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Transplant results in adults with Fanconi anaemia

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Summary

The outcomes of adult patients transplanted for Fanconi anaemia (FA) have not been well described. We retrospectively analysed 199 adult patients with FA transplanted between 1991 and 2014. Patients were a median of 16 years of age when diagnosed with FA, and underwent transplantation at a median age of 23 years. Time between diagnosis and transplant was shortest (median 2 years) in those patients who had a human leucocyte antigen identical sibling donor. Fifty four percent of patients had bone marrow (BM) failure at transplantation and 46% had clonal disease (34% myelodysplasia, 12% acute leukaemia). BM was the main stem cell source, the conditioning regimen included cyclophosphamide in 96% of cases and fludarabine in 64%. Engraftment occurred in 82% (95% confidence interval [CI] 76–87%), acute graft-versus-host disease (GvHD) grade II–IV in 22% (95% CI 16–28%) and the incidence of chronic GvHD at 96 months was 26% (95% CI 20–33). Non-relapse mortality at 96 months was 56% with an overall survival of 34%, which improved with more recent transplants. Median follow-up was 58 months. Patients transplanted after 2000 had improved survival (84% at 36 months), using BM from an identical sibling and fludarabine in the conditioning regimen. Factors associated with improved outcome in multivariate analysis were use of fludarabine and an identical sibling or matched non-sibling donor. Main causes of death were infection (37%), GvHD (24%) and organ failure (12%). The presence of clonal disease at transplant did not significant impact on survival. Secondary malignancies were reported in 15 of 131 evaluable patients.

Keywords: Fanconi anaemia, allogeneic transplant, myelodysplasia, inborn bone marrow failure syndrome.

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Fanconi anaemia (FA) is a rare inherited bone marrow (BM) failure syndrome. The underlying disorder is a DNA damage repair defect. Currently at least 20 genes have been identified to be associated with FA (Dong *et al*, 2015; Bluteau *et al*, 2016), leading to highly variable patterns of disease presentation. Patients may present with birth defects but up to 30% of new cases have no apparent stigmata (Shimamura & Alter, 2010; Wang & Smogorzewska, 2015).

The most common presenting symptom is progressive BM failure in the first or second decade of life, and increased *in vitro* chromosomal breakage is the diagnostic hallmark.

Fanconi anaemia patients have a greatly increased risk of cancer, including leukaemia at a young age as well as squamous cell carcinomas at a (somewhat) older age (Rosenberg *et al*, 2003). Due to the toxicity experienced by FA patients as a result of increased sensitivity to chemo- and radiotherapy, attenuated treatment protocols have been developed.

Patients may be diagnosed with FA at an adult age with BM failure as the presenting symptom, or myelodysplasia. Patients may also present at a young age with a diagnosis of a squamous cell carcinoma, sometimes in combination with a mild macrocytic anaemia and/or thrombocytopenia. Finally a family history of increased toxicity from chemo- or radio therapy may also lead to the diagnosis.

Although androgens can be used to treat BM failure, allogeneic haematopoietic stem cell transplantation (HSCT) is the only curative therapy. In recent years outcomes in young FA patients have greatly improved (Peffault de Latour *et al*, 2013; Smetsers *et al*, 2016); this is partly due to the introduction of fludarabine in the conditioning regimen as well as better donor availability, improved human leucocyte antigen (HLA) matching and supportive care.

Peffault de Latour *et al* (2013) retrospectively analysed a large series of transplants for FA and identified age at transplant as an important risk factor for outcome. This European Society for Blood and Marrow Transplantation (EBMT) study included 795 patients transplanted between 1972 and 2010, 64 of whom were over 20 years of age at transplant. Age over 20 years resulted in a hazard ratio (HR) of 1·92 (95% confidence interval [CI] 1·25–2·94). Age below 10 years at transplant was associated with good outcome.

For this reason we decided to study a larger group of patients with FA who were transplanted as adults during a more recent time period.

Patients, materials and methods

Data collection

This retrospective multicentre study was conducted through the Severe Aplastic Anaemia Working Party (SAA-WP) of the EBMT. A list of centres contributing to this retrospective study is listed in Appendix 1.

Data was taken from the EBMT registry, to which the individual centres provided information. Additional case report forms (CRF) were distributed among the participating centres, which were actively approached to complete the forms. In case of remaining questions regarding submitted data, centres were contacted by the Data Office (Leiden, the Netherlands). Informed consent was obtained according to local standards, following the Declaration of Helsinki. EBMT publication rules were followed.

Inclusion criteria

Patients were included if diagnosed with FA and were more than 18 years of age when first transplanted between 1991 and 2014. Second transplants were excluded. The database was closed in July 2016 and data was analysed.

Definitions

Engraftment was defined as achieving an absolute neutrophil count of $0{\cdot}5 \times 10^9$/ for at least three consecutive days. Acute and chronic graft-versus-host disease (GvHD) were defined and graded according to previously published criteria (Glucksberg *et al*, 1974). Non-relapse mortality was defined as all deaths not due to recurrence of disease. Survival was calculated from date of transplant to date of last follow-up or death.

Statistical methods

Analyses used July 2016 as the reference date. Data are presented as numbers (percentages) or median (range or interquartile range). Missing patient characteristics at transplant were handled by multiple imputation by chained equations (Rubin & Schenker, 1991). All variables considered in the multivariate model for overall survival were used in the

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imputation model, as well as the baseline hazard for overall survival (White & Royston, 2009). Given that roughly 50% of patients had missing predictors, 50 independent imputed data sets were generated and analysed separately (White *et al*, 2011). Estimates were then pooled over the 50 imputations according to Rubin and Schenker (1991) to provide point estimates and confidence intervals (CI) for each parameter. For missing outcomes, an extreme case scenario was considered where patients with no reported engraftment, GvHD or relapse were assumed not to have experienced the event. For engraftment, multiple imputation as described for baseline characteristics was also used. In the extreme case scenario, missing times of occurrence of events were imputed from the empirical distribution of available data. Death was considered a competing risk in the analyses of acute and chronic GvHD, relapse and secondary malignancy. Factors associated with overall survival were analysed with a Cox proportional hazards model. The linearity of the effect of continuous predictors was tested by using cubic splines and testing for a non-linear effect. If linearity was challenged, data transformation (e.g. logarithmic) was used. A backward model selection procedure was used, based on the Wald tests for the pooled regression coefficients with *P* value cut-off mimicking the use of Akaike Information Criterion (AIC) (Wood *et al*, 2008; Vergouwe *et al*, 2010). This rule corresponds to a *P* value of 0·157 for a variable with one degree of freedom. Once variables were selected, two-way interactions between all retained variables were tested sequentially, but none was found significant. All tests were two-sided. Analyses were carried out using the R statistical software version 3.2.1 (The R Foundation for Statistical Computing, Vienna, Austria).

Results

Patients' characteristics

The general characteristics of the included patients are given in Table I.

Information regarding the Fanconi characteristics was available in 119 patients.

Forty of the 119 (34%) patients had head anomalies. Hand/arm symptoms were present in 26 patients (22%) and kidney/urogenital findings were present in 26 (22%) cases. Both gastrointestinal and cardiovascular symptoms were found in 3% of patients. Disease genotype was reported in 19% of patients (n = 38): *FANCA* was present in 76% (n = 29) of those, *FANCC* in 11% (n = 4), *FANCD2* in 5% (n = 2) and *FANCG* in 8% (n = 3).

Fifty-one of 117 evaluable patients (44%) were treated with androgens prior to HSCT.

(Disease) status at transplant

The median age at diagnosis of FA was 16 (0–48) years. Eighty-one (41%) patients were transplanted between 2009 and 2014 at a median age of 23 years. Thirty-seven patients (19%) were over 30 years of age at time of HSCT. Age at transplant was dependent on best available donor: the median time from diagnosis to transplant was 2 (1–8) years in patients with an available HLA-identical sibling donor, and 9 (2–17) years in those patients with an unrelated donor. Disease status at transplant was known in 118 patients: 64 patients (54%) had BM failure, 40 (34%) myelodysplasia and 14 patients (12%) had acute leukaemia.

Donor, stem cell source and conditioning regimen

An identical sibling donor was used in 91 (46%) patients, 47 (24%) were transplanted from a matched unrelated donor and 40 patients (20%) received a mismatched unrelated donor transplant. BM was the main source of stem cells (58% of transplants) with a very limited number of cord blood transplants (11/198 evaluable patients, 6%).

The conditioning regimen contained cyclophosphamide in 96% of evaluable patients and fludarabine was used in 62%. A further 18% received busulfan and irradiation was part of the conditioning regimen in 29% of cases.

Transplant outcome: engraftment, GvHD

Transplant outcome is summarized in Table II. The data presented below are based on available data for analysis. Engraftment occurred in 82% of patients. Three per cent of patients died before engraftment could be expected. The median follow-up was 58 months (7 days to 264 months).

Acute GvHD grade 2–4 occurred in 22% of patients before day 100. Cumulative incidence of acute GvHD 2–4 at 100 days was 31·6% (95% CI 23·2–40·4) in those patients with BM as stem cell source and 24·5% (95% CI 14·8–35·5) if transplanted with peripheral blood stem cells (P = not significant).

Chronic GvHD increased, from 19% at 12 months to 26% at 96 months post-transplant.

The cumulative incidence of chronic GvHD at 48 months was 27·1% (95% CI 18·6–36·2) when BM was used as the graft source and 26·8 (15·9–38·9) when peripheral blood stem cells were used. The HR for peripheral blood stem cells vs BM was 0·96 (95% CI 0·51–1·79; P = 0·90).

Extreme scenario analysis, considering that patients with no reported engraftment, GvHD or relapse did not experience the event, showed similar estimates in comparison to complete cases analysis (data not shown).

Survival, causes of death, secondary malignancies

Overall non-relapse mortality increased from 42% at 12 months post-transplant to 56% at 96 months post-transplant.

Overall survival was estimated at 34% (95% CI 27–43%) at 96 months post-transplant (Fig 1).

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Table I. Patient characteristics and transplant data.

Characteristic	All patients	MSD	Other related donor	URD
Patients, *N*	199	91	20	87
Year of transplant, *n* (%)				
1991–2000	51 (26)	25 (27)	6 (30)	19 (22)
2001–2008	67 (34)	30 (33)	7 (35)	30 (34)
2009–2014	81 (41)	36 (40)	7 (35)	38 (44)
Age at diagnosis (years), median (range)	16 (0–48)	21 (0–42)	9 (0–38)	12 (0–48)
Age at transplant (years), median (range)	23 (18–48)	24 (18–44)	23 (18–40)	23 (18–48)
N (%)				
18–20	62 (31)	27 (30)	7 (35)	28 (33)
21–30	99 (50)	48 (53)	10 (50)	40 (47)
31–45	37 (19)	16 (18)	3 (15)	18 (21)
Gender, *n* (%)				
Female	100 (50)	45 (49)	9 (45)	45 (52)
Male	99 (50)	46 (51)	11 (55)	42 (48)
Time from diagnosis to transplant (years), median (Q1;Q3)	7 (1–14)	2 (1–8)	13 (4–17)	9 (2–17)
Bone marrow status at transplant, *n* (%)				
AA	64 (54)	26 (51)	7 (50)	31 (58)
MDS	40 (34)	23 (45)	5 (36)	12 (23)
AL	14 (12)	2 (4)	2 (14)	10 (19)
Missing data (*n*)	81	40	6	34
Donor, *n* (%)				
Identical sibling	91 (46)	91 (100)	0 (0)	0 (0)
Matched other relative	6 (3)	0 (0)	6 (30)	0 (0)
Matched unrelated	47 (24)	0 (0)	0 (0)	47 (54)
Mismatched relative	14 (7)	0 (0)	14 (70)	0 (0)
Mismatched unrelated	40 (20)	0 (0)	0 (0)	40 (46)
Missing data (*n*)	1	0	0	0
Stem cell source, *n* (%)				
BM	115 (58)	57 (63)	7 (35)	51 (59)
PB	72 (36)	34 (37)	13 (65)	25 (29)
CB	11 (6)	0 (0)	0 (0)	11 (13)
Missing data (*n*)	1	0	0	0
Donor/recipient gender matching, *n* (%)				
Female/male	27 (14)	11 (12)	3 (15)	13 (15)
Other combinations	171 (86)	80 (88)	17 (85)	74 (85)
Missing data (*n*)	1	0	0	0
Donor/recipient CMV status, *n* (%)				
Negative/negative	38 (27)	8 (14)	5 (29)	25 (38)
Negative/positive	24 (17)	9 (15)	2 (12)	13 (20)
Positive/negative	12 (8)	4 (7)	1 (6)	7 (11)
Positive/positive	68 (48)	38 (64)	9 (53)	21 (32)
Missing data (*n*)	57	32	3	21
Conditioning				
Cyclophosphamide, *n* (%)				
No	8 (4)	3 (4)	1 (5)	4 (5)
Yes	173 (96)	78 (96)	18 (95)	77 (95)
Missing data (*n*)	18	10	1	6
Fludarabine, *n* (%)				
No	65 (36)	39 (48)	7 (37)	19 (23)
Yes	116 (64)	42 (52)	12 (63)	62 (77)
Missing data (*n*)	18	10	1	6
Busulfan, *n* (%)				
No	148 (82)	71 (88)	16 (84)	61 (75)
Yes	33 (18)	10 (12)	3 (16)	20 (25)
Missing data (*n*)	18	10	1	6

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Table I. (*Continued*)

Characteristic	All patients	MSD	Other related donor	URD
TBI, *n* (%)				
No	137 (71)	73 (83)	13 (65)	51 (61)
Yes	55 (29)	15 (17)	7 (35)	33 (39)
Missing data (*n*)	7	3	0	3
ATG, *n* (%)				
No	68 (38)	41 (51)	4 (21)	23 (28)
Yes	113 (62)	40 (49)	15 (79)	58 (72)
Missing data (*n*)	18	10	1	6
Ex-vivo T-cell manipulation, *n* (%)				
No	151 (84)	83 (99)	13 (68)	55 (71)
Yes	29 (16)	1 (1)	6 (32)	22 (29)
Missing data (*n*)	19	7	1	10

AA, aplastic anaemia; AL, acute leukaemia; ATG, anti-thymocyte globulin; BM, bone marrow; CB, cord blood; CMV, cytomegalovirus; MDS, myelodysplastic syndrome; MSD, matched sibling donor; PB, peripheral blood; TBI, total body irradiation; URD, unrelated donor.

Table II. Transplant outcome.

Outcome	*N* missing	*N* events	Estimate (95% CI)
Engraftment	6	159	82% (76–87)
Engraftment (%)		159 (82)	
Primary graft failure (%)		18 (9)	
Secondary graft failure (%)		10 (5)	
Death without engraftment (%)		6 (3)	
Acute GvHD grade 2–4	27*	39	
100 days			22% (16–28)
Chronic GvHD	12	44	
12 months			19% (13–25)
48 months			26% (20–33)
96 months			26% (20–33)
Relapse	1	19	
12 months			7% (4–11)
48 months			11% (7–17)
96 months			11% (7–17)
NRM	1	102	
12 months			42% (35–49)
48 months			51% (43–58)
96 months			54% (46–62)
Secondary malignancy	68†	15†	
12 months			2% (0–5)
48 months			11% (6–18)
96 months			14% (8–22)
Overall survival	0	120	
12 months			54% (47–62)
48 months			38% (31–47)
96 months			34% (27–43)

CI, confidence interval; GvHD, graft-versus-host disease; NRM, non-relapse mortality.

*Nine missing event indicators and 18 missing times of occurrence only.

†Three of these patients had secondary malignancy reported (18 events) but no time of occurrence recorded.

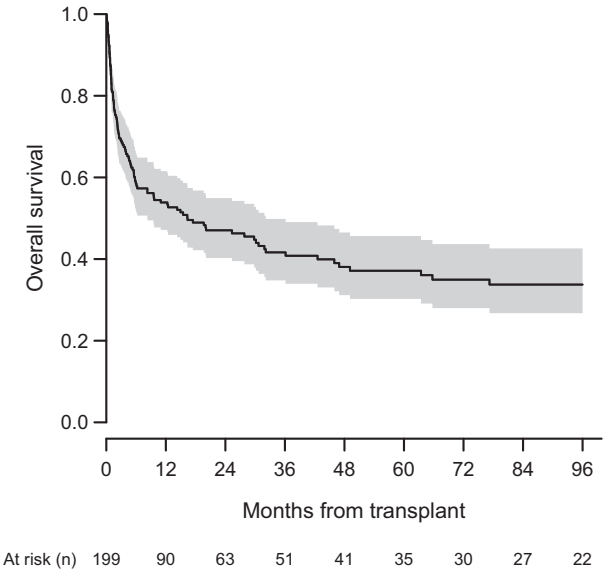

Fig 1. Overall survival of the whole group of patients. The grey area represents the 95% confidence interval.

The main causes of death are given in Table III.

Secondary malignancies were reported after transplant in 18 cases. Eight of these patients, all of whom were transplanted for BM failure, were diagnosed with solid tumours. One patient developed *de novo* leukaemia post-transplant. A secondary malignancy was reported in nine patients but the exact nature was not specified.

Risk factor analysis

Table IV summarizes factors associated with overall survival. In multivariate analysis, identical sibling and matched non-sibling donor availability (*versus* non-matched unrelated donors) and the use of fludarabine in the conditioning regimen were statistically significantly associated with a better chance of survival ($P < 0{\cdot}0001$ and $0{\cdot}01$ respectively).

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Table III. Causes of death.

	N = 120
1. Infection	44 (37)
2. GvHD	29 (24)
3. Relapse/progression	7 (6)
4. HSCT-related	8 (7)
5. Secondary malignancy/PTLD	11 (9)
6. Organ damage/failure	14 (12)
7. Unknown	6 (5)

GvHD, graft-versus-host disease; HSCT, haematopoietic stem cell transplantation; PTLD, post-transplant lymphoproliferative disorder.

Figure 2 illustrates the impact of BM status at transplant on outcome. Despite the apparently reduced survival in patients with acute leukaemia at the time of transplant, the difference was not statistically significant. Overall survival at 48 months post-transplant for patients with aplasia, myelodysplastic syndrome and acute leukaemia at the time of transplant was 48% (95% CI 36–62), 41% (95% CI 27–64) and 17% (95% CI 3–87) respectively.

Attempting to identify and evaluate the most optimal transplant scenario, we analysed the subgroup of patients restricted to those transplanted with BM as stem cell source and receiving fludarabine as part of the conditioning regimen. We identified 52 patients transplanted since 2000. Their survival at 36 months post-transplant was 61% (95% CI 49–77) compared to 42% (35–50) for the whole group. Restricting the group further to those having an identical sibling donor, there were 22 cases, with an overall survival at 36 months of 84% (95% CI 70–100).

Discussion

We present here the largest series of patients with FA undergoing stem cell transplantation at an adult age. Recent reports of children with FA undergoing HSCT demonstrate excellent outcomes, with survival of up to 90% (MacMillan *et al*, 2015; Smetsers *et al*, 2016). The main reason for this improvement over time is the use of fludarabine (Peffault de Latour et al, 2013; Smetsers *et al*, 2016). Peffault de Latour (2013) identified age at transplant as an adverse risk factor for outcome, with age above 10 years being the cut-off. Recently, Mehta *et al* (2017), using a radiation-free conditioning regimen, reported excellent results in children under 10 years of age using a low-dose busulfan containing regimen. In this series, five patients were transplanted between the ages of 22 and 44 years, with considerable comorbidities. Only one adult survived the transplant period.

We also confirm a poorer HSCT outcome in adult patients compared to that seen in younger patients. Even in the modern era (2009–2014), survival in this study is limited to 50%.

Our results raise several important issues: should all FA patients with signs of BM failure undergo HSCT at a young age? This concern is supported by a number of observations: Svahn *et al* (2016) recently described a fairly large Italian patient cohort in which 33% of patients improved or maintained mild-to-moderate cell counts over time, illustrating the uncertain course of BM failure in a substantial subgroup of FA patients. Secondly, there remains a risk of transplant-related mortality (TRM), even at a young age. Furthermore, there is a cumulative risk of developing secondary malignancies after transplant, which increases with time. Exposing FA patients to chemo- and/or radiotherapy may induce malignant transformation (Rosenberg *et al*, 2005). Whether this holds true for modern fludarabine-based regimens requires long-term follow-up. This may also be true for other late effects after transplant for FA, such as endocrinopathies and organ damage (Anur *et al*, 2016; Barnum *et al*, 2016). The presence of chronic GvHD is also associated with an increased risk of developing cancer (Rosenberg *et al*, 2005). These data support the case against performing transplants at an early age if not clearly necessary.

Khan *et al* (2016) developed a model to predict the benefits of pre-emptive HSCT (PE-HSCT) (i.e. before the onset of symptoms) for FA in varying scenarios. They concluded that PE-HSCT is of limited value at an adult age, due to the high risk of TRM. In children, PE-HSCT may contribute to a better life-expectancy, presuming a low TRM and a conditioning regimen that does not increase the risk of solid tumours. Our data would further support this approach.

Our results identify a high risk of a poorer outcome when using a mismatched non-sibling donor, and this warrants strong caution.

Current conditioning regimens may be less ablative, thus leading to mixed chimerism. Persisting mixed chimerism in a recipient with Fanconi-type, patient-derived haematopoietic cells post-chemotherapy exposure may pose a long term leukaemia risk. However, compelling data is still lacking.

Counselling patients and their relatives regarding if and when to proceed to HSCT thus remains an individual process. Tight monitoring of haematopoiesis and clonal evolution may help guide this.

Increasing awareness that patients with inborn BM failure syndromes may present at an adult age with unusual cancers, detection of familial cases of myelodysplasia or BM failure and/or unexpected major toxicities of chemo- and radiotherapy will lead to more adults being diagnosed with FA. In turn, this will mean that more patients will face the risks of transplant at an adult age.

From our data, it is difficult to define the best conditioning regimen for FA patients. It should include fludarabine, but whether adding low dose busulfan or low dose irradiation facilitates engraftment is, at this point, still unclear. There is however, a clear need to further develop study protocols for HSCT in adults with FA. The ClinicalTrials.gov database includes several ongoing trials that include transplantation for adult FA patients. One of these trials evaluates a busulfan 0·8 mg/kg twice daily for 2 days based regimen,

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Table IV. Factors associated with overall survival.

	Univariate analysis		Full multivariate analysis		After variable selection	
Variable	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Period						
1991–2000	1	0·070	1	0·34		
2001–2008	0·82 (0·53–1·26)		0·71 (0·40–1·27)			
2009–2014	0·58 (0·36–0·92)		0·60 (0·30–1·20)			
Age at HSCT (years)						
18–20	1	0·62	1	0·39		
21–30	1·21 (0·79–1·84)		1·28 (0·81–2·02)			
31–45	1·24 (0·74–2·08)		1·46 (0·83–2·57)			
Time to transplant (years), as log	1·16 (1·04–1·31)	0·011	1·11 (0·97–1·28)	0·13	1·11 (0·98–1·26)	0·096
Donor						
Identical sibling	1	<0·0001	1	<0·0001	1	<0·0001
Matched non-sibling	1·80 (1·13–2·86)		2·32 (1·26–4·24)		1·77 (1·07–2·93)	
Mismatched non-sibling	3·28 (2·10–5·12)		4·41 (2·40–8·10)		3·84 (2·30–6·40)	
Stem cell source						
BM	1	0·078	1	0·55		
PB	1·09 (0·74–1·60)		1·30 (0·78–2·17)			
CB	2·23 (1·11–4·49)		1·38 (0·57–3·36)			
Gender matching						
Female/male	1	0·61	1	0·36		
Other combinations	0·88 (0·53–1·45)		0·76 (0·42–1·36)			
Donor/recipient CMV status						
Negative/negative	1	0·86	1	0·57		
Negative/positive	1·08 (0·56–2·07)		1·34 (0·65–2·77)			
Positive/negative	1·15 (0·52–2·54)		1·11 (0·45–2·72)			
Positive/positive	0·89 (0·53–1·50)		1·60 (0·83–2·83)			
Cyclophosphamide						
No	1	0·50	1	0·15		
Yes	0·74 (0·32–1·75)		0·48 (0·18–1·30)			
Fludarabinee						
No	1	0·19	1	0·010	1	0·001
Yes	0·77 (0·52–1·14)		0·44 (0·24–0·83)		0·48 (0·31–0·75)	
Busulfan						
No	1	0·011	1	0·19	1	0·070
Yes	1·82 (1·15–2·89)		1·47 (0·83–2·62)		1·55 (0·96–2·51)	
TBI						
No	1	0·47	1	0·68		
Yes	1·16 (0·77–1·74)		0·89 (0·52–1·53)			
ATG						
No	1	0·70	1	0·49		
Yes	1·08 (0·73–1·58)		1·17 (0·75–1·83)			
Ex-vivo T-cell manipulation						
No	1	0·12	1	0·62		
Yes	1·47 (0·90–2·41)		0·86 (0·41–1·70)			

ATG, anti-thymocyte globulin; BM, bone marrow; CB, cord blood; CI, confidence interval; CMV, cytomegalovirus; HR, hazard ratio; PB, peripheral blood; TBI, total body irradiation.

including FA patients up to age of 44 years (clinicaltrials.gov. NCT00258427). Ongoing studies developing gene therapy for FA may offer reductions in the risks of HSCT, thus being especially relevant to adult patients (Ebens *et al*, 2017), although their limited stem cell reservoir may hamper a gene therapy approach.

Graft-versus-host disease should be avoided in these FA patients, especially as it raises the risk for secondary malignancies (Svahn *et al*, 2016). Our data indicate that both acute and chronic GvHD are important issues.

Although our dataset is incomplete, clonal disease at transplant led to an inferior outcome, particularly if overt leukaemia was present. This is in line with previous findings: Ayas *et al* (2013) analysed a group of 113 patients with cytogenetic abnormalities, myelodysplastic syndrome or acute leukaemia at transplant. Young age and the presence of

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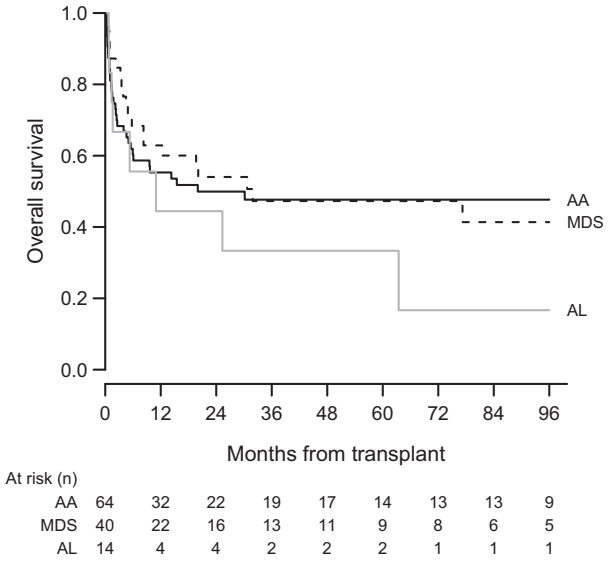

Fig 2. Overall survival by bone marrow status at transplant. Data were missing for 81 patients. No significant difference in overall survival was found ($P = 0{\cdot}28$). AA, aplastic anaemia; AL, acute leukaemia; MDS, myelodysplastic syndrome.

cytogenetic abnormalities only (i.e. no overt myelodysplasia or leukaemia) at transplant led to a better outcome. Peffault de Latour and Soulier (2016) recently described their experience in case of clonal disease in FA patients.

There are some limitations to our study, most inherently linked to the retrospective nature of this registry analysis that precluded complete data sets being available. However, this retrospective series is of a magnitude that cannot be achieved prospectively. It stresses the urgent need for long term follow-up of these patients with a highly increased susceptibility to develop malignancies. We also note that the transition of patients from paediatric care systems to adult health care has proven challenging.

Fanconi anaemia is a rare, complex disease in which treatment at an adult age for BM failure, clonal haematopoietic disease and solid tumours are all difficult. Increased awareness that this disorder may present at an adult age, and therefore better detection rates, raises the sense of urgency to develop networks to share information and develop trials for these patients.

Author's contributions

MB, CB, RPL, RP and CD designed the study, analysed the data and wrote the manuscript. MA, PM, FB, AT, AE, GM, GS, TO, CH, BC, DN, MZ, NK, MM, OR and GE contributed patient data and critically reviewed the analysis and the manuscript. CK collected the data and initialized the analysis.

Conflicts of interest

The authors report no conflicts of interest.

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