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Impact of primary disease on outcome after allogeneic stem cell transplantation for transformed secondary acute leukaemia

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Summary

Myelodysplastic syndromes (MDS), myeloproliferative neoplasms (MPN) and chronic myelomonocytic leukaemia (CMML) can progress to secondary acute myeloid leukaemia (sAML). We compared the outcome of 4214 sAML patients who received allogeneic haematopoietic stem cell transplantation (allo-HSCT) from an unrelated (62%) or human leucocyte antigen (HLA)-identical sibling donor (38%) according the underlying disease: MDS (n = 3541), CMML (n = 251) or MPN (n = 422). After a median follow up of 46·5 months, the estimated 3-year progression-free (PFS) and overall survival (OS) for the entire group was 36% (34–37%) and 41% (40–43%), respectively. The cumulative incidence of relapse and non-relapse mortality (NRM) was 37% (35–39%) and 27% (26–29%), respectively. In a multivariable analysis for OS, besides age (P < 0·001), unrelated donor (P = 0·011), cytomegalovirus ± constellation (P = 0·007), Karnofsky index ≤ 80 (P < 0·001), remission status (P < 0·001), peripheral blood as stem cell source (P = 0·009), sAML from MPN (P = 0·003) remained a significant factor in comparison to sAML from MDS, while worse outcome of sAML from CMML did not reach statistical significance (P = 0·06). This large registry study demonstrates a major impact of the underlying disease on outcome of sAML after allo-HSCT.

Keywords: allogeneic stem cell transplantation, MDS, myeloproliferative neoplasm, chronic myelomonocytic leukaemia, secondary acute myeloid leukaemia.

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Haematological myeloid malignancies, such as myelodysplastic syndrome (MDS), chronic myelomonocytic leukaemia (CMML) or myeloproliferative neoplasms (MPN) may transform to secondary acute myeloid leukaemia (sAML) during the course of the disease (Swerdlow, 2008). The percentage of transformation to sAML differs between the underlying diseases and is about 20–30% for MDS (Malcovati *et al*, 2006), 15–30% for CMML (Itzykson *et al*, 2013; Elena *et al*, 2016), and 8–25% for MPN (Cervantes *et al*, 1991; Okamura *et al*, 2001). sAML has been reported to be associated with worse outcome compared to *de novo* AML in some studies (Smith *et al*, 2003; Koh *et al*, 2010; Miesner *et al*, 2010) and poor outcome may be related to poor cytogenetics, more comorbidities and older age in those patients (Mesa *et al*, 2005). For sAML, allogeneic haematopoietic stem cell transplantation (allo-HSCT) is a curable treatment approach in transplant-eligible patients (Witherspoon & Deeg, 1999; Lussana *et al*, 2014; Symeonidis *et al*, 2015; Kroger *et al*, 2017). A recent epidemiological study suggested different outcomes in the non-transplant setting if sAML was transformed from MDS or other myeloid malignancies such as CMML or MPN (Granfeldt Ostgard *et al*, 2015).

The aim of the present study was to investigate, in a large cohort of patients with sAML who received allo-HSCT, whether patients whose underlying disease was MDS, MPN or CMML had different outcomes after adjustment for other risk factors, such as age, performance status, cytogenetics and donor source.

Patients and methods

We searched the European Society for Blood and Marrow Transplantation (EBMT) database for patients with transformed sAML from MDS, MPN or CMML who received an allo-HSCT between 2000 and 2014. We excluded patients who received stem cell transplantation from human leucocyte antigen (HLA)-mismatched related, unrelated donors or cord blood or were younger than 18 years at time of transplantation. We identified 4214 patients with a median age of 58 years (range 18–78). The primary disease was either MDS (n = 3541), CMML (n = 251) or Philadelphia chromosome-negative myeloproliferative neoplasm (n = 422). The patient characteristics are listed according to their primary disease in Tables I and SI.

Cytogenetic classification was according to the revised International Prognostic Scoring System (IPSS-R; Greenberg *et al*, 2012) for MDS and CMML, and the Mayo criteria (Hussein *et al*, 2010) for MPN. The cytogenetic results were separated into good (IPSS good; very good, favourable and normal according to Mayo), intermediate (IPSS intermediate), and poor (IPSS poor and very poor; unfavourable and others according to Mayo).

This study was performed in accordance with the principles of the Declaration of Helsinki and approved by the Chronic Malignancies Working Party of the EBMT. The EBMT is a non-profit, scientific society representing more than 600 transplantation centres located mainly in Europe. The EBMT promotes all activity aiming to improve stem cell transplantation or cellular therapy, which includes registering all the activity relating to stem cell transplants. 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. Quality control measures include several independent systems: confirmation of validity of the entered data by the reporting team, selective comparison of the survey data with minimum essential data-A (MED-A) data sets in the EBMT registry database, cross-checking with the National Registries, and regular in-house and external data audits. All patients whose transplant data are reported to the EBMT by participating centres provide informed consent to use the information for research purposes in an anonymous way.

Statistical analysis

The primary goal of the analysis was to identify risk factors significantly associated with overall survival (OS), progression-free survival (PFS), relapse and non-relapse mortality (NRM) within the first 3 years after allo-HSCT. Subsequently, events occurring after 36 months were artificially censored. Median follow-up was determined using the reverse Kaplan-Meier method. OS and PFS were estimated using the Kaplan-Meier product limit estimation method, and differences in subgroups were assessed by the Log-Rank test. Cumulative incidences of relapse (CIR) and NRM were analysed together in a competing risks framework. Competing risks analyses were also separately applied to estimate

Table I. Patients characteristics.

	MDS			CMML			MPN		
	Missing	*N*	%	Missing	*N*	%	Missing	*N*	%
Primary diagnosis		3541	84		251	6		422	10
Interval diagnosis to treatment (years)									
Median (range)		0·6 (0·1–35·5)			0·8 (0·1–13·5)			4·1 (0·1–32)	
Age (years)									
Median (range)		57 (18–78)			58 (18–75)			59 (21–73)	
Patient sex									
Male	3	2140	60		153	61		260	62
Female		1398	40		98	39		162	38
Remission status									
CR	124	1809	53	9	113	47	12	177	43
Prior to allo-HSCT									
No CR		1608	47		129	53		233	57
Donor									
HLA-identical sibling		1384	39		83	33		152	36
Matched unrelated		2157	61		168	67		270	64
Stem cell source									
BM		385	11		25	10		29	7
PB		3156	89		226	90		393	93
Cytomegalovirus									
Seronegative	566	1037	35	26	88	39	13	151	37
Seropositive		1938	65		136	60		258	63
Conditioning intensity									
Standard	51	1455	42	3	87	35	4	142	34
Reduced		2035	58		161	65		276	66
Total body irradiation									
No	19	2608	74	1	193	77		339	80
Yes		914	26		57	23		83	20
Karnofsky score									
≤80	258	873	27	17	81	35	27	140	35
>80		2410	73		153	65		255	65
Cytogenetics									
Good	2341	632	53	193	35	60	300	69	57
Intermediate		281	23		14	24		8	7
Poor		287	24		9	16		45	37
Ex vivo T-cell depletion									
No	87	3331	96	7	236	97	7	410	99
Yes		123	4		8	3		5	1

Patient characteristics stratified by disease classification at diagnosis. allo-HSCT, allogeneic haematopoietic stem cell transplantation; BM, bone marrow; CMML, chronic myelomonocytic leukaemia; CR, complete remission; HLA, human leucocyte antigen; MDS, myelodysplastic syndrome; MPN, myeloproliferative neoplasm; PB, peripheral blood.

acute graft-versus-host disease grade II-IV (aGvHD) with the competing event death without aGvHD, at 100 days, and limited and extensive chronic GvHD (cGvHD) with the competing event death without cGvHD, at 36 months. Subgroup differences in cumulative incidences were assessed using Gray's test (Iacobelli, 2013).

Cox proportional hazards regression was used to assess the impact of potential risk factors on OS, PFS, CIR and NRM. CIR and NRM were analysed in a competing risks framework in which the cause-specific hazards (CSH) were modelled. Risk factors for all Cox models were patient age at transplant in decades, disease classification (MDS – CMML – MPN), donor type (related – unrelated), stem cell source (bone marrow [BM] or peripheral blood [PB]), remission status at transplantation (complete remission [CR] – no CR), categorized Karnofsky score (≤80 and ≥90), cytomegalovirus (CMV) serostatus of the patient (positive – negative), cytogenetics (good – intermediate – poor), *ex-vivo* T-cell depletion (yes – no), total body irradiation (yes – no) and conditioning regimen intensity (standard – reduced). To account for missing information for a number of these risk factors, we used multiple imputation (MI) by chained equations to generate 25 completed datasets (Buuren, 2012). Risk factors used in the imputation models were the factors mentioned above,

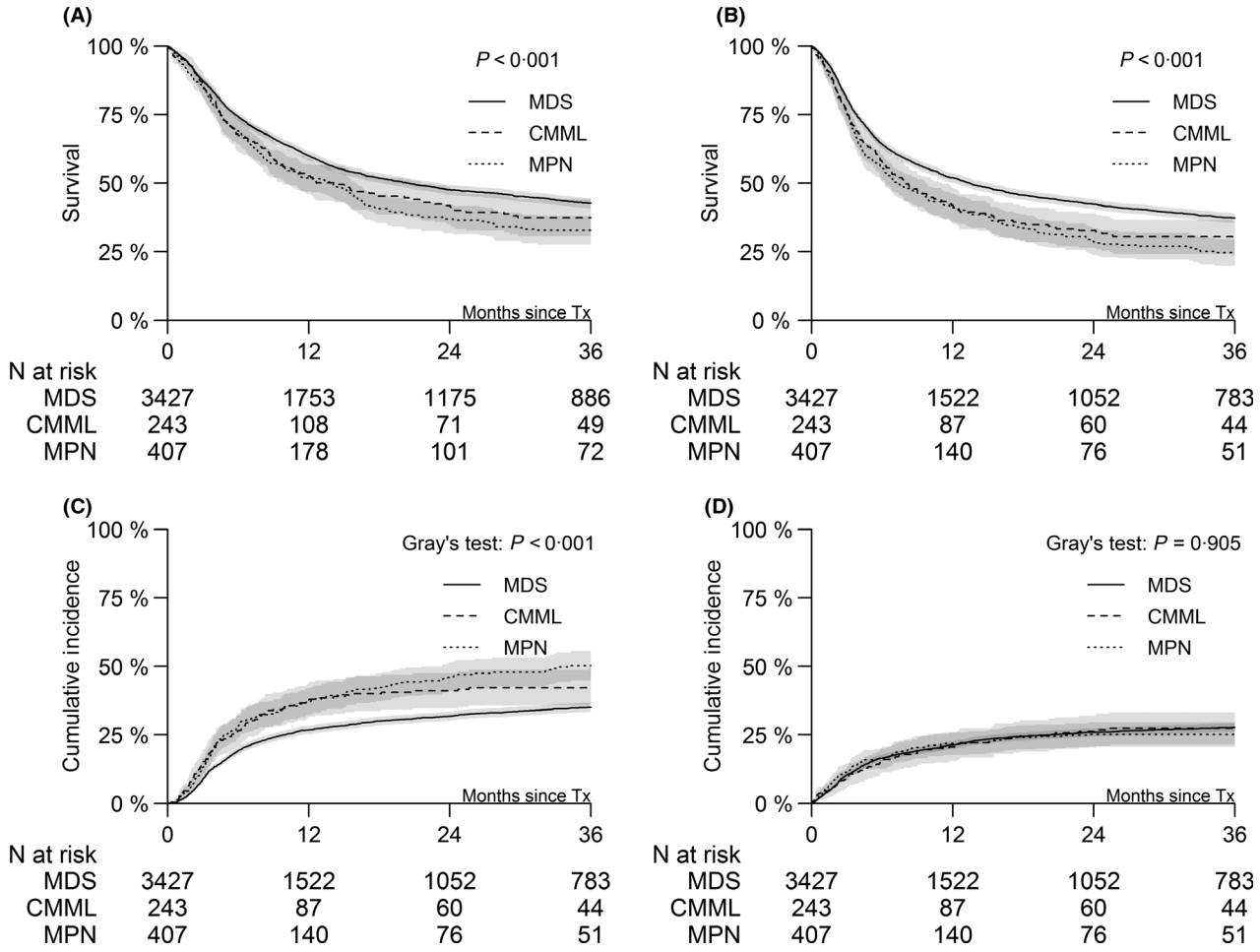

Fig 1. Overall survival (A), progression-free survival (B), cumulative incidence of relapse (C) and non-relapse mortality (D), stratified by disease classification at diagnosis within the first 3 years after allogeneic haematopoietic stem cell transplantation. For each outcome, the number of patients at risk at 12-month intervals is indicated below the respective graph and corresponding *P*-values are reported in the figures. The 95% confidence intervals are represented by the shaded regions. CMML, chronic myelomonocytic leukaemia; MDS, myelodysplastic syndrome; MPN, myeloproliferative neoplasm; Tx, treatment.

in addition to the cumulative hazard and status indicator of the respective outcomes.

Stepwise backward variable selection was performed to select the most important predictors among the variables given above. Selection based on the Akaike Information Criterion (AIC) was performed for each imputed dataset separately, always keeping disease classification. Risk factors which were selected in at least 10 out of 25 models were included in a single model. Pooled estimates based on fitting these models on all MI datasets were then derived by means of Rubin's rules. The resulting pooled model coefficients were then exponentiated to obtain the hazard ratios. Corresponding 95% confidence intervals (CIs) were calculated by pooling the upper and lower bounds of the confidence intervals for the individual model coefficients using Rubin's rules, and exponentiating the resulting estimates. This procedure was performed separately for OS, PFS, CIR and NRM.

All estimates are reported with corresponding 95% CIs. All *P*-values were two-sided and $P < 0{\cdot}05$ was considered significant. Statistical analyses were performed in R version 3.3.2 (R Development Core Team, Vienna, Austria), using packages 'survival', 'prodlim', 'MICE' and 'cmprsk'.

Results

Univariable analysis

All survival outcomes are reported for patients with complete relapse information ($n = 4077$). Median follow-up was 46·5 months. The estimated 3-year PFS and OS for the entire study group was 36% (34–38%) and 40% (39–42%), respectively. The cumulative incidences of relapse and non-relapse mortality at 3 years were 37% (35–39%) and 27% (26–29%). Univariable analysis found no difference in NRM at 3 years between patients with primary disease: MDS 28%

Table II. Multivariable cox regression models.

	OS	*P*	RFS	*P*	CIR	*P*	NRM	*P*
Primary diagnosis								
MDS	1		1		1		1	
CMML	1·18 (0·99–1·41)	0·06	1·23 (1·05–1·45)	0·012	1·47 (1·18–1·81)	<0·001	0·99 (0·77–1·27)	0·912
MPN	1·23 (1·07–1·41)	0·003	1·3 (1·15–1·48)	<0·001	1·59 (1·35–1·87)	<0·001	0·98 (0·8–1·2)	0·874
Age (decades)	1·07 (1·03–1·12)	0·001	1·07 (1·03–1·11)	<0·001	1·07 (1·01–1·13)	0·02	1·05 (1·0–1·11)	0·062
Remission status								
CR	1		1		1		1	
No CR	1·39 (1·27–1·52)	<0·001	1·32 (1·21–1·44)	<0·001	1·17 (1·05–1·32)	0·007	1·53 (1·35–1·74)	<0·001
Donor								
HLA-identical sibling	1		1		1		1	
Matched unrelated	1·12 (1·03–1·22)	0·011			0·81 (0·73–0·91)	<0·001	1·44 (1·26–1·63)	<0·001
Stem cell source								
BM	1		1		1		1	
PB	0·83 (0·73–0·96)	0·009	0·82 (0·72–0·94)	0·003	0·81 (0·68–0·96)	0·015	0·83 (0·68–1·01)	0·056
CMV								
Seronegative	1		1		1		1	
Seropositive	1·14 (1·04–1·25)	0·007	1·14 (1·04–1·25)	0·006			1·3 (1·13–1·48)	<0·001
Conditioning intensity								
Standard					1			
Reduced					1·11 (0·98–1·26)	0·092		
TBI								
No	1							
Yes	1·08 (1·23–1·63)	0·132						
Karnofsky score								
>80	1		1		1		1	
≤80	1·47 (1·33–1·62)	<0·001	1·43 (1·3–1·56)	<0·001	1·17 (1·03–1·33)	0·015	1·76 (1·55–2·0)	<0·001
Cytogenetics								
Good	1		1		1		1	
Intermediate	1·42 (1·23–1·63)	<0·001	1·41 (1·24–1·6)	<0·001	1·55 (1·3–1·86)	<0·001	1·26 (1·04–1·54)	0·022
Poor	1·81 (1·6–2·05)	<0·001	1·72 (1·51–1·96)	<0·001	2·03 (1·68–2·44)	<0·001	1·41 (1·18–1·69)	<0·001
Ex vivo T-cell depletion								
No	1		1		1		1	
Yes	1·32 (1·04–1·67)	0·021	1·36 (1·09–1·7)	0·007	1·44 (1·08–1·93)	0·014	1·32 (0·93–1·88)	0·126

Risk factors and associated pooled hazard ratios for NRM, relapse, RFS and OS within the first 3 years after allogeneic haematopoietic stem cell transplantation based on multivariable Cox (cause-specific) regression hazard models. Missing data were handled by means of multiple imputation. All hazard ratios are reported with 95% confidence intervals and *P*-values. BM, bone marrow; CIR, cumulative incidence of relapse; CMML, chronic myelomonocytic leukaemia; CMV, cytomegalovirus; CR, complete remission; HLA, human leucocyte antigen; MDS, myelodysplastic syndrome; MPN, myeloproliferative neoplasm; NRM, non-relapse mortality; OS, overall survival; PB, peripheral blood; RFS, relapse-free survival; TBI, total body irradiation.

(26–29%), CMML 27% (21–33%) and MPN 25% (21–30%) ($P = 0·9$), whereas the incidence of relapse was highest in MPN 50% (45–56%), followed by CMML 43% (36–49%) and MDS 35% (33–37%), ($P < 0·001$), resulting in a 3-year relapse-free and OS of 37% (35–39%) and 43% (41–45%) for MDS, 30% (24–36%) and 37% (31–44%) for CMML, and 25% (20–29%) and 33% (28–38%) for MPN, ($P < 0·001$) (see Fig 1A–D).

Acute GvHD. The overall incidence of aGvHD grade II–IV at 100 days was 26% (25–28%), and the incidence of death without aGvHD grade II–IV by this time was 9% (8–10%). The incidences of aGvHD were similar across the different disease classifications: MDS 27% (25–28%), CMML 25% (20–31%) and MPN 25% (21–29%) ($P = 0·7$), although death without aGvHD was lower in MDS, compared to CMML and MPN: 9% (8–10%) vs. 13% (9–18%) and 13% (9–16%) respectively ($P = 0·003$).

Chronic GvHD. At 36 months, the overall incidence of limited cGvHD was 26% (24–27%), extensive cGvHD was 22% (20–23%) and death without cGvHD was 32% (30–33%). Incidences of limited cGvHD were similar between disease classifications: MDS 26% (24–28%), CMML 22% (15–28%) and MPN 27% (22–33%); $P = 0·5$, as were those of extensive cGvHD: MDS 21% (20–23%), CMML 27% (20–35%) and MPN 22% (17–27%); $P = 0·4$. The incidence of death without cGvHD was higher in MPN, compared to MDS and

CMML: 40% (34–47%) vs. 31% (29–33%) and 31% (24–39%) respectively ($P = 0{\cdot}028$).

Multivariable analysis

NRM. Multivariable analysis showed that NRM was not influenced by the underlying primary disease. Significant risk factors for NRM were unrelated donor: HR 1·44 (1·26–1·63, $P < 0{\cdot}001$), not being in CR: HR 1·53 (1·35–1·74, $P < 0{\cdot}001$), Karnofsky ≤80: HR 1·76 (1·55–2·0, $P < 0{\cdot}001$), CMV seropositive status: HR 1·3 (1·13–1·48, $P < 0{\cdot}001$), intermediate and poor cytogenetics: HR 1·26 (1·04–1·54, $P = 0{\cdot}022$) and 1·41 (1·18–1·69, $P < 0{\cdot}001$) respectively (Table II).

Relapse. Relapse was significantly higher in CMML: HR 1·47 (1·18–1·81, $P < 0{\cdot}001$) and MPN: HR 1·59 (1·35–1·87, $P < 0{\cdot}001$) in comparison to MDS. Other significant risk factors for relapse were: lower risk of relapse for unrelated donors: HR: 0·81 (0·73–0·91, $P = 0{\cdot}005$) and higher risk of relapse for older age: HR 1·07 (1·01–1·13, $P = 0{\cdot}02$), not being in CR: HR 1·17 (1·05–1·32, $P < 0{\cdot}001$), Karnofsky ≤80: HR 1·17 (1·03–1·33, $P = 0{\cdot}015$), intermediate: HR 1·55 (1·3–1·86, $P < 0{\cdot}001$), and poor cytogenetics: HR 2·03 (1·68–2·44, $P < 0{\cdot}001$) and *ex vivo* T-cell depletion: HR 1·44 (1·08–1·93, $P = 0{\cdot}014$). Conditioning intensity was not associated with a significant impact: HR 1·11 (0·98–1·26, $P = 0{\cdot}092$) (Table II).

Relapse-free survival. CMML: HR 1·23 (1·05–1·45, $P = 0{\cdot}012$) and MPN: HR 1·3 (1·15–1·48, $P < 0{\cdot}001$) in comparison to MDS as primary disease had a significant impact on PFS in the multivariable analysis. Other significant factors were age: HR 1·07 (1·03–1·11, $P < 0{\cdot}001$), PB as stem cell source: HR 0·82 (0·72–0·94, $P = 0{\cdot}003$), not being in CR: HR 1·32 (1·21–1·44, $P < 0{\cdot}001$), Karnofsky ≤80: HR 1·43 (1·3–1·56, $P < 0{\cdot}001$), CMV seropositivity: HR 1·14 (1·04–1·25, $P = 0{\cdot}005$), intermediate cytogenetics: HR 1·41 (1·24–1·6, $P < 0{\cdot}001$), and poor risk cytogenetics: HR 1·72 (1·51–1·96, $P < 0{\cdot}001$) (Table II).

Overall survival. In a multivariable analysis of OS according to the underlying disease, CMML had an HR of 1·18 (0·99–1·41), which did not reach statistical significance in comparison to MDS ($P = 0{\cdot}06$) while MPN had a significantly worse survival in comparison to MDS: HR 1·23 (1·07–1·41, $P = 0{\cdot}003$). Other significant risk factors for OS were unrelated donor: HR 1·12 (1·03–1·22, $P = 0{\cdot}01$), PB as stem cell source: HR 0·83 (0·73–0·96, $P = 0{\cdot}009$), not being in CR: HR 1·39 (1·27–1·52, $P < 0{\cdot}001$), older age: HR 1·07 (1·03–1·12, $P = 0{\cdot}001$), Karnofsky ≤80: HR 1·47 (1·33–1·62, $P < 0{\cdot}001$), CMV seropositivity: HR 1·14 (1·04–1·25, $P = 0{\cdot}007$), intermediate cytogenetics: HR 1·42 (1·23–1·63, $P < 0{\cdot}001$), poor cytogenetics: HR 1·81 (1·6–2·05, $P < 0{\cdot}001$) and *ex-vivo* T-cell depletion: HR 1·32 (1·04–1·67, $P = 0{\cdot}021$) (Table II).

Discussion

This large EBMT registry study regarding the outcome of allo-HSCT for sAML, demonstrated that outcome differs according to the underlying myeloid disease, suggesting different biology, not only in comparison to *de novo* AML but also within the summarized group of secondary AMLs. Beside the well-known factors that influence relapse-free survival for sAML, such as older age, no CR at time of transplantation, low performance status, and unfavourable cytogenetics, multivariable analysis showed better outcome for sAML if derived from MDS in comparison to sAML from CMML, and was even worse in comparison to sAML derived from MPN. These results are in line with several reports about outcome of transformed leukaemia in a non-transplant setting (Granfeldt Ostgard *et al*, 2015).

A Japanese study reported a worse outcome of sAML derived from MPN in comparison to MDS (Koh *et al*, 2010). In this small study of 95 patients, the preceding haematological disorder did result in different rates of CR to induction therapy, and besides the preceding haematological disorder, adverse cytogenetics impacted outcome.

In a recent large Danish, population-based cohort study, a difference in response and outcome of sAML patients depending on the underlying primary disease in a non-transplant setting has been described for sAML derived from CMML or MPN in comparison to transformed MDS (Granfeldt Ostgard *et al*, 2015). In this study, which included 1567 patients who received intensive chemotherapy, the response rate to induction therapy and survival were poorer in sAML than in *de novo* AML and were worse in sAML transformed from MPN in comparison to sAML transformed from MDS. Smaller single centre studies described dismal outcome of transformed MPN and CMML (Mesa *et al*, 2005). Reports about allo-HSCT in transformed leukaemia are mainly published regarding the preceding haematological disease such as MDS (Koenecke *et al*, 2015), MPN (Lussana *et al*, 2014), CMML (Symeonidis *et al*, 2015) or aplastic anaemia (Hussein *et al*, 2014). Larger systematic reports are lacking. Here we focused on MDS, CMML and MPN, and excluded transformed aplastic anaemia and blast crisis of chronic myeloid leukaemia.

Before transplantation, the number of patients who were in CR was slightly lower in MPN (43%) in comparison to CMML (47%) and MDS (53%). However, after adjustment in a multivariate analysis, the outcome of patients with CMML or MPN as the underlying disease remained poorer in contrast to those with MDS. A different biology of sAML derived from MDS *versus* MPN or CMML is further supported by a higher risk of relapse while the NRM was nearly identical in all 3 groups.

This study provided evidence that the success of allo-HSCT for secondary, transformed leukaemia also depends on the underlying disease. In these cases, decisions regarding transplantation and procedures should consider the underlying disease.

Author contributions

NK designed the study and wrote the paper, DJK and LCW performed statistical analyses, LK collected the data, DB, JF, CK, DN, MB, VP, CW, JM, MT, GK, MIR, GW, PK, EF, HG and TM provided patient data. IY, YC, MR, NK, DJE and LCW interpreted the data. All authors approved the final version.

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Conflict of interest

None of the authors declared any conflict of interest.

Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table SI. Patients characteristics stratified by donor.

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