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LATE COMPLICATIONS AFTER AUTOLOGOUS HSCT FOR AUTOIMMUNE DISEASES: a retrospective survey from the Autoimmune Diseases Working Party (ADWP), Transplant Complications Working Party (TCWP) and Paediatric Diseases Working Party (PDWP) of the European Society for Blood and Marrow Transplantation (EBMT)

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Abstract

Background: Autologous hematopoietic stem cell transplantation (aHSCT) has evolved as a treatment for severe autoimmune diseases (ADs). Advances in transplant procedures and supportive care have led to improvements in long-term survival but there is limited data on 'late effects'.

Objective: The aim of this retrospective EBMT registry study is to assess the incidence of 'late effects' after aHSCT for ADs.

Results: All EBMT centers were invited and data were received for 579 patients (median age 37 years, range 2.7-73.8), who received aHSCT between 1997 and 2016. Median follow-up was 89 months (IQR 82.4-95.5). Indications included multiple sclerosis (MS, 46.8%), systemic sclerosis (SSc, 28.7%), Crohn's disease (CD, 12.6%), systemic lupus erythematosus (SLE, 2.4%) and other ADs (9.5%). Conditioning was mainly based on Cy/ATG (51.9%) or BEAM/ATG (25.3%). At 10-years, the cumulative incidence of secondary ADs was 10.3% (95% CI: 7.7-13.3), new post-transplant cancers 4.1% (95% CI: 2.2-6.8), endocrine complications 16.2% (95% CI: 12.6-20.1), and cardiovascular complications 14.7% (95% CI: 11.2-18.6). Median time to endocrine events (15.4 months) was generally sooner than median times to secondary ADs (24.5 months) and cardiovascular (25.3 months), with new cancers occurring relatively late (median time 81.7 months). Overall, at 10-years, progression-free survival (PFS) was 40.1% (95% CI: 34.7-45.4), overall survival (OS) 83.5% (95% CI: 79.3-86.9) and non-relapse mortality (NRM) 5.0% (95% CI: 3.2-7.4). By multivariate analysis, secondary ADs were relatively higher in CD vs SSc (HR=4.93, p=0.01) and MS (HR=2.05, p=0.055), while cardiovascular complications were significantly increased in SSc compared to MS (HR=8.85, $p<10^{-3}$) or CD (HR=3.45, p=0.016). The incidence of post-aHSCT cancers was related to increasing age (HR per 10y=2.26, $p<10^{-3}$), without significant association with disease type. Incidence of endocrine complications were significantly lower in SSc compared to MS (HR=0.35, p=0.027) and CD (HR=0.33, p=0.041) and significantly more frequent in females (HR=4.27, $p<10^{-3}$).

Conclusions: Autologous HSCT for ADs is associated with a cumulative burden of non-infectious late complications, including thyroid dysfunction, osteoporosis, cardiovascular complications, gonadal dysfunction, secondary ADs and subsequent cancers. These impact all ages of patient and vary depending on AD indication, reflecting disease characteristics and other treatments. This study highlights the importance of screening, monitoring, and treatment of late effects in this setting.

Key words: autoimmune diseases, autologous haematopoietic stem cell transplantation, late effects

Introduction

Over the last several decades, autologous haematopoietic stem cell transplantation (aHSCT) has emerged as a treatment strategy for severe and refractory autoimmune diseases (ADs) [1-3]. Most of transplants are performed for MS and SSc, currently the two 'standard' indications for aHSCT in ADs according to the recent EBMT guidelines [4].

In common with aHSCT for hematologic malignancies, use of this treatment in ADs may be associated with late complications or so called 'late effects'. The term 'late effects' has been defined by the US National Cancer Institute (NCI) as: "[A] health problem[s] that occur[s] months or years after a disease is diagnosed or after treatment has ended. Late effects may be caused by cancer or cancer treatment. They may include physical, mental and social problems, and second cancers" [5]. For the purposes of this study, this definition will be extended to non-malignant disorders i.e. autoimmune diseases treated with aHSCT.

International guidelines and recommendations cover screening and management of 'late effects' following HSCT [6, 7]. While some of these complications (e.g., cardiovascular complications, end-stage renal disease, new cancers) may contribute to late non-relapse mortality among transplant survivors, others (e.g., premature ovarian failure, avascular necrosis) may not directly impact mortality but can impair quality of life (QoL) [8]. Late effects following aHSCT result not only from the transplant regimen and the potentially beneficial altered post-transplant immune reconstitution generated [9], but inevitably there are also varying contributions from previous immunosuppressive therapies and underlying autoimmune disease along with progressive age-related effects.

Since 2012 'late effects' follow-up has been highlighted in the EBMT guidelines and recommendations for HSCT in ADs [3,10], but published analyses are very limited in patients treated with aHSCT for ADs. Recent disease specific retrospective studies have documented the incidence of some late complications and causes of late non-relapse mortality [11-13]. In addition, an increased incidence of secondary autoimmune diseases has been reported after aHSCT for ADs, either *de novo* or within the spectrum of the original AD [3,8,9]. However, the impact of these complications on long-term survivors and on late non-relapse mortality (NRM) requires further characterization for implementation of best clinical practice in order to improve outcomes. Given that the ADs have become the fastest growing indication group for aHSCT [4], and, inevitably, as numbers of aHSCT survivors are continuously increasing, the incidence and

prevalence of 'late effects' will be an evolving issue. Scoping the scale of the problem, detailed information on the long-term follow up for this patient group will be of value in clinical decision-making and service planning prior to aHSCT and in informing future clinical trials across various ADs.

Methods

The study was designed as a retrospective, multicenter study analyzing data available in the European Society for Blood and Marrow Transplantation (EBMT) registry and additional information requested in a specifically designed questionnaire. EBMT centres are required to obtain signed informed consent from patients for transfer of de-identified data in accordance with data protection regulations. As per EBMT procedures, this study was formally approved by the ADWP.

The aims were to investigate the nature, incidence and prevalence of 'late effects' occurring after aHSCT for ADs. Risk factors for the development of 'late effects' related to the patient, disease and treatments, were investigated. The study focused on newly occurring cancers, secondary ADs, cardiovascular events, endocrine/reproductive failure and bone events occurring at any stage following aHSCT in patients (adults and paediatrics). Mortality beyond day +100 was also evaluated.

All EBMT centers were invited to participate and report data from patients with ADs who received the first aHSCT between 1997 and 2016. We excluded patients treated with aHSCT performed primarily for other diseases than ADs and patients treated with a combination of autologous and allogeneic HSCT.

Late effects were defined as first event if the patient experienced several events in one category of: 1) 'any new cancer' (defined as any appearance of biopsy-proven malignant disease after aHSCT); 2) 'Secondary autoimmune diseases' (defined as any appearance of a new autoimmune disease developing after auto-HSCT. i.e. autoimmune manifestations occurring after the date of the aHSCT which had not been recorded pre-aHSCT); 3) 'Cardiovascular event' (defined as any new diagnosis and event developing after aHSCT, including ischaemic cardiac disease, dysrhythmia, cardiac failure and/or cardiomyopathy, cerebrovascular events (ischaemic or haemorrhagic stroke), peripheral vascular disease, venous thrombo-embolism or other well-defined cardiovascular disease); 4) 'Endocrine and bone event' (defined as any new diagnosis of endocrinopathy (including clinical/subclinical/biochemical +/- evidence of autoimmunity

developing after aHSCT, including thyroid disease, type I or II diabetes mellitus, or other evidence of insulin resistance, gonadal and reproductive dysfunction, including biochemical compensated hypogonadism, change in menstrual status (date of last menstrual period/menopause) for females, and infertility, adrenal failure (steroid related and non-steroid related), pituitary failure (anterior or posterior pituitary), growth impairment in children and adolescents, or endocrine neoplasia, or osteoporosis/osteopenia, based on DEXA scanning if performed, other well-defined endocrine or bone disease). There was the potential of a steering committee to adjudicate categories, if necessary. Items reported outside the above categories were not used as a defining primary endpoint late effect 'event' in the statistical analysis.

The primary objective of the study was to define the cumulative incidence of late effects, and risk factors for their development, after aHSCT for width spectrum of ADs including multiple sclerosis (MS), systemic sclerosis (SSc), Crohn's disease (CD), systemic lupus erythematosus (SLE) and other ADs. Secondary endpoints included overall survival (OS), relapse or progression of the primary AD (RI), Progression-Free Survival (PFS), NRM and the incidence of each specific category of event occurring after aHSCT.

OS was defined as the time from aHSCT to death, regardless of the cause. PFS was defined as survival without evidence of relapse or progression. NRM was defined as death without relapse or progression. Cumulative incidence was used to estimate the endpoints of NRM, RI, and all late effects to accommodate for competing risks, death being the competing event for each late effect. Probabilities of PFS and OS were calculated using the Kaplan-Meier method. Univariate analyses were done using the Gray's test for cumulative incidence functions and the log rank test for OS and PFS. A multivariate analysis adjusting for potential confounding factors was performed using a Cox's proportional-hazards regression model for each specific late effect occurring after aHSCT. Results were expressed as the hazard ratio (HR) with the 95% confidence interval (95% CI). All tests are 2-sided. The type I error rate is fixed at 0.05 for the determination of factors associated with time-to-event outcomes. Statistical analyses were performed with R 4.2.3 (R Core Team (2023).

Results

Study cohort and transplant procedure

Data were received for 579 patients (median age 37 years, range 2.7-73.8) from 29 centers in 11 countries (Italy, United Kingdom, Germany, Spain, France, the Netherlands, Russia, Australia,

Belgium, Colombia, and Czech Republic, in descending order of contribution). Patient, disease and transplant characteristics are summarized in table 1.

Patients received aHSCT for severe ADs between 1997 and 2016. Overall, 4.3% (n= 25) were children below 18 years. Females were 378 (65.3%) and males 201 (34.7%). Indications included multiple sclerosis (MS, 46.8%), systemic sclerosis (SSc, 28.7%), Crohn's disease (CD, 12.6%), and systemic lupus erythematosus (SLE, 2.4%) and other ADs (9.5%). Median follow-up was 89 months (IQR 82.4-95.5).

Graft source consisted mainly of peripheral blood stem cells (PBSCs) in 568 cases (98.3%), mobilized with cyclophosphamide (Cy) and granulocyte colony-stimulating factor (G-CSF) in 518 cases (93%). Ex-vivo manipulation of the cells was performed in 181 patients (31%), with CD34+ selection for all patients, predominantly in patients with SSc (69%), reflecting previous and current evidence-based best practice guidelines [21,22]. Most patients (n=558, 96.5%) achieved standard haematopoietic recovery and engraftment criteria successfully.

Conditioning regimen was mainly based on Cy/ATG (n=300, 51.9%) or BEAM/ATG (n=146, 25.3%). ATG was given in 500 patients (88.5%), mainly from rabbit (83.2 %), horse (14.7%), and goat (1.2%). As rATG-brand is not entered directly into the EBMT registry, it was deduced by total dose range of rATG entered: for this dataset rATG-brand Thymoglobulin^{TM} (dose ≤15 mg/kg), n=378, median dose (range) = 7.5 mg/kg (2.2-15), rATG-brand Grafalon^{TM} (dose >15 mg/kg), n=31, median dose (range) = 30 mg/kg (20-90), hATG, n=73, median dose (range) = 60 mg/kg (15-160).

Overall, across all types of ADs at 10-years post-transplant, OS was 83.5% [95% CI: 79.3-86.9], PFS 40.1% [95% CI: 34.7-45.4] and NRM 5.0% [95% CI: 3.2-7.4], with relapse incidence of 54.9% [95% CI:49.3-60.1]. By 6 months post-transplant, the cumulative incidence for all short-term transplant-related severe non-infectious toxicities including respiratory insufficiency, cardiotoxicity, haemorrhagic cystitis, serotonin syndrome, multiorgan failure, anaphylactic shock, cerebral hemorrhage, interstitial pneumonitis, pulmonary oedema, ATG toxicity and ARDS, was 4.5% [95% CI: 2.9-6.5].

Late effects

a) *Incidence across all ADs, with relative frequencies*

Across all ADs, at 10-years the cumulative incidence for secondary ADs was 10.3% [95% CI: 7.7-13.3], cardiovascular complications 14.7% [95% CI: 11.2-18.6]. newly-diagnosed cancers 4.1% [95% CI: 2.2-6.8] and endocrine complications 16.2% [95% CI: 12.6-20.1] (figure 1). Median time from aHSCT to late effects event are presented in table 2, with endocrine events occurring sooner than secondary ADs and cardiovascular events, and new cancers occurring relatively late, with a wide range of variability for all complications.

Post-aHSCT cancers were confirmed in 21 cases out of 533 patients with available data. In this group, non-melanoma skin cancer (NMSC) was the most common cancer (23.8%) with other solid tumours (47.8%) and haematological malignancies (28.6%).

Secondary ADs were found in 57 patients out of 539 patients with available data (51 patients with 1 secondary AD, 5 patients with 2 secondary AD, and 1 patient with 3 secondary AD). In this group, autoimmune thyroid disease was the most common secondary AD (57.1%), then secondary rheumatic AD (14.3%), haematological AD (12.7%), neurological AD (4.8%), gastrointestinal AD (3.2%) and various other types of secondary ADs in the remainder (7.9%).

Cardiovascular complications post-aHSCT were found 71 patients out of 546 patients with available data (48 patients with 1 cardiovascular complication, 14 with 2 complications, 4 with 3, 4 with 4 complications, and 1 patient with 5 cardiovascular complications). In this group, arrhythmia was the most common cardiovascular complication (30.8%), followed by cardiac failure (17.0%), ischaemic heart disease (9.5%), thrombotic events (8.5%), with various other cardiovascular complications in the remainder (34%).

Endocrine complications were found in 85 patients out of 478 patients with available data (66 patients with 1 complication, 12 with 2, 5 with 3, 1 patient with 4 and 1 with 5 complications). Gonadal and reproductive dysfunction was the most common endocrine/bone late effect (43.9%), then osteoporosis/osteopenia (28.1%), non-AD thyroid disease (15.8%) and other endocrine late effects in the remainder 12.3%.

Incidence of late effects according to conditioning regimen (Cy/ATG vs BEAM/ATG) is presented in table 3. Incidence of endocrine late effects were higher in BEAM/ATG group ($p=0.003$) and cardiovascular – in Cy/ATG group ($p=0.001$). However, because baseline (and potentially subsequent) cardiovascular disease is an intrinsic feature of SSc, a separate analysis in MS patient cohort was conducted (table 4), which showed no difference for cardiovascular

events between Cy/ATG versus BEAM+ATG, supporting the higher incidence of cardiovascular events with Cy/ATG in the analysis of the overall cohort to be best explained by the almost universal (79.5%) use of Cy/ATG conditioning in the SSc group (table 5).

With respect to paediatric patients (<18 years), there was limited information, but the number of late complications reported in the 25 children transplanted were 4 cardiovascular, 2 endocrine, 1 secondary AD, and no secondary malignancy. No information was available on growth and development.

With respect to reproductive health, we cannot provide a precise data on women who conceived because the EBMT registry does not routinely collect information on the desire for children, on fertility issues or infertility treatments and their outcomes. Successful pregnancy outcomes were reported in 7 women (median age 30 years, range 24-37). No men were reported as fathering children post-transplant, but this data is not routinely collected in the EBMT registry. In both sexes/genders this is a multifactorial issue which depends upon a variety of factors, including age, personal preference, partner status, and gamete/embryo cryopreservation prior to aHSCT.

b) *Cumulative incidence for specific ADs*

Cumulative incidence of secondary ADs, cardiovascular complications, post-aHSCT cancer and endocrine complications per disease are illustrated on figure 2a, 2b, 2c and 2d, respectively.

c) Multivariate analysis in relation to specific groups

By multivariate analysis comparing relative incidence among the main AD groups, secondary ADs were most pronounced in CD vs SSc (HR=4.93, 95% CI: 1.47-16.5, p=0.01) and MS (HR=2.05, 95% CI: 0.99-4.26, p=0.055), while cardiovascular complications were significantly increased in SSc compared to MS (HR=8.85, 95% CI: 3.53-22.2, $p<10^{-3}$) or CD (HR=3.45, 95% CI: 1.25-9.09, p=0.016). The incidence of newly-diagnosed post-aHSCT cancers was related to increasing age (HR per 10y=2.26, 95% CI: 1.4-3.7, $p<10^{-3}$), without significant association with any specific AD. Incidence of endocrine complications were significantly lower in SSc compared to MS (HR=0.35, 95% CI: 0.14-0.89, p=0.027) and CD (HR=0.33, 95% CI: 0.11-0.95, p=0.041), and significantly more frequent in females (HR=4.27, 95% CI: 1.91-9.55, $p<10^{-3}$).

Discussion

This is the first large retrospective multicenter study reporting the incidence of late effects and long-term complications in children and adults who underwent aHSCT for ADs. The study also

reported PFS, OS and NRM. Our analysis showed a cumulative incidence over 10 years post-aHSCT of a range of late effects including secondary ADs (10.3%), newly-diagnosed cancers (4.1%), endocrine/bone complications (16.2%), and cardiovascular complications (14.7%). Median time to endocrine events (15.4 months) was generally sooner than median times to secondary ADs (24.5 months) and cardiovascular (25.3 months), with new cancers occurring relatively late (median time 81.7 months), although there was a wide range of variability for all complications.

Data on safety and efficacy of aHSCT for ADs both in children and adults have been reported over the years in many analyses [10-16]. However, only limited data were previously reported according to the long-term outcomes and late effects of aHSCT for ADs. Studies reported width spectrum of secondary ADs (0 – 12%) and newly-diagnosed cancers (0 – 5.6%) for MS, but have been relatively limited in numbers across all AD types. This study is the largest to date where the focus has been on incidence and type of late effects following aHSCT, including 579 patients with good quality data in different ADs from the EBMT registry, allowing both assessment of late effects in ADs overall, and comparative analysis between the commoner disease indications.

This large study offers novel and clinically-useful information, although, as with most EBMT registry analyses, the retrospective multi-center data collection, its completeness and analysis are associated with inevitable limitations.

Firstly, the sample reflected actively responding EBMT centers, and not every center that had registered patients treated with aHSCT for ADs between 1997-2016. Even so, the data completion from the 29 participating centers for that period provided good numbers with clinically meaningful long-term follow up data for this study. Although it reflected a historical cohort and not necessarily the risks of patients treated in the current era, these observations will remain relevant to the modern treatment of patients, particularly as conditioning regimens have not changed greatly between treatment guidelines [17-21], with over three-quarters of patients in this study being treated with ‘standard’ cyclophosphamide/ATG or BEAM/ATG conditioning, and other types and intensities of regimens being variable and infrequent for meaningful analysis.

Secondly, it is challenging to separate primary disease-related aspects from ‘late effects’ of aHSCT, particularly in multisystem diseases, and/or where some patients have received multiple lines of treatment before aHSCT. Only carefully designed prospective studies and clinical trials

incorporating detailed baseline and repeated assessments can realistically define the 'late effects' impact of aHSCT. However, this retrospective analysis helps to inform such future studies.

Thirdly, the study did not include early or late infectious events. These, however, should be recognized as ongoing late problems that may affect both the quality and quantity of life. Rather than being incorporated into the present analysis, they were considered more appropriately as the focus of a separate registry-based study to be conducted subsequently.

Other limitations included lack of routinely collected data on reproductive health and pregnancy, and small numbers of paediatric patients (<18 years), and associated growth and development, in this predominantly adult patient cohort.

Interestingly, the analysis highlighted some relative differences in the incidence of 'late effects' between major AD categories, which are worthy of discussion and further evaluation. The increased rate of reported late cardiovascular complications in patients with SSc compared to those with MS or Crohn´s disease is expected, given the multisystemic nature of SSc. This likely reflects the inherent cardiovascular risks in SSc patients [22, 23] and illustrates a limitation of a retrospective registry-based study in distinguishing disease-related cardiovascular effects from the acquired 'late effects' of aHSCT. In the analysis of the overall AD cohort (table 3), there was a higher incidence of cardiovascular complications with Cy/ATG conditioning, best explained by baseline (and potentially subsequent) intrinsic cardiovascular disease in SSc. The impact of Cy/ATG was not seen in the separate analyses (tables 4 & 5) of the large sub-group of patients with MS, where the use of cyclophosphamide-based conditioning was not associated with an increase late cardiovascular events in ADs (such as MS) where there is no intrinsic cardiovascular disease process.

As expected, the incidence of post-aHSCT cancers was significantly associated with increasing age per decade, although no significant relationship was observed with disease indication. Cancer incidence naturally increases with age in the general population, and it was beyond the scope of this analysis to determine whether any excess risk exists in the transplanted AD population. Future studies, potentially using propensity matching or other comparative approaches, will help to assess cancer incidence relative to the general or non-transplanted AD populations and to better evaluate additional risk factors.

Endocrine complications were highly significantly increased in females, although the increased incidence in MS is not so clear. The relatively increased incidence of secondary ADs in patients with Crohn's disease compared with SSc and MS is less easily explained and could be the focus of further investigation.

These novel retrospective observations provide a strong rationale for detailed prospective collection of baseline and longitudinal data to better define the additional and cumulative burden of 'late effects' for each disease over time following aHSCT.

In terms of immediate impact, this study strongly supports routine screening, monitoring, and early interventional management of late effects after aHSCT for ADs, as well as the continued, detailed collection of registry data over an indefinite timeline. Future guidelines for harmonization of late-effects monitoring following aHSCT for ADs are needed, and, in addition to improving detection rates and pre-emptive management strategies, will also promote standardized data reporting to the EBMT registry for ADs. Such guidelines should build upon - but remain distinct from - the generic EBMT-CIBMTR guidelines [7], given the specific considerations for patients with ADs versus patient with malignant diseases. Ideally, prospective observational studies should be performed in this field, and with the increasing number of clinical trials in common AD indications such as MS and SSc, there are opportunities to integrate 'late effects' monitoring into trial protocols to generate high quality, disease-specific data.

In summary, aHSCT for ADs in adults and children is associated with a cumulative burden of non-infectious late complications, including cardiovascular complications, endocrine dysfunction, secondary ADs and newly-diagnosed cancers, with incidence varying with disease type. Although not all 'late effects' can be solely attributed to the aHSCT procedure, as many patients will have received various immunosuppressive and other treatments prior to aHSCT, these data enable estimation of the magnitude of risks over the years following aHSCT for various ADs and highlight the importance of routine screening, monitoring, and proactive management of late effects in this setting. These findings will support development of specific guidelines for 'late effects' monitoring and data registry reporting. Based on this analysis, it is clear that teams must remain vigilant and reactive for late effects at any point in the follow-up. Whilst is it not possible to mandate the optimum model of follow-up care, annual screening for late effects from 12 months (ideally, indefinitely) would be sensible and methodical in order to capture the majority of late endocrine, secondary AD, cardiovascular and newly-diagnosed cancer events, so that correction of risk factors, lifestyle advice and early interventions for

established disease can be effectively delivered. As the evidence base in the field of haematopoietic cellular therapy in autoimmune diseases evolves further, prospective studies of late effects are warranted, and late effects monitoring and long-term follow up should be integrated into clinical trials. Further analyses should include matched studies with general population and non-transplanted disease cohorts to evaluate the 'excess' late' risks of aHSCT.

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28835464.

Table 1. Patient, disease and transplant characteristics

Characteristics		**Overall (range)**
Median Age [IQR] at transplantation		37 [29.3-46.5] years
Male/Female, N(%)		201 (34.7%) / 378 (65.3%)
Disease type, N (%)		
	MS	271 (46.8%)
	SSc	166 (28.7%)
	Crohn	73 (12.6%)
	SLE	14 (2.4%)
	Other AD	55 (9.5%)
Graft source		
	PBSC	568 (98.3%)
	BM	9 (1.6%)
	BM+PB	1 (0.2%)
	missing (n=1)	
Mobilization		
	Cyclophosphamide+G-CSF	518 (93%)
	G-CSF alone	39 (7%)
	Missing (n=12)	
Conditioning Regimen		
	Cy/ATG	300 (51.9%)
	BEAM/ATG	146 (25.3%)
	Cyclophosphamide	41 (7.1%)
	Cyclophosphamide+BCNU+ATG	17 (2.9%)
	Cyclophosphamide+thiotepa	15 (2.6%)
	BEAM	10 (1.7%)
	Other regimen	49 (8.6%)
	missing (n=1)	
ATG type		
	Rabbit	416 (83.2%)
	Horse	73 (14.6%)
	Horse then Rabbit	1 (0.2%)
	Goat	6 (1.2%)
	missing (n=4)	

Table 2. Median time from aHSCT to event, (range) [IQR]

Event	Months
Cardiovascular event	25.3 (0,03-214,5) [6,6-78,4]
Endocrine event	15.4 (0,03-234,3) [5,2-43,4]
Secondary AD	24.5 (0,2-214,0) [9,8-51,3]
Post-aHSCT cancer	81.7 (13,9-235,0) [38,4-137,3]

Table 3. Incidence of late effects according to conditioning regimen (Cy/ATG vs BEAM/ATG)

	conditioning	sec. AD	Endocrine	Cardiovascular	Post-aHSCT cancer
1 y	Cy/ATG	1.8%[0.7-3.9]	5.1%[2.9-8.1]	6%[3.6-9.2]	0%
	BEAM/ATG	3.6%[1.3-7.7]	9%[3.9-16.6]	0%	0%
5 y	Cy/ATG	8.5%[5.6-12.2]	9.4%[6.2-13.3]	11.8%[8.2-15.9]	0.8%[0.2-2.6]
	BEAM/ATG	10.9%[5.9-17.5]	24.1%[14.7-34.9]	1.5%[0.3-4.9]	4.4%[1.6-9.5]
10y	Cy/ATG	11.2%[7.4-15.9]	11.3%[7.3-16.1]	19.7%[14-26.1]	3.8%[1.2-8.7]
	BEAM/ATG	10.9%[5.9-17.5]	24.1%[14.7-34.9]	1.5%[0.3-4.9]	4.4%[1.6-9.5]
	P value	0,56	0,003	0,001	0,14

Table 4. Analysis of cardiovascular events in MS group

MS	**1 y**	**5 y**	**10 y**
Cy/ATG	2.8%[0.5-8.8]	4.2%[1.1-10.8]	4.2%[1.1-10.8]
BEAM/ATG	0%	1.5%[0.3-4.9]	1.5%[0.3-4.9]
P value	0.21	0.21	0.21

Table 5. Types of conditioning regimens in MS and SSc groups

Conditioning regimen	**MS (n=218)**	**SSc (n=132)**	P
Cy/ATG	72 (33%)	132 (100%)	< 0.0001
BEAM/ATG	146 (67%)	0 (0%)	

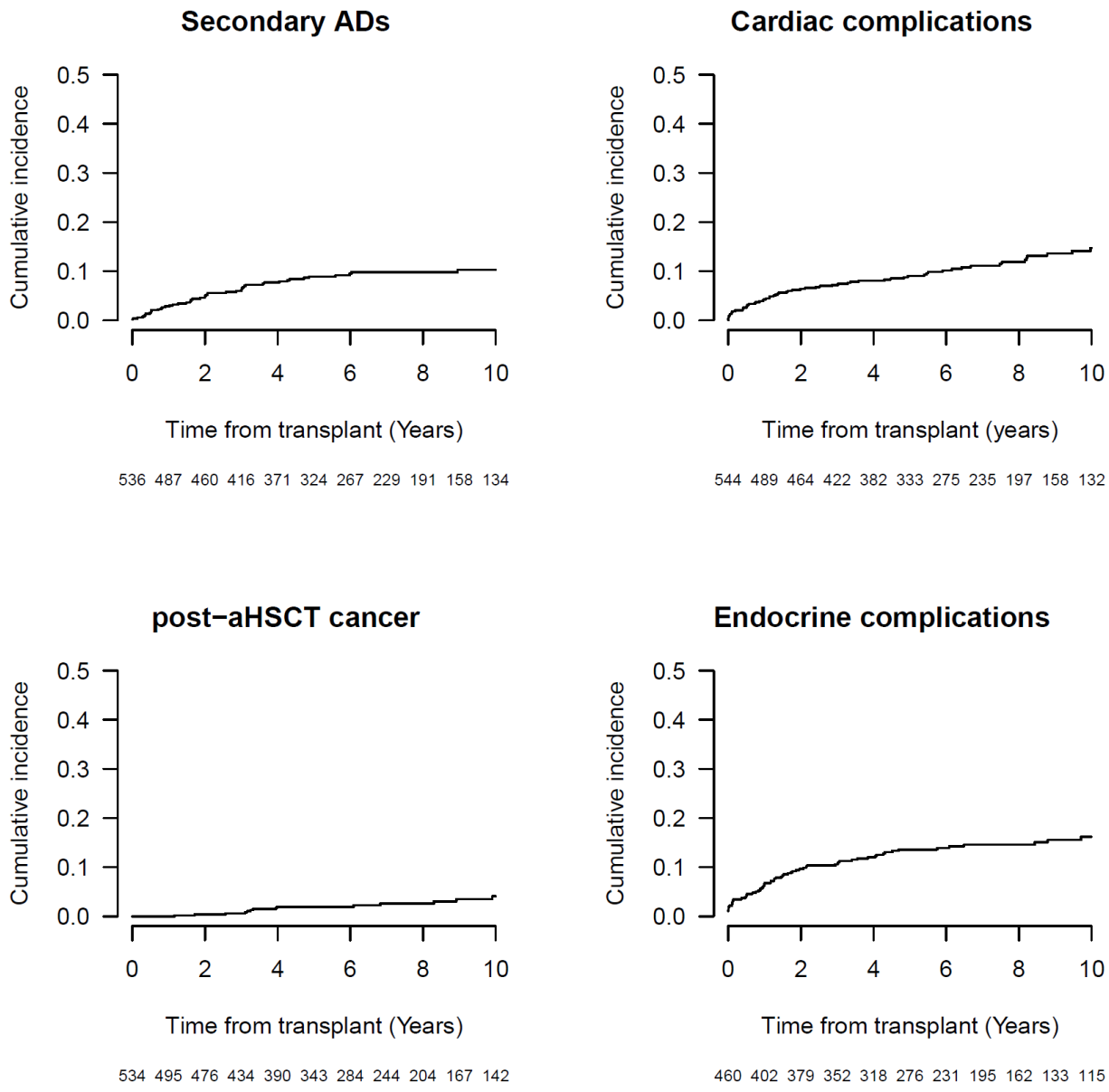


Figure 1. Cumulative incidence of late effects at 1, 5 and 10 years (secondary autoimmune disease, 2.8% (95% CI, 1.7-4.5), 8.9% (95% CI, 6.6-11.7) and 10.3% (95% CI, 7.7-13.3); cardiovascular complications, 4.3% (95% CI, 2.8-6.2), 9% (95% CI, 6.7-11.7) and 14.7% (95 CI, 11.2-18.6); post-aHSCT cancer, 0%, 1.9% (95% CI, 1-3.5) and 4.1% (95% CI, 2.2-6.8) and endocrine complications, 6.8% (95% CI, 4.7-9.3), 13.6% (95% CI, 10.6-17) and 16.2% (95% CI, 12.6-20.1).

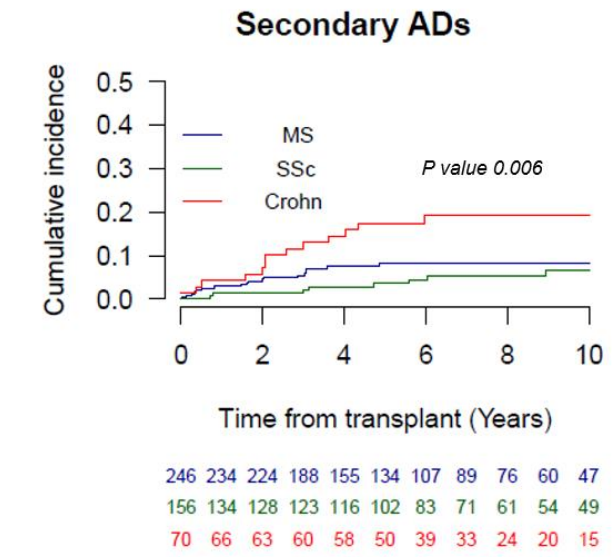


Fig 2a. Cumulative incidence of secondary ADs per disease. Cumulative incidence of secondary AD at 1, 5 and 10 years were as follows: MS, 2.9% (95% CI, 1.3-5.5), 8.1% (95% CI, 5-12.3) and 8.1% (95% CI, 5-12.3); SSc, 1.4% (95% CI, 0.3-4.4), 3.6% (95% CI, 1.3-7.6) and 6.6% (95% CI, 3-12.2); CD, 4.3% (95% CI, 1.1-10.9), 17.4% (95% CI, 9.5-27.2) and 19.4% (95% CI, 10.8-29.7).

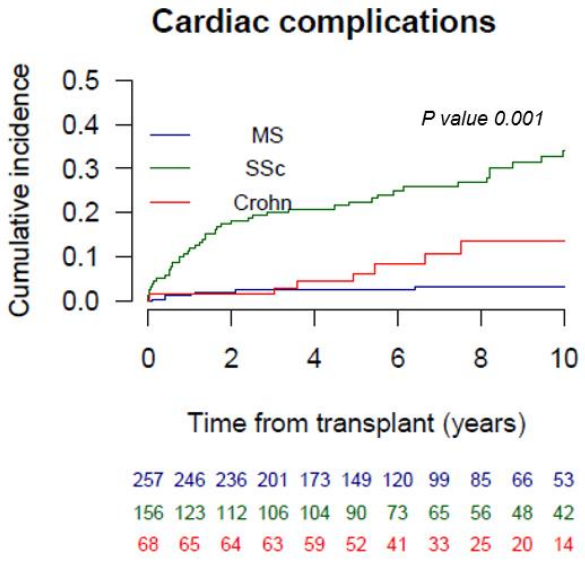


Figure 2b. Cumulative incidence of cardiovascular complications per disease. Cumulative incidence of cardiovascular complications at 1, 5 and 10 years were as follows: MS, 1.2% (95% CI, 0.3-3.2), 2.4% (95% CI, 1-4.9) and 3.3% (95% CI, 1.4-6.5); SSc, 12% (95% CI, 7.4-17.7), 22.3% (95% CI, 16-29.4) and 34% (95% CI, 25.5-42.6); Crohn, 1.5% (95% CI, 0.1-7.1), 6.3% (95% CI, 2-14.1) and 13.6% (95% CI, 5.7-25.1).

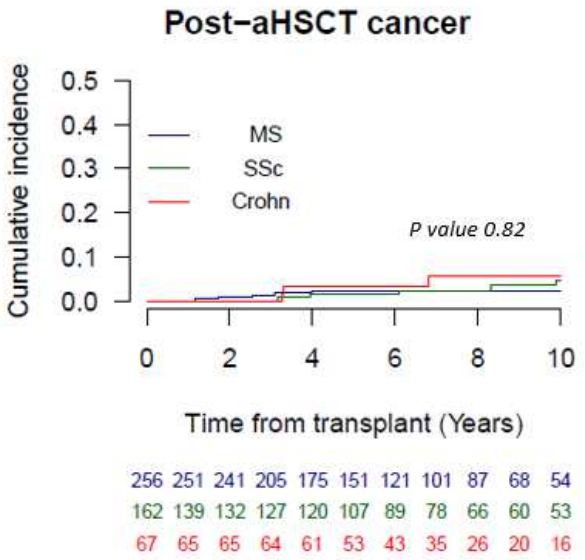


Fig.2c. Cumulative incidence of post-aHSCT cancer per disease. Cumulative incidence of newly-diagnosed cancer at 1, 5 and 10 years were as follows: MS, 0%, 2.3% (95% CI, 0.8-5) and 2.3% (95% CI, 0.8-5); SSc, 0%, 1.4% (95% CI, 0.3-4.5) and 4.7% (95% CI, 1.7-10.2); Crohn, 0%, 3.1% (95% CI, 0.6-9.6) and 5.5% (95% CI, 1.4-14.3).

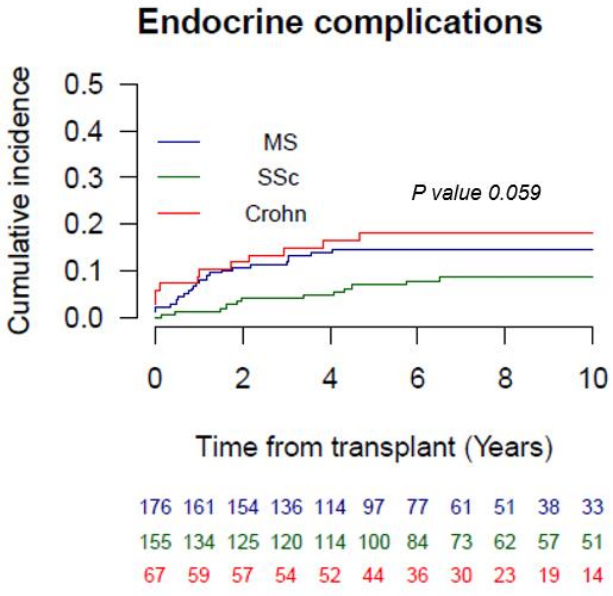
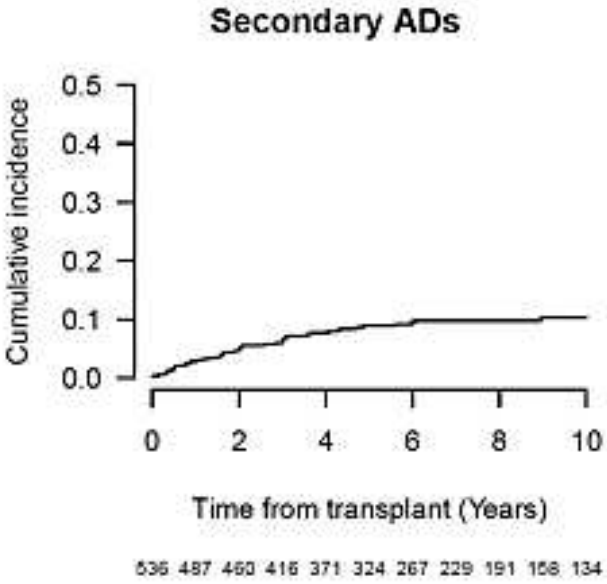
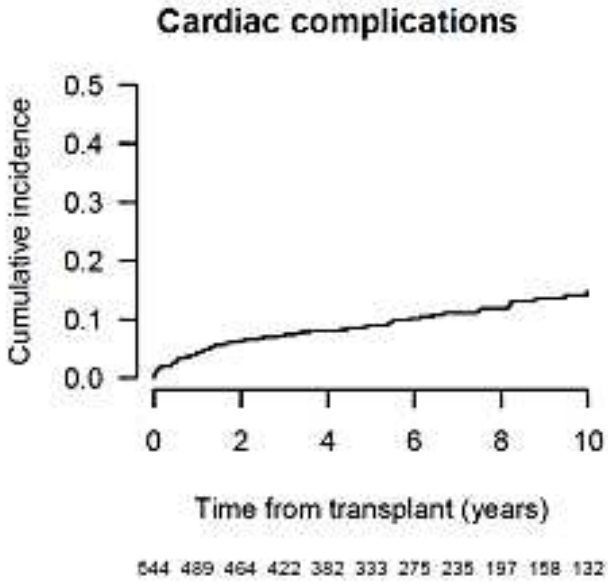
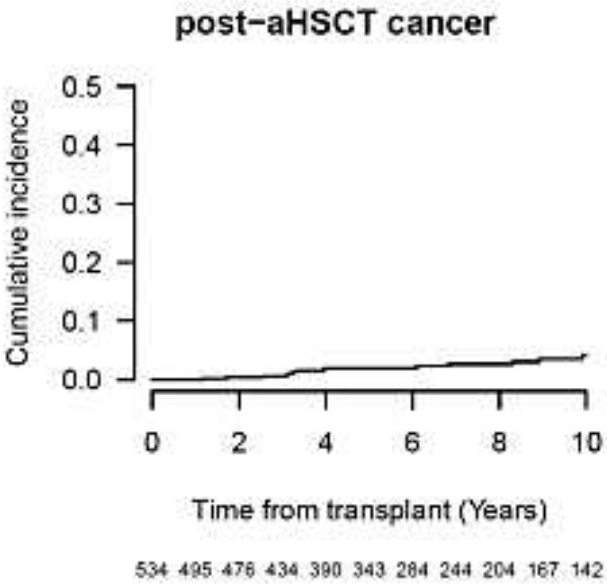


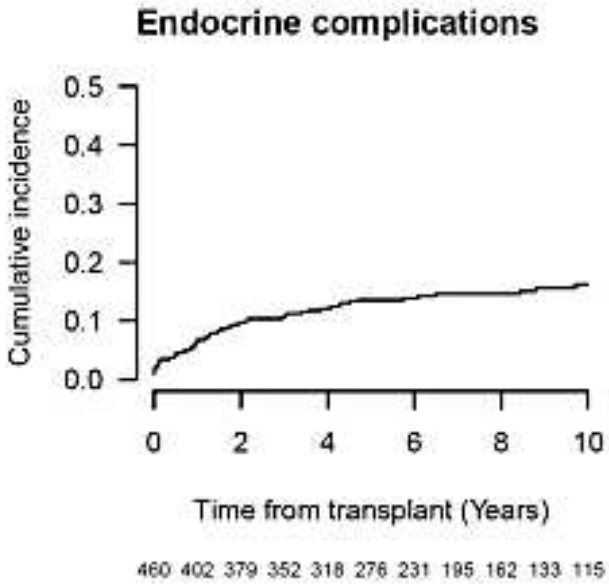
Fig. 2d. Cumulative incidence of Endocrine complications per disease. Cumulative incidence of endocrine complications at 1, 5 and 10 years were as follows: MS, 7.9% (95% CI, 4.5-12.5), 14.7% (95% CI, 9.8-20.5) and 14.7% (95% CI, 9.8-20.5); SSc, 1.3% (95% CI, 0.3-4.4), 7%

(95% CI, 3.6-12) and 8.8 (95% CI, 4.8-14.4); Crohn, 10.3% (95% CI, 4.5-19), 18.2% (95% CI, 9.9-28.5) and 18.2% (95% CI, 9.9-28.5).


Secondary ADs
Cumulative incidence
0.5
0.4
0.3
0.2
0.1
0.0
0
2
4
6
8
10
Time from transplant (Years)
536 487 460 416 371 324 267 229 191 158 134


Cardiac complications
Cumulative incidence
0.5
0.4
0.3
0.2
0.1
0.0
0
2
4
6
8
10
Time from transplant (years)
544 489 464 422 382 333 275 235 197 158 132


post−aHSCT cancer
Cumulative incidence
0.5
0.4
0.3
0.2
0.1
0.0
0
2
4
6
8
10
Time from transplant (Years)
534 495 476 434 390 343 284 244 204 167 142


Endocrine complications
Cumulative incidence
0.5
0.4
0.3
0.2
0.1
0.0
0
2
4
6
8
10
Time from transplant (Years)
460 402 379 352 318 276 231 195 162 133 115

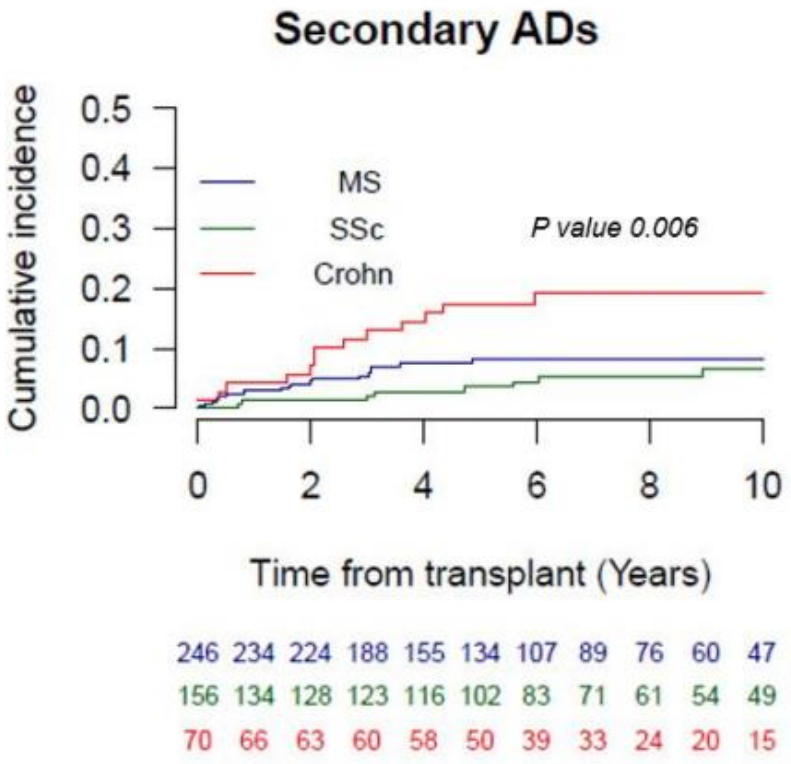

Secondary ADs
Cumulative incidence
0.5
0.4
0.3
0.2
0.1
0.0
MS
SSc
Crohn
P value 0.006
0
2
4
6
8
10
Time from transplant (Years)
246 234 224 188 155 134 107 89 76 60 47
156 134 128 123 116 102 83 71 61 54 49
70 66 63 60 58 50 39 33 24 20 15

Fig 2a.

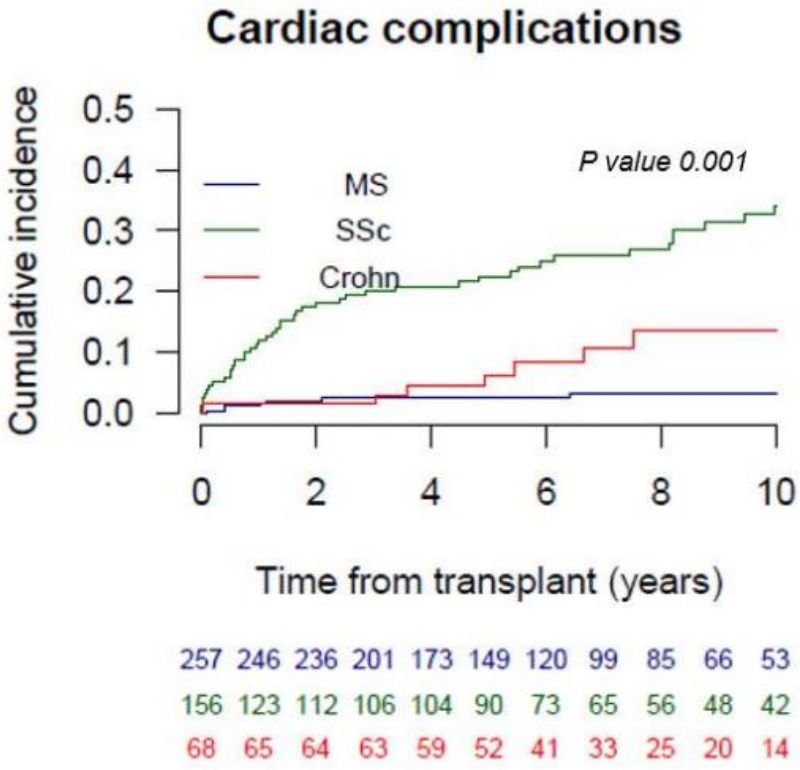

Cardiac complications
Cumulative incidence
0.5
0.4
0.3
0.2
0.1
0.0
MS
SSc
Crohn
P value 0.001
0
2
4
6
8
10
Time from transplant (years)
257 246 236 201 173 149 120 99 85 66 53
156 123 112 106 104 90 73 65 56 48 42
68 65 64 63 59 52 41 33 25 20 14

Fig 2b.

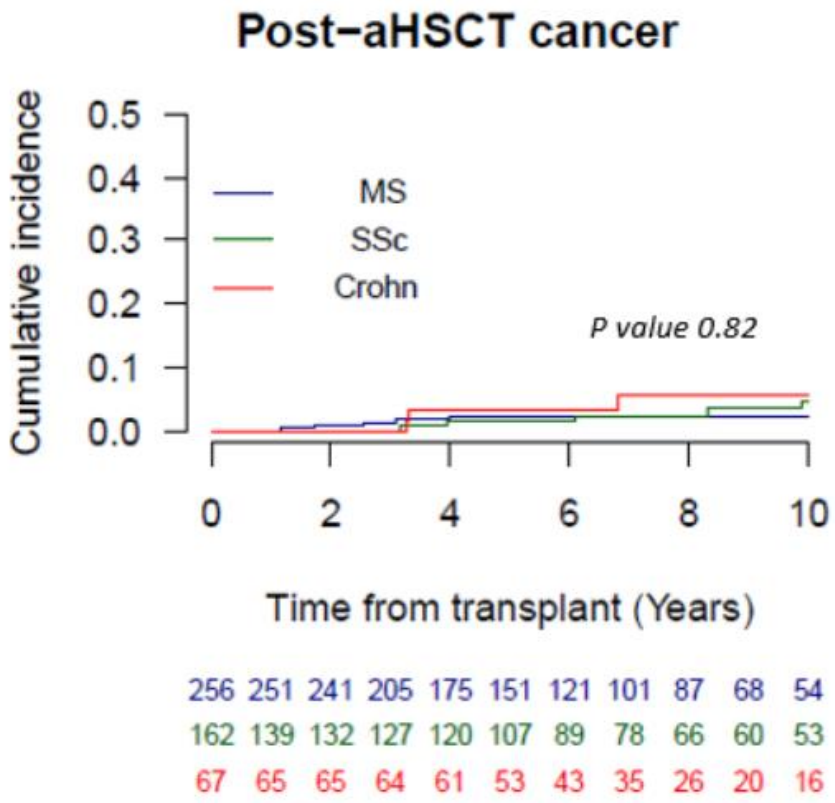

Post−aHSCT cancer
Cumulative incidence
0.5
0.4
0.3
0.2
0.1
0.0
MS
SSc
Crohn
P value 0.82
0
2
4
6
8
10
Time from transplant (Years)
256 251 241 205 175 151 121 101 87 68 54
162 139 132 127 120 107 89 78 66 60 53
67 65 65 64 61 53 43 35 26 20 16

Fig 2c.

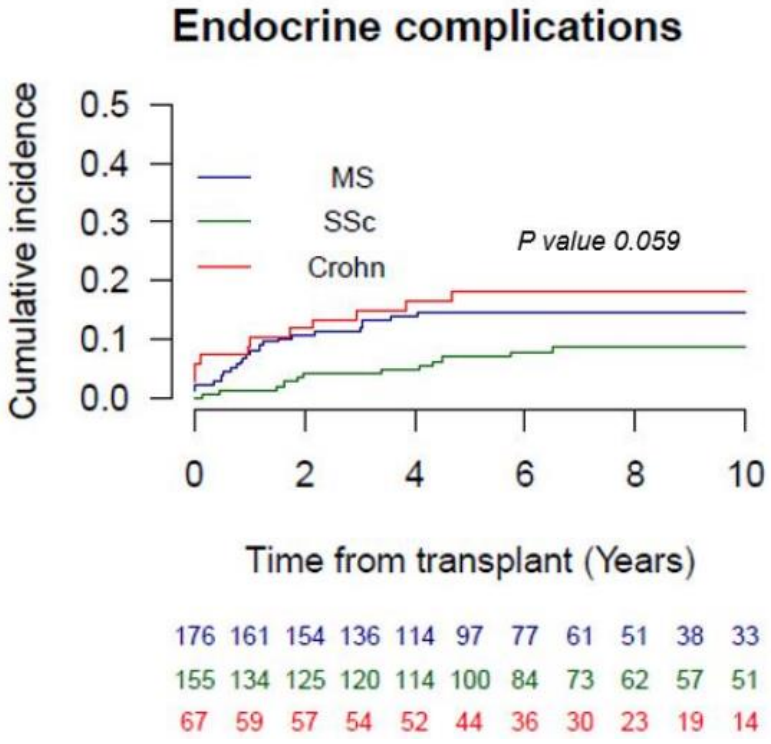

Endocrine complications
Cumulative incidence
0.5
0.4
0.3
0.2
0.1
0.0
MS
SSc
Crohn
P value 0.059
0
2
4
6
8
10
Time from transplant (Years)
176 161 154 136 114 97 77 61 51 38 33
155 134 125 120 114 100 84 73 62 57 51
67 59 57 54 52 44 36 30 23 19 14

Fig 2d.

Table 1. Patient, disease and transplant characteristics

Characteristics		**Overall (range)**
Median Age [IQR] at transplantation		37 [29.3-46.5] years
Male/Female, N(%)		201 (34.7%) / 378 (65.3%)
Disease type, N (%)		
	MS	271 (46.8%)
	SSc	166 (28.7%)
	Crohn	73 (12.6%)
	SLE	14 (2.4%)
	Other AD	55 (9.5%)
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	BM	9 (1.6%)
	BM+PB	1 (0.2%)
	missing (n=1)	
Mobilization		
	Cyclophosphamide+G-CSF	518 (93%)
	G-CSF alone	39 (7%)
	Missing (n=12)	
Conditioning Regimen		
	Cy/ATG	300 (51.9%)
	BEAM/ATG	146 (25.3%)
	Cyclophosphamide	41 (7.1%)
	Cyclophosphamide+BCNU+ATG	17 (2.9%)
	Cyclophosphamide+thiotepa	15 (2.6%)
	BEAM	10 (1.7%)
	Other regimen	49 (8.6%)
	missing (n=1)	
ATG type		
	Rabbit	416 (83.2%)
	Horse	73 (14.6%)
	Horse then Rabbit	1 (0.2%)
	Goat	6 (1.2%)
	missing (n=4)	

Table 2. Median time from aHSCT to event, (range) [IQR]

Event	Months
Cardiovascular event	25.3 (0,03-214,5) [6,6-78,4]
Endocrine event	15.4 (0,03-234,3) [5,2-43,4]
Secondary AD	24.5 (0,2-214,0) [9,8-51,3]
Post-aHSCT cancer	81.7 (13,9-235,0) [38,4-137,3]

Table 3. Incidence of late effects according to conditioning regimen (Cy/ATG vs BEAM/ATG)

	conditioning	**sec. AD**	**Endocrine**	**Cardiovascular**	**Post-aHSCT cancer**
1 y	Cy/ATG	1.8%[0.7-3.9]	5.1%[2.9-8.1]	6%[3.6-9.2]	0%
	BEAM/ATG	3.6%[1.3-7.7]	9%[3.9-16.6]	0%	0%
5 y	Cy/ATG	8.5%[5.6-12.2]	9.4%[6.2-13.3]	11.8%[8.2-15.9]	0.8%[0.2-2.6]
	BEAM/ATG	10.9%[5.9-17.5]	24.1%[14.7-34.9]	1.5%[0.3-4.9]	4.4%[1.6-9.5]
10y	Cy/ATG	11.2%[7.4-15.9]	11.3%[7.3-16.1]	19.7%[14-26.1]	3.8%[1.2-8.7]
	BEAM/ATG	10.9%[5.9-17.5]	24.1%[14.7-34.9]	1.5%[0.3-4.9]	4.4%[1.6-9.5]
	P value	0,56	0,003	0,001	0,14

Table 4. Analysis of cardiovascular events in MS group

MS	**1 y**	**5 y**	**10 y**
Cy/ATG	2.8%[0.5-8.8]	4.2%[1.1-10.8]	4.2%[1.1-10.8]
BEAM/ATG	0%	1.5%[0.3-4.9]	1.5%[0.3-4.9]
P value	0.21	0.21	0.21

Table 5. Types of conditioning regimens in MS and SSc groups

Conditioning regimen	**MS (n=218)**	**SSc (n=132)**	P
Cy/ATG	72 (33%)	132 (100%)	< 0.0001
BEAM/ATG	146 (67%)	0 (0%)	