colombia, Brazil, Jordan, Saudi Arabia, Singapore and South Africa) reported the same trends for outcomes with an 86% OS, 49% PFS and 5.3% NRM at 5-year follow-up after AHSCT for AD [13]. The difference in PFS and NRM can be explained by the type of AD predominantly considered in each retrospective study analysis. In France, SSc patients represented the first indication (60%), while in UK, inflammatory arthritis (36%) and connective tissue disease (31%) were the predominant indication [40] and in the European cohort, MS (43%), which is at lower risk of death among all AD transplanted, was by far the first indication [13].

The present SFGM-TC study has some limitations. First, its retrospective design with missing data, despite all EBMT registry queries and on site chart evaluation. Building the adequate network with close partnership between each AD specialists and the transplant centre is important to collect more accurate data in the future. Second, the heterogeneity of the AD diseases within this SFGM-TC cohort did not allow multivariate analysis. However, this type of retrospective study improves the quality of collected data, and the present study enabled us to correct four misclassified AHSCT for AD (three hemopathies and one genetic myopathy).

More than half of theses 94 AD patients were transplanted on an individual basis, outside any clinical trials, underlying the need to evaluate activity and to promote education at the national level. Today, indications for the major AD subtypes are well validated, and implementation of GCP guidelines and ad hoc information in a collaborative approach between different specialists and national societies will improve patient outcome. The MATHEC working group (Maladies Autoimmune et Thérapie Cellulaire) (https://www.mathec.com) within the SFGM-TC has developed a specific web-based platform, free of access for any SFGM-TC member, in order to offer the necessary tools for patient evaluation, validation of AHSCT indication, mobilisation, conditioning regimen and patient follow-up.

Acknowledgments The authors would like to thank all physicians and professionals who participated in this study:
Mathieu Allez (Paris Saint Louis)
Pauline Belenotti (Marseille)
Denis Caillot (Dijon)
Frederick Christy (Marseille)
Catherine Cordonnier (Créteil)
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Compliance with ethical standards

This study was performed in accordance with the ethical guidelines of the 1975 Declaration of Helsinki. Informed consent was obtained from all patients before AHSCT.

Disclosures None.

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