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ARTICLE

Trends in allogeneic haematopoietic cell transplantation for myelofibrosis in Europe between 1995 and 2018: a CMWP of EBMT retrospective analysis

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Abstract

We performed a retrospective assessment of patient- and transplant-specific characteristics and outcomes for 4142 patients undergoing allogeneic haematopoietic cell transplant for myelofibrosis between 1995 and 2018 across 278 centres. Activity increased steadily across the four analysed eras (<2006, 2006–2010, 2011–2014 and 2015–2018). Median recipient age increased over time between the earliest and most recent cohort (49.4 years (range, 20.1–68) versus 59.3 years (range, 18.1–78.1). Increasing number of patients with a Karnofsky performance status <90 underwent transplant over time. Increased utilisation of matched unrelated donors was apparent (<2006, 22.5% versus 2015–18, 45.2%; $p < 0.001$). Decreased use of myeloablative conditioning, increased use of busulphan-based platforms and anti-thymocyte globulin was evident. Of note, rates of acute (a)GVHD grade II-IV by day +100 decreased over time ($p = 0.027$) as did rates of chronic (c) GVHD, predominantly extensive cGVHD (<2006, 36% (31–41%) versus 2015–18, 23% (21–25%); $p = 0.001$). Overall, significant factors associated with worse overall survival and non-relapse mortality (NRM) remained older age, use of donors other than matched sibling, recipient CMV seropositivity and a lower Karnofsky performance status (<90). Multivariable analysis demonstrated improvements in overall survival and reductions in relapse risk over time with stable NRM rates despite increasing numbers of older, less fit patients and use of unrelated donors.

Introduction

Myelofibrosis (MF), a 'Philadelphia Chromosome negative' myeloproliferative neoplasm (MPN) with an estimated incidence rate of 0.1–1 per 100,000 per year, is a markedly heterogeneous disorder [1]. Clinical phenotypes remain highly varied, ranging from an indolent phase, frequently with an absence of disease-related symptoms or events, through to more advanced phases with profound symptom burdens, bulky splenomegaly, cytopaenias and an inherent risk of transformation to acute leukaemia [2]. Although the last decade has observed major advances in available therapeutic approaches, allogeneic haematopoietic cell transplantation (allo-HCT) remains the only curative approach for patients with higher risk MF. Current combined EBMT/European LeukaemiaNet (ELN) guidelines suggest that "Patients with intermediate-2- or high-risk disease according to the IPSS, DIPSS or DIPSS-plus and age <70 years should be considered potential candidates for allogeneic HCT". Patients with "intermediate-1-risk disease and age <65 years should be considered as candidates if they present with either refractory, transfusion-dependent anaemia, or a percentage of blasts in peripheral blood >2%, or adverse (as defined by the DIPSS-plus classification) cytogenetics [3]. Both EBMT and Center for International Blood and Marrow Transplant Research (CIBMTR) data confirm increasing MF allo-HCT activity over the last two decades, particularly over the last 5–10 years, yet it remains clear that practice with regard to patient selection and indication, transplant-conditioning intensity/protocols, GVHD prophylaxis strategies, use of JAK inhibitors prior to allo-HCT and management of relapse varies

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markedly [4–6]. We hereby report on a dynamic assessment of trends over time in patient- and transplant-specific characteristics and outcomes for patients undergoing first allo-HCT for MF registered within the EBMT society between 1995 and 2018.

Methods

This was a retrospective, multicentre, registry-based analysis approved by the Chronic Malignancies Working Party of EBMT. The EBMT is a non-profit, scientific society representing more than 600 transplant centres mainly in Europe. Data are entered, managed, and maintained in a central database with internet access; each EBMT centre is represented in this database. There are no restrictions on centres for reporting data, except for those required by the law on patient consent, data confidentiality and accuracy. All patients whose transplant data are reported to the EBMT by participating centres provide informed consent to use such information for anonymized research projects. Patient selection was performed by identifying adult patients who underwent first allo-HCT for MF between 1995 and 2018, using either Reduced Intensity Conditioning (RIC) or Myeloablative conditioning (MAC) as defined by standard EBMT criteria [7]. Patient-, disease-, and transplant-related variables were expressed as median and range or interquartile range (IQR) for continuous variables and frequencies for categorical variables. The outcomes of interest were OS, non-relapse mortality (NRM), relapse/progression, relapse/progression-free survival (RFS), acute(a) and chronic (c) GvHD and graft failure. Outcomes are provided at three years after allo-HCT. OS and RFS were estimated using the Kaplan–Meier product limit estimation method, and differences in subgroups were assessed by the Log-Rank test. Median follow-up was determined using the reverse Kaplan–Meier method. The cumulative incidences of relapse and NRM were analysed together in a competing risks framework. Neutrophil engraftment was defined as an absolute neutrophil count $\geq 0.5 \times 10^9$/L for three consecutive days. Platelet engraftment was defined as an absolute platelet count $\geq 20 \times 10^9$/L for three consecutive days. The cumulative incidences of neutrophil and platelet engraftment are provided by day 100 after allo-HCT, with the competing event being death without engraftment. Competing risks analyses were also applied to estimate the incidences of grade II-IV aGvHD and limited and extensive cGvHD and primary and secondary graft failure, by day 100 and three-years post allo-HCT respectively, each with the competing event death. Subgroup differences in cumulative incidences were assessed using Gray's test. Multivariable Cox regression was applied to investigate the simultaneous impact of multiple covariates on outcomes, when a sufficient number of patients and subsequent events were available. Considered covariates for all models were donor (matched unrelated donor (MUD), mismatched related (MMRD), mismatched unrelated (MMUD) versus identical sibling/matched related), disease stage (not in complete remission (CR), CR versus untreated), stem cell source (bone marrow (BM)/BM + peripheral blood (PB) versus PB), age (decades), interval diagnosis – allo-HCT (months), patient sex (female versus male), conditioning intensity (RIC versus MAC), karnofsky performance status (KPS; <90, missing versus 90–100), patient cytomegalovirus (CMV) status (+ versus −), in vivo T cell depletion (TCD; yes versus no) and allo-HCT year. Interactions by allo-HCT year were included if significant by likelihood ratio test. For OS and progression free survival (PFS), hazard ratios are provided, whereas for the competing risks outcomes relapse, NRM, primary and secondary graft failure, aGvHD and cGvHD, cause-specific hazard ratios are provided for the events of interest, both denoted as HR. All estimates are reported with corresponding 95% confidence intervals. Statistical analyses were performed with SPSS 25 (SPSS Inc./IBM, Armonk, NY) and R version 3.6.0 (R Development Core Team, Vienna, Austria), using packages 'survival', 'prodlim' and 'cmprsk'. This study was performed in accordance with the principles of the Declaration of Helsinki.

Results

Patient characteristics

A total of 4142 MF patients were analysed who underwent allo-HCT between 1995 and 2018 (24-year period) across 278 centres based on data reported to the EBMT registry. Patient-, donor- and transplant-conditioning specific details are summarised in Table 1. For subsequent comparative analysis, four distinct cohorts were considered based on year of allo-HCT: <2006 $n = 389$ (9.4%), 2006–2010 $n = 910$ (22%), 2011–2014 $n = 1148$ (27.7%) and 2015–2018 $n = 1695$ (40.9%) (Table 1). A steady increase in MF allo-HCT activity over time was apparent paralleled with increasing numbers of participating transplant centres (Fig. 1A). For the entire cohort, median recipient age was 57.2 years (IQR 50.4–62.7, range 18.1–78.1). Of particular note, median recipient age increased over time by almost a decade between the earliest cohort and most recent cohort: <2006, median transplant recipient age 49.4 years (IQR, 43.1–55.3, range 20.1–68) versus 59.3 years (IQR, 53.4–64.8, range 18.1–78.1) for the 2015–2018 period (Fig. 1B). Prior to 2006, patients >60 years accounted for only 8.7% of MF patients undergoing allo-HCT whereas for the 2015–2018 cohort recipients >60 years accounted for 47% of activity.

Table 1 Patient and transplant characteristics across each analysed era.

	Group	Total		<2006	2006–2010	2011–2014	2015–2018	*p*
		Missing	*N* (%)	*N* (%)	*N* (%)	*N* (%)	*N* (%)	
Total			4142 (100%)	389 (100%)	910 (100%)	1148 (100%)	1695 (100%)	
Patient sex	Male		2603 (62.8%)	239 (61.4%)	566 (62.2%)	738 (64.3%)	1060 (62.5%)	0.664
	Female		1539 (37.2%)	150 (38.6%)	344 (37.8%)	410 (35.7%)	635 (37.5%)	
Classification at allo-HCT	Primary MF		3271 (79%)	363 (93.3%)	742 (81.5%)	916 (79.8%)	1250 (73.7%)	<0.001
	PPV/PET MF		871 (21%)	26 (6.7%)	168 (18.5%)	232 (20.2%)	445 (26.3%)	
Interval diagnosis to allo-HCT	Median (IQR), months		31.1 (10.9–96.3)	20.8 (8.9–62.2)	31.1 (11.3–87.1)	30.7 (10.2–94.9)	36.2 (11.6–107.5)	<0.001
Recipient Age at allo-HCT (yrs)	Median (IQR)		57.2 (50.4–62.7)	49.4 (43.1–55.3)	55.6 (49–60.5)	57.8 (51.2–62.7)	59.3 (53.4–64.8)	<0.001
Stem Cell Source	BM/BM + PB	1 (0 %)	427 (10.3%)	95 (24.4%)	101 (11.1%)	103 (9%)	128 (7.6%)	<0.001
	PB		3683 (88.9%)	291 (74.8%)	800 (88%)	1030 (89.7%)	1562 (92.2%)	
	CB/PB + CB		31 (0.7%)	3 (0.8%)	8 (0.9%)	15 (1.3%)	5 (0.3%)	
Donor Type	MSD	364 (8.8 %)	1430 (37.9%)	237 (61.4%)	363 (41.9%)	384 (36.5%)	446 (30.3%)	<0.001
	MUD		1554 (41.1%)	87 (22.5%)	346 (39.9%)	455 (43.3%)	666 (45.2%)	
	MMRD		226 (6%)	16 (4.1%)	14 (1.6%)	44 (4.2%)	152 (10.3%)	
	MMUD		537 (14.2%)	43 (11.1%)	136 (15.7%)	153 (14.6%)	205 (13.9%)	
	CB		31 (0.8%)	3 (0.8%)	8 (0.9%)	15 (1.4%)	5 (0.3%)	
Donor age	Median (IQR) (yrs)	1167 (28.2%)	38.3 (28–50.8)	44.8 (35.2–53.9)	42.3 (32.4–51.3)	39.5 (28.2–51.3)	35.3 (26.3–49)	<0.001
Donor sex	Male	47 (1.1%)	2695 (65.8%)	228 (58.6%)	558 (62.1%)	755 (66.6%)	1154 (68.9%)	<0.001
	Female		1400 (34.2%)	161 (41.4%)	340 (37.9%)	378 (33.4%)	521 (31.1%)	
CMV R:D	−/−	288 (7%)	1127 (29.2%)	77 (26.8%)	233 (28.6%)	344 (30.9%)	473 (28.8%)	<0.001
	−/+		387 (10%)	45 (15.7%)	89 (10.9%)	115 (10.3%)	138 (8.4%)	
	+/−		768 (19.9%)	36 (12.5%)	159 (19.5%)	235 (21.1%)	338 (20.6%)	
	+/+		1572 (40.8%)	129 (44.9%)	333 (40.9%)	419 (37.6%)	691 (42.1%)	
KPS	<90		1156 (32.5%)	26 (19.7%)	219 (29%)	332 (31.2%)	579 (36.1%)	<0.001
	90–100	587 (14.2%)	2399 (67.5%)	106 (80.3%)	536 (71%)	731 (68.8%)	1026 (63.9%)	
Ex vivo TCD	No	82 (2%)	3967 (97.7%)	340 (93.9%)	875 (97.5%)	1107 (98.1%)	1645 (98.3%)	<0.001
	Yes		93 (2.3%)	22 (6.1%)	22 (2.5%)	21 (1.9%)	28 (1.7%)	
In vivo TCD	No	118 (2.8%)	1185 (29.4%)	165 (51.2%)	278 (32.1%)	288 (25.2%)	454 (26.8%)	<0.001
	Yes		2839 (70.6%)	157 (48.8%)	588 (67.9%)	856 (74.8%)	1238 (73.2%)	
Conditioning	MAC	63 (1.5%)	1504 (36.9%)	217 (57.6%)	306 (34.1%)	393 (34.7%)	588 (35.2%)	<0.001
	RIC		2575 (63.1%)	160 (42.4%)	591 (65.9%)	740 (65.3%)	1084 (64.8%)	
TBI	No	25 (0.6%)	3642 (88.5%)	247 (63.8%)	772 (85.9%)	1058 (92.7%)	1565 (92.6%)	<0.001
	Yes		475 (11.5%)	140 (36.2%)	127 (14.1%)	83 (7.3%)	125 (7.4%)	
Treatment	Never treated	222 (5.4%)	1332 (34%)	209 (59.4%)	374 (43.4%)	368 (33.4%)	381 (23.7%)	<0.001
	CR		170 (4.3%)	25 (7.1%)	33 (3.8%)	43 (3.9%)	69 (4.3%)	

PV polycythaemia vera, *ET* essential thrombocythaemia, *BM* bone marrow, *PB* peripheral blood, *CB* cord blood, *IQR* interquartile range, *KPS* Karnofsky performance status, *TCD* T cell depletion, *TBI* total body irradiation, *MAC* myeloablative conditioning, *RIC* reduced intensity conditioning, *yrs* years, *MUD* matched unrelated donors, *MSD* matched sibling donors, *MMRD* mismatched related donors, *MMUD* mismatched unrelated donor, *CMV* cytomegalovirus.

For the entire cohort, a total of 2603 (62.8%) patients were male, 3239 (78.2%) had primary MF, 409 (9.9%) and 494 (11.9%) post-Polycythaemia Vera (PPV-) and post-Essential Thrombocythaemia (PET-) MF, respectively. Of interest, with regard to MF sub-classification, increasing numbers of PPV- and PET MF patients underwent allo-HCT over time (Table 1; $p < 0001$). Reliable disease prognostication scores, such as the International Prognostic Scoring System (IPSS) or Dynamic IPSS (DIPSS), were not available to assess if changes in assigned disease risk groups of individuals undergoing allo-HCT were apparent over time. Disease stage regarding chronic phase versus accelerated phase was not accurately recorded. An increased median interval between diagnosis and allo-HCT was evident (<2006; median interval 20.8 (IQR, 8.9–62.2) months versus 36.2 (IQR, 11.6–107.5) months in 2015–2018 period ($p < 0.001$), potentially reflecting increased availability of therapeutics in more recent eras (untreated patients in the era <2006 = 59.4% versus 23.7% in the 2015–2018 period). A total of 593 patients received JAK inhibitors. With regard to performance status, increasing numbers of patients with a KPS < 90 underwent allo-HCT over time (<2006 = 19.7% versus 36.1% 2015–18; $p < 0.001$, Table 1), indicating that more frail patients were being considered for allo-HCT approaches in more recent eras.

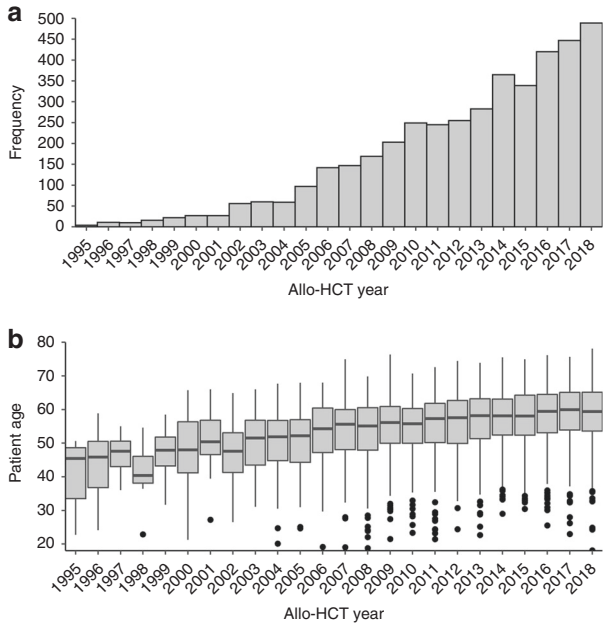

Fig. 1 Changes over time in transplant activity and recipient age. **A** Dynamic changes in registered Myelofibrosis allo-HCT activity over the 24-year period. **B** Changes in recipient age over time, highlighting older recipients in more recent eras.

Stem cell source, donor- and transplant-conditioning characteristics

PB was the predominant stem cell source and utilisation increased over time, accounting for 74.8% <2006 and 92.2% within the 2015–2018 era. Cord blood utilisation was limited to <1% throughout the entire 24-year study period. Significant shifts towards use of MUD in more recent periods was apparent with 22.5% MUD utilisation in the <2006 era, 39.9% between 2006 and 2010, 43.3% between 2011 and 2014 and 45.2% between 2015 and 2018 ($p < 0.001$) paralleled with a decrease in matched sibling donors (MSD; 61.4% in the pre-2006 era versus 30.3% in 2015–2018 period). Reflective of increased unrelated donor use, median donor age decreased over time ($p < 0.001$). An increased use of MMRD was particularly evident within the 2015–2018 cohort; $n = 152$ (9%) versus $n = 74$ (3%) cumulative for other 3 cohorts combined; $p < 0.001$. With regard to conditioning, decreased use of MAC was evident over time reflective of the increasing expansion of RIC protocols and increased age of recipients (era < 2006, MAC 57.6% versus 35.2% for 2015–2018 ($p < 0.001$; Table 1). Additionally, use of Total Body Irradiation (TBI) containing protocols decreased over time accompanied by increased use of busulphan-based regimens (<2006: 44.2% versus 2015–2018: 72%). Regarding TCD strategies, trends demonstrated increased use of anti-thymocyte globulin (ATG) over time (<2006: 37.3% vs 69.9% 2015–2018; $p < 0.001$) and significant decreases in ex vivo TCD.

Engraftment, graft failure and GVHD rates

Median time to both neutrophil (median 18 days across all cohorts) and platelet engraftment $>20 \times 10^9$/L (medians between 21 and 23 days across cohorts) were similar, with no significant variation when stratified by period of transplantation. For primary (PGF) and secondary (SGF) graft failure, as defined by reporting physicians, no significant differences in rates were seen across analysed eras on initial univariate analysis (Table 2). However, on multivariable analysis, a significant 'year effect' on donor type was observed affecting rates of PGF (Table 3). In the earlier periods, patients transplanted utilising a MMUD donor were much more likely to experience PGF than patients transplanted with a graft from a MSD (HR 4.55 (2.53–8.18), $p < 0.001$), although this higher rate of PGF is reduced by 12% per year (HR 0.88 (0.78–0.99), $p = 0.041$), demonstrating improvements over time. Interestingly, comparable initial PGF rates were seen following use of a MMRD ((HR 4.4 (1.89–10.25), $p < 0.001$), yet here no such year effect was observed, suggesting PGF after MMRD allo-HCT still remains a significant problem. For SGF, no such interaction between year and donor type was observed. SGF rates were higher in patients undergoing RIC allo-HCT (HR 1.77 (1.27–2.49), $p < 0.001$). However, this 'negative effect' of RIC on SGF rate is reduced by 10% per year compared to standard intensity conditioning (HR 0.9 (0.84–0.97), $p = 0.006$), again highlighting improvements over time. Of note, splenectomy status did not affect rates of either PGF or SGF.

Rates of (a)GVHD grade II-IV by day +100 decreased from the earliest cohort <2006 (35% (20–40%)) compared to the later groups (28% (26–30%); $p = 0.027$) on univariate analysis (Table 2). Rates of grade III-IV aGVHD did not significantly differ. Regarding timing of onset, aGVHD occurring before day+30 post allo-HCT was significantly reduced in more recent transplants by 3% per year (HR 0.97 (0.95–1), $p = 0.024$). Patients were significantly less likely to develop extensive cGvHD over time (rates of extensive cGvHD reduced by 4% per year (HR 0.96 (0.94–0.98), $p < 0.001$; Table 4, Fig. 2A), but this did not translate into a survival advantage

Relapse incidence, non-relapse mortality and overall survival

For the entire cohort, with a median follow up of 48 months (confidence interval 46.5–50.7), estimated 3-year overall survival (OS) was 58% (56–60%). Estimated Non-relapse mortality (NRM) and relapse incidence was 29% (28–31%)

Table 2 Main transplant-related outcomes as delineated by transplant period (univariate analysis).

Outcome	Time point	<2006	2006–2010	2011–2014	2015–2018	*p*
OS	36 months	55% (50–60%)	60% (56–63%)	58% (55–61%)	58% (55–61%)	0.3
RFS	36 months	47% (42–52%)	50% (46–53%)	49% (46–52%)	49% (46–52%)	0.7
Relapse	36 months	22% (18–26%)	24% (21–27%)	21% (19–24%)	21% (19–24%)	0.4
NRM	36 months	31% (26–36%)	26% (23–29%)	30% (27–33%)	30% (27–32%)	0.14
Primary GF	6 months	2% (0–3%)	2% (1–3%)	3% (2–4%)	4% (3–4%)	0.16
Secondary GF	36 months	4% (2–7%)	8% (6–9%)	7% (6–9%)	7% (6–9%)	0.3
Death w/o GF	36 months	38% (33–43%)	33% (30–36%)	34% (31–37%)	33% (30–35%)	0.2
aGvHD II-IV	100 days	35% (30–40%)	28% (25–31%)	28% (26–31%)	28% (26–30%)	0.027
aGvHD III-IV	100 days	16% (12–19%)	14% (12–16%)	12% (10–14%)	14% (12–16%)	0.3
Death w/o aGvHD	100 days	6% (4–9%)	6% (4–7%)	6% (4–7%)	6% (5–8%)	0.9
cGvHD	36 months	57% (52–62%)	50% (47–54%)	49% (46–52%)	44% (42–47%)	<0.001
Limited	36 months	19% (15–24%)	18% (16–21%)	21% (18–23%)	19% (17–21%)	0.5
Extensive	36 months	36% (31–41%)	30% (27–34%)	27% (24–29%)	23% (21–25%)	<0.001
Death w/o cGvHD	36 months	22% (17–26%)	22% (19–25%)	26% (24–29%)	31% (28–33%)	$p < 0.001$

Numbers in brackets represent confidence intervals.

OS overall survival, *RFS* relapse free survival, *NRM* non-relapse mortality, *GVHD* graft versus host disease, *a* acute, *c* chronic, *GF* graft failure, *w/o* without.

Table 3 Multivariable analysis of primary and secondary graft failure.

		Primary graft failure		Secondary graft failure	
Covariate	Group	HR (95% CI)	*p*	HR (95% CI)	*p*
Donor	MSD				
	MUD	1.55 (0.86–2.8)	0.15	1.49 (1.08–2.06)	0.016
	MMRD	4.4 (1.89–10.25)	<0.001	2.12 (1.17–3.84)	0.014
	MMUD	4.55 (2.53–8.18)	<0.001	1.6 (1.04–2.46)	0.031
Allo-HCT year		1.08 (0.97–1.19)	0.16	1.14 (1.05–1.24)	0.003
Conditioning intensity	MAC				
	RIC	1.53 (0.98–2.41)	0.06	1.77 (1.27–2.49)	<0.001
Stem cell source	PB				
	BM/BM + PB	2.84 (1.7–4.74)	<0.001	1.3 (0.81–2.08)	0.3
Ex vivo TCD	No				
	Yes	3.04 (1.21–7.6)	0.018	1.79 (0.79–4.07)	0.16
Patient CMV status	Negative				
	Positive	1.47 (0.96–2.26)	0.08	1.29 (0.96–1.72)	0.09
Recipient Age (decades)		1.05 (0.84–1.32)	0.7	1.04 (0.88–1.21)	0.7
	MUD x allo-HCT year	0.98 (0.85–1.12)	0.7		
	MMRD x allo-HCT year	0.98 (0.82–1.17)	0.8		
	MMUD x allo-HCT year	0.88 (0.78–0.99)	0.041		
Cond. intensity x allo-HCT year				0.9 (0.84–0.97)	0.006
Stem cell source x allo-HCT year				0.93 (0.85–1.01)	0.1
Patient CMV status x allo-HCT year				0.94 (0.88–1.01)	0.08

BM bone marrow, *PB* peripheral blood, *CB* cord blood, *KPS* Karnofsky performance status, *TCD* T cell depletion, *TBI* total body irradiation, *MAC* myeloablative conditioning, *RIC* reduced intensity conditioning, *yrs* years, *MUD* matched unrelated donors, *MSD* matched sibling donors, *MMRD* mismatched related donors, *MMUD* mismatched unrelated donor, *CMV* cytomegalovirus.

and 22% (21–23%) at 36 months, respectively. In the overall cohort, most common causes for NRM remained GVHD (31%) and infection (31%). Significant factors associated with worse OS and NRM remained older age, a worse KPS (<90), recipient CMV positivity and use of a donor other than a MSD. Focusing on patient age within each era, an adverse effect of older age >60 years compared to those <50 years was evident for OS. For these older individuals >60 years however, estimated 3-year OS did improve from the earliest era to most recent (<2006 = 35% (18–51%), 2006–2010 = 46% (40–53%), 2011–2014 = 51% (46–56%) and 2015–2018 = 52% (47–56%); $p = 0.03$). For those less than age 60, OS improved over time ($p = 0.04$) and NRM decreased ($p = 0.03$). Use of ex vivo TCD was also associated with worse OS. There was no effect of stem cell source on survival outcomes. Estimated 3-year OS, NRM and cumulative incidence of relapse (CIR) for each cohort are highlighted in Table 2 and Fig. 2B–D. Multivariable analysis of OS, PFS, relapse and NRM outcomes are shown in Table 5. Despite increasing numbers of older, less fit patients undergoing allo-HCT over time, the mortality rate reduced by 2% per year (HR 0.98 (0.97–1), $p = 0.019$) and the relapse rate was reduced by 2% per year (HR 0.98 (0.96–1), $p = 0.044$), highlighting a year of allo-HCT effect. There was no demonstrable improvement in NRM over time.

Discussion

The landscape of transplantation for MF has certainly evolved over the last few decades, particularly in the era of JAK inhibitors and other novel agents, and the EBMT have led on many of these developments. The first prospective trial of the Fludarabine, Busulphan and ATG platform for MF, led by Kroger et al. from the EBMT working group, revolutionised MF allo-SCT practice in many centres [8]. In addition, we have analysed umbilical cord blood stem cell and MMRD transplant outcomes in MF, investigated

Table 4 Multivariable analysis of GvHD.

		aGvHD II-IV		cGvHD	
Covariate	Group	HR (95% CI)	*p*	HR (95% CI)	*p*
Donor	Id. Sib/MRD				
	MUD	1.48 (1.24–1.76)	<0.001	0.96 (0.8–1.14)	0.6
	MMRD	1.07 (0.77–1.49)	0.7	0.67 (0.45–1)	0.05
	MMUD	1.94 (1.56–2.4)	<0.001	1.29 (1.04–1.61)	0.022
Stage	Untreated				
	CR	0.74 (0.47–1.16)	0.19	1.16 (0.77–1.75)	0.5
	not in CR	1.42 (1.21–1.67)	<0.001	1.03 (0.88–1.21)	0.7
Stem cell source	PB				
	BM/BM + PB	0.92 (0.72–1.17)	0.5	0.66 (0.5–0.86)	0.003
Recipient Age (decades)		1 (0.92–1.08)	>0.99	1.15 (1.05–1.25)	0.002
Interval diagnosis-allo-HCT (yr)		1 (0.99–1.01)	0.4	1 (0.99–1.01)	0.4
Patient sex	Male				
	Female	1.07 (0.93–1.24)	0.4	0.95 (0.81–1.1)	0.5
Conditioning intensity	MAC				
	RIC			1.05 (0.89–1.24)	0.6
KPS	90–100				
	<90	0.94 (0.8–1.1)	0.4	0.8 (0.68–0.95)	0.01
	Missing	1.25 (1–1.57)	0.05	0.83 (0.63–1.09)	0.17
Patient CMV	Negative				
	Positive	0.99 (0.86–1.15)	0.9	0.98 (0.84–1.13)	0.7
In vivo TCD	no				
	yes	0.68 (0.58–0.8)	<0.001	0.58 (0.49–0.69)	<0.001
Allo-HCT year	<30 days	0.97 (0.95–1)	0.024	0.96 (0.94–0.98)	<0.001
	>30 days	1.03 (1–1.05)	0.021		

BM bone marrow, *PB* peripheral blood, *CB* cord blood, *KPS* Karnofsky performance status, *TCD* T cell depletion, *TBI* total body irradiation, *MAC* myeloablative conditioning, *RIC* reduced intensity conditioning, *yrs* years, *MUD* matched unrelated donors, *MSD* matched sibling donors, *MMRD* mismatched related donors, *MMUD* mismatched unrelated donor, *CMV* cytomegalovirus, *aGVHD* Acute GVHD, *cGVHD* chronic GVHD.

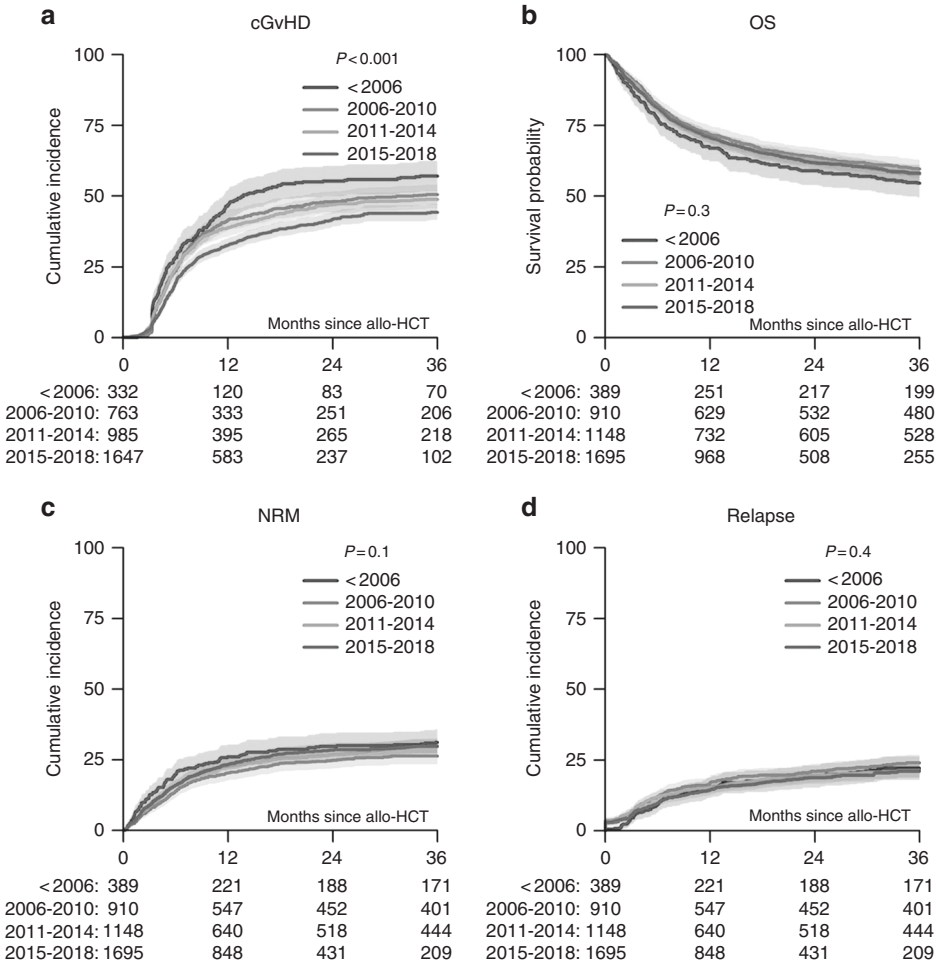

Fig. 2 Outcomes of allo-HCT for Myelofibrosis over time as per 4-analysed cohorts based on year of allo-HCT. Panels **A**–**D**: Unadjusted cumulative incidences of cGvHD (**A**), Kaplan–Meier curves of OS and cumulative incidence curves of NRM (**C**) and relapse (**D**), stratified by allo-HCT period. The shaded areas indicate 95% confidence intervals.

potential predictors of outcomes and explored the incidence and management of relapse, a particular challenge within the field, to name a few recent areas [6, 9–11].

This data, spanning a 24-year period, suggests increased utilisation of allo-HCT over time with increased uptake of participating transplant centres, albeit as we do not have the background incidence of diagnosed MF within each country, we cannot state how this relates to the overall pool of potential transplant eligible patients. Additionally, in more recent times, increasing numbers of centres have registered with EBMT and hence overall activity reporting has improved in general.

This study confers several pivotal messages. Although our data suggests slight improvements in OS and relapse risk over time, it is important to note that the complexity of MF allo-HCT has certainly increased with a higher proportion of older patients and those with a worse KPS undergoing allo-HCT paralleled with increased use of both MUD/MMUD and MMRD donors. The transplanted cohort in the most recent era were on average approximately a decade older overall compared with those in the earliest analysed cohort and in the most recent era, recipients >60 years accounted for 47% of activity. Sub-analyses demonstrate that for those >60 years at transplant, 3-year estimated OS has actually improved over time when the earliest cohort was compared to the more recent eras. Together, these findings likely reflect a shift in the perceived risk benefit ratio and more acceptance of the role of allo-HCT for MF amongst clinicians and patients alike accompanied by overall improvements in transplant-directed care. Increasing recipient age, recipient CMV seropositivity, utilisation of donor grafts other than a MSD and poor recipient performance status adversely affected OS in multivariable analysis.

Rates of GVHD have decreased over time, in particular the incidence of extensive cGVHD as shown in the multivariable analyses, albeit this did not translate into an apparent survival advantage. This is despite older recipient age and worse performance status, more use of PB-derived stem cells over time and increased use of alternate donors. Increased use of ATG over the analysed period was evident which may well account, at least in part, for these findings alongside decreased use of myeloablative conditioning. We recognise, however, that as the historic EBMT registry-based cGVHD definitions are based upon ‘limited’ or

Table 5 Multivariable analysis of OS, PFS, relapse and NRM.

		OS		PFS		Relapse		NRM	
Covariate	Group	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*
Donor	MSD								
	MUD	1.21 (1.06–1.38)	0.005	1.1 (0.98–1.24)	0.11	0.9 (0.75–1.07)	0.2	1.3 (1.11–1.54)	0.001
	MMRD	1.51 (1.16–1.97)	0.002	1.3 (1.03–1.64)	0.026	0.81 (0.55–1.2)	0.3	1.76 (1.32–2.36)	<0.001
	MMUD	1.67 (1.41–1.97)	<0.001	1.44 (1.24–1.68)	<0.001	0.99 (0.77–1.26)	0.9	1.9 (1.56–2.31)	<0.001
Stem cell source	PB								
	BM/BM + PB	0.91 (0.75–1.12)	0.4	0.96 (0.81–1.15)	0.7	0.97 (0.74–1.28)	0.9	0.95 (0.75–1.21)	0.7
Recipient Age (decades)		1.3 (1.21–1.4)	<0.001	1.23 (1.15–1.3)	<0.001	1.12 (1.02–1.23)	0.013	1.31 (1.21–1.42)	<0.001
Interval diagnosis-allo-HCT (yr)		0.99 (0.98–0.99)	0.002	0.99 (0.99–1)	0.18	1 (0.99–1.01)	0.8	0.99 (0.98–1)	0.041
Patient sex	Male								
	Female	0.94 (0.84–1.07)	0.4	0.92 (0.82–1.02)	0.12	0.92 (0.78–1.09)	0.3	0.92 (0.79–1.06)	0.2
Conditioning intensity	MAC								
	RIC	0.93 (0.82–1.05)	0.2	0.97 (0.86–1.08)	0.6	1.08 (0.9–1.29)	0.4	0.9 (0.77–1.04)	0.15
KPS	90–100								
	<90	1.39 (1.23–1.58)	<0.001	1.3 (1.16–1.46)	<0.001	1.25 (1.04–1.49)	0.015	1.35 (1.16–1.56)	<0.001
	missing	1.55 (1.29–1.86)	<0.001	1.42 (1.2–1.68)	<0.001	1.2 (0.93–1.57)	0.17	1.61 (1.29–2)	<0.001
Patient CMV	Negative								
	Positive	1.25 (1.11–1.41)	<0.001	1.11 (1–1.23)	0.05	0.93 (0.8–1.09)	0.4	1.27 (1.1–1.46)	0.001
Allo-HCT year		0.98 (0.97–1)	0.019	0.98 (0.97–1)	0.016	0.98 (0.96–1)	0.044	0.99 (0.97–1)	0.14

BM bone marrow, *PB* peripheral blood, *CB* cord blood, *KPS* Karnofsky performance status, *TCD* T cell depletion, *MAC* myeloablative conditioning, *RIC* reduced intensity conditioning, *yrs* years, *MUD* matched unrelated donors, *MSD* matched sibling donors, *MMRD* mismatched related donors, *MMUD* mismatched unrelated donor, *CMV* cytomegalovirus, *PFS* progression free survival, *OS* overall survival, *NRM* non-relapse mortality.

'extensive' only, they do not reflect the more recent National Institute of Health (NIH) consensus cGVHD grading practice and hence more accurate assessments of dynamic changes in cGVHD rates may in fact be missed. [12] As demonstrated, more recently there has been increased use of PTCy and resultant effects on GVHD incidence will be of interest in future analyses. Of note, given the overall numbers we did not perform a specific analyses focused on outcomes related to PTCy use.

Relapse and NRM remain major causes of treatment failure following MF allo-HCT. Cumulative incidence of relapse remained significant at >20% by 36-months in all analysed eras. Whether the increasing adoption of JAK inhibitors being utilised prior to MF allo-SCT improves outcomes by modification of the relapse incidence remains unknown presently but is a subject of great interest. There was no significant year effect on NRM rates, highlighting no significant changes over time.

Limitations of our study remain those inherent to retrospective analyses based on registry data spanning a long duration and a lack of comprehensive prognostic scoring and mutational status at the time of allo-HCT.

In conclusion, this is the first large study to delineate the dynamic landscape of patient- and transplant characteristics of MF allo-SCT over a 24-year period from EBMT registered centres. Despite a marked increase over this period in recipient age, RIC regimen utilisation and use of both unrelated donors and MMRD, this comprehensive analysis demonstrates improvements in OS, reductions in relapse risk and stable NRM rates. It is clear that further work is required to improve both the considerable NRM and relapse rates.

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Compliance with ethical standards

Conflict of interest The authors declare no competing interests.

Appendix

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