Title : Excellent overall and chronic GVHD free event free survival in Fanconi patients undergoing matched related and unrelated donor BMT using Alemtuzumab/Fludarabine/Cyclophosphamide conditioning

Short title : HSCT for Fanconi patients : UK experience

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Abstract

Haematopoietic stem cell transplantation (HSCT) remains the only curative option in Fanconi anaemia (FA). We analysed the outcome of children transplanted for FA between 1999 and 2018 in UK. A total of 94 transplants were performed in 82 patients. 51.2% of the donors were matched related donors (MRD) while the remaining were alternative donors. Most patients received a fludarabine-cyclophosphamide (Flu-Cy) based conditioning regimen (86.6%) and in vivo-T-cell depletion with alemtuzumab (69.5%). 5y-OS was 85.4% [70.4-93.2] with MRD, 95.7% [72.9-99.4] with matched unrelated donors (MUD), 44.4% [6.6-78.5] with mismatched unrelated donors (MMUD) and 44.4% [13.6-71.9] with MMRD ($p<0.001$). Other factors significantly impacting OS were pre-transplant bone marrow status, source of stem cells, CMV

serostatus, preparation with Flu-Cy, use of TBI and Alemtuzumab as serotherapy. In multivariate analysis, absence of MDS or leukemia, bone marrow as source of stem cells, CMV other than +/- (Recipient/Donor) and Flu-Cy were protective factors for 5y-OS. 5y-chronic GVHD free EFS was 75.4% with the same risk factors except for CMV serostatus. 5y-non-relapse mortality was 13.8% [7.3-22.3]. Only 5 patients (6.1%) developed grade II-IV acute GVHD and 2 patients chronic GVHD. These data confirm the excellent outcome of matched related or unrelated HSCT in children with FA.

Introduction

Fanconi anaemia is an inherited DNA repair disorder characterised by congenital abnormalities, bone marrow failure (BMF) and a predisposition to develop malignancies, especially acute myeloid leukaemia (AML) and squamous cell carcinoma(SCC) [1]. Pathogenic variants in at least 22 FA-genes coding for proteins involved in a complex network for DNA damage repair, have been identified as causative for FA. With bi-allelic disruption, they lead to a heterogenous constellation of phenotypes. In most cases, transmission is autosomal recessive [2].

To date, haematopoietic stem cell transplantation (HSCT) still represents the only curative option for FA-associated BMF but does not prevent secondary malignancies or other organ dysfunctions. Historically, standard conditioning regimen relied mainly on alkylating agents and HSCT in FA patients was characterised by very poor outcome [3]. Through the last three decades, thanks to optimization of preparative conditioning regimen, GVHD prophylaxis, HLA-typing and supportive care, excellent results were achieved in matched sibling donor (MSD) transplantations [4]. With alternative donors, despite marked improvements in outcomes, the best strategy is yet to be determined [3]. Another remaining challenge will be to minimize the risks for long-term morbidity and secondary malignancies, potentially increased post-HSCT [3].

In this study, we aimed to evaluate the outcome and risk factors after HSCT in a recent cohort of paediatric FA patients.

Methods

Patients

We conducted a retrospective study on paediatric patients diagnosed with Fanconi anaemia who underwent HSCT in the UK. All patients younger than 20 years and transplanted between 01.01.1999 and 31.12.2018 in the participating centres were included. Data were collected in each centre from medical records and processed anonymously in a dedicated study database. We collected data on patient demographics, disease characteristics and pre-transplant status, donor type, stem cell source, conditioning regimen, engraftment, graft-versus-host disease (GVHD), chimaerism, outcome and duration of follow-up. All data were carefully checked and centres physicians were contacted if any inconsistencies were detected. Informed consent was obtained from all parents/patients according to the local centre and European Society for Blood and Marrow Transplantation and Declaration of Helsinki guidelines.

Disease and transplant characteristics

Congenital abnormalities were defined as any extra-haematopoietic manifestation of FA including skin abnormalities. Reason for transplants was BMF (defined as severe neutropenia <0.5 x 10^9/L and/or persistent transfusion need), myelodysplastic syndrome and/or clonal abnormalities (MDS) or acute leukaemia. All stem cell sources were included : bone marrow (BM), peripheral blood stem cells (PBSC) or umbilical cord blood (UCB). Donors were classified as matched donors if the HLA-compatibility was 10/10 when BM or PBSC was used or 6/6 when UCB was used, and as mismatched donors when HLA-compatibility was ≤9/10 for BM and PBSC or ≤5/6 for UCB. For comparison purposes in dates of HSCT, 2 time periods were set as 1999-2008 and 2009-2018.

Endpoints

Primary endpoint was overall survival at 5 years post-HSCT (5y-OS). Chronic GVHD free event free survival at 5 years post-HSCT (5y-cGVHD free EFS) was defined as survival free from cGVHD, graft failure or relapse of MDS/leukemia. Non-relapse mortality (NRM) was defined as any cause of death other than return of marrow to its status before transplant as in Peffault de Latour et al [4]. Primary graft loss was defined by either absence of neutrophil recovery or neutrophil recovery with autologous reconstitution. Secondary graft failure was defined as occurrence of secondary autologous reconstitution while neutrophil recovery with donor chimaerism was achieved before. Acute GVHD (aGVHD) was scored according to the modified Glucksberg criteria [5].

Statistical analysis

For outcomes analyses, only data of first transplants were included. The reverse Kaplan-Meier approach was used to calculate the median follow-up duration. OS at 5 years post-HSCT was estimated using Kaplan-Meier curves. Log-rank tests were used to compare survival between groups in univariate analysis. Factors associated with 5y-OS were studied using Cox-Proportional hazards regression in multivariate analysis. All variables that were significant in univariate analysis were included in the multivariate model. Final multivariate model was selected based on the Akaike information criteria (AIC). The same methods were applied to 5y-cGVHD free EFS. Individuals with no missing data in any of the variables were included in multivariate analyses (n=75). Cumulative incidences of NRM were obtained using the cumulative incidence function in competing risk package (cmprsk) in R [6]. The statistical significance level was set at <0.05. Data analyses were carried out using the statistical software "R" version 3.6.2 with "Rcmdr" package version 2.6.1, version 2.6.1, "survival" package and "cmprsk2" packages.

Results

Patients and disease characteristics

Eighty-two patients were included in the study, with a median follow-up post-transplant of 74.4 months. Patients and Fanconi disease characteristics are shown in Table 1. Median age at first transplant was 8.7 years. The most frequently identified causative gene, when known,

was *FANCA*. 69 patients (84%) received HSCT for BMF while 8 (10%) had developed MDS and 3 (4%) AML at the time of transplant (data unavailable for 2 patients). Details of pre-transplant treatments and transfusion needs are shown in Table 1.

Transplant characteristics

A total of 94 transplants were performed during the study period in the participating centres, with a majority (58 HSCT) between 2009 and 2018. An average of 4 transplants were performed each year, with only 1 transplant in 2002 and 2003.

Eighty-two were first transplants and details for these procedures are shown in Table 2. Approximately half of the donors were matched related donors (MRD), while the other half were alternative donors. Mismatched unrelated donors (MMUD) displayed 1 HLA-mismatch in 4 patients, and 2 mismatches in 2 patients. All mismatched related donors (MMRD) were haplo-identical (5/10 or 6/10). A fludarabine-cyclophosphamide (Flu-Cy) based conditioning regimen was used in most cases (71 patients, 86.6%). TBI was added in 10 patients with a dose of either 300 cGy (n=5) or 450 cGy (n=5). Three patients transplanted in the first years of the study period received a conditioning regimen consisting of thoraco-abdominal irradiation (TAI) 5 Gy and cyclophosphamide. Eight more patients received either fludarabine or cyclophosphamide alone or busulphan. Serotherapy was used in all but 7 patients and Alemtuzumab was chosen in most cases (69.5% of all patients). Ex vivo T cell depletion with CD34 selection (n=6) or TCRαβ depletion (n=2) was used in the majority of transplants from mismatched donors. 91% received GVHD prophylaxis with cyclosporin or tacrolimus.

Ten patients received a second transplant. Nine of them were initially transplanted for BMF from a MMRD in 4, MMUD in 2, MUD in 2 and MRD in 1. One had pre-transplant MDS and received a MMUD transplant. Second transplants were performed for primary (7 patients) or secondary (2 patients) graft failures, or post-HSCT relapse of MDS (1 patient). Time from first to second transplant ranged from 1.1 to 6.9 months. 7/10 were prepared with a fludarabine-cyclophosphamide based conditioning regimen and 3 received TBI (200 or 500 cGy).

One patient, transplanted for MDS, received 3 HSCTs in 14 months from an unrelated donor due to primary graft failure followed by transformation to acute myeloid leukaemia and then to leukaemic relapse.

Haematopoietic recovery and engraftment

Median time for neutrophil recovery was 18 days (range : 9-35 days). Data on chimaerism were available in 59 of 71 evaluable patients (alive and without graft failure at D100) and was ≥95% donor cells in 49 of them. Primary graft failure occurred in 8 patients (9.8%). Secondary graft failure occurred in 2 patients. Both had received a haplo-identical HSCT for BMF. All were retransplanted. Of note, patients who underwent more than one transplant had a significantly worse 5y-OS (36.4% vs 87.0%, $p<0.001$).

Acute and chronic GVHD

Only 5 patients (6.1%) developed grade II-IV aGVHD. Only one had received alemtuzumab and one ATG. In the 2 patients who developed grade IV aGVHD, HSCT was performed without *in vivo* or *ex vivo* T-cell depletion. Two patients developed cGVHD, one was extensive. Donors were MRD for one and MMRD for the other and both HSCTs were performed without

serotherapy or T-cell depletion. Of note, no acute or chronic GHVD was reported after MUD or MMUD HSCTs.

Survival

Overall survival at 5 years post-HSCT on the whole cohort was 79.9% [69.2-87.2]. Survival was compared according to pre-transplant characteristics : date of HSCT, age at HSCT, gender, presence of congenital abnormalities, previous treatment with androgens, platelet-transfusion dependency, RBC-transfusion dependency and reason for transplant. Pre-transplant MDS or leukaemia lead to significantly lower 5y-OS than BMF (39.8% [11.0-68.0] vs 88.2% [77.8-93.9], p<0.001) as shown in Figure 1A. Other pre-transplant characteristics did not impact survival. 5y-OS was high with matched related or unrelated donors, respectively 85.4% [70.4-93.2] and 95.7% [72.9-99.4]. Overall survival was significantly decreased in recipients of MMUD (44.4% [6.6-78.5]) or MMRD (44.4% [13.6-71.9]) grafts, p<0.001 (Figure 2A). As shown in Figure 2C, use of BM as the stem cell source was associated with improved OS compared to PBSC or UCB (p=0.01). Regarding conditioning regimen, Flu-Cy based conditioning regimen, absence of TBI and use of Alemtuzumab significantly improved 5y-OS (Figure 3A and 3C). A CMV +/- (R/D) status resulted in lower OS (p=0.02) while gender match had no influence. Transplantation before transformation, use of fludarabine-based conditioning, bone marrow as the stem cell source and CMV serostatus other than CMV+/- were associated with improved OS in multivariate analysis as shown in Table 3.
cGHVD free EFS at 5 years was 75.4% [64.5-83.4] on the whole cohort. It was 85.6% [70.8-93.3], 87.0% [64.8-95.6], 0%, 44.4% [13.6-71.9] in recipients of MRD, MUD, MMUD, and MMRD grafts respectively (p<0.0001, Figure 2B). 5y-GVHD free EFS was also significantly improved in BMF vs MDS/leukaemia (p<0.01, Figure 1B), when BM stem cells were used (p=0.01, Figure 2D), and when conditioning regimen included Flu-Cy (p<0.0001, Figure 3B), alemtuzumab (p<0.0001, Figure 3D) and did not contain irradiation (p=0.01). There was also a trend for better 5y-GVHD free EFS in CMV serostatus other than CMV+/- (p=0.05). Table 3 reports results of multivariate analysis.

Causes of deaths

Figure 4 describes mortality from relapse and NRM over time. NRM at 5 years was 13.8% [7.3%-22.3%]. Most deaths (12/18) occurred within a year from HSCT. Late deaths were attributed to: relapse of MDS/leukaemia (2), gliomatosis cerebri (1), chronic GVHD complicated with sepsis (1), bronchiolitis obliterans with chronic lung disease (1), and undetermined cause (1).
Death was due to viral infection in 2 patients (adenovirus) transplanted for BMF. Of note, both patients received 2 HSCTs from haplo-identical donors due to graft failure. One patient had received Alemtuzumab before his first transplant and then ATG, the other received only ATG as part of conditioning for both HSCTs.

Post-HSCT malignancies

Secondary malignancies were recorded in 3 patients. One was diagnosed with gliomatosis cerebri at the age of 16 years, 9 years post-transplant. He died one year later from

progression. One patient developed gingival SCC at the age of 23 years (7 years post-transplant) and oesophagus 4 years later. He was treated with resection and local radiotherapy and was alive at last follow-up. The third patient developed a tumour of the tongue at the age of 26 years (7 years post-transplant). All these patients had received irradiation as part as their conditioning regimen : TAI 5 Gy for the first patient, TBI 4.5 Gy for the others. None of them had developed previous cGVHD.

Discussion

In this study, we have reviewed the outcomes of HSCT for paediatric patients with FA in the UK in the modern era. Despite the limitations inherent in a retrospective study, our data provide important insights into prognostic factors in this patient group. Overall outcomes were good with 79.9% OS and 75.4% GVHD free EFS at 5 years post-transplant, confirming the improvement of outcomes with time reported by Smetsers *et al* on the Dutch cohort [7]. Results of MSD HSCT have dramatically improved over the last decades with the decrease in doses of cyclophosphamide, the introduction of fludarabine and the limited use of radiotherapy [4]. Nevertheless, unrelated donor HSCT is still considered as alternative in FA patients. MacMillan et al [8] first showed an improvement in alternative donor transplant with a 5y-OS of 58%. Factors for improved survival in the latter study were use of fludarabine and of lower doses of TBI, younger age, no prior opportunistic infection and positive recipient CMV serostatus. Later, the same group confirmed these very encouraging results in alternative donor transplants and obtained a 5y-OS of 86% with the use of low dose TBI [9]. Efforts have been made through the years to avoid TBI in FA patients as regards to their increased risk of secondary malignancies and endocrine late effects [3]. Excellent results have also been reported using radiation-free fludarabine based conditioning regimens in a small German cohort [10] and on a recent US Phase II trial [11]. In our cohort, the outcome of MUD HSCT was excellent with a 5y-OS of 95.7% and 5y-GVHD free EFS of 87.7%. All these patients had received a Flu-Cy conditioning regimen, with the addition of low dose TBI in only 3 of 23 patients. Our real-life data confirms that MUD transplantation without irradiation in FA patients can lead to excellent results and given the high risk of secondary malignancy in this cohort indicate radiation should be avoided in the context of 10/10 HLA match. Moreover, these data indicate that 10/10 MUD HSCT should not be considered an alternative transplant in FA and is an equally valid approach if no MRD is available. However, outcomes following other alternative donors HSCT in our cohort were very poor. Recent studies on alternative donor transplants [9-11] did not discriminate outcomes of mismatched donors from MUD. Despite limitations related to the size of the cohort, our study suggests that outcomes of mismatched transplants in FA patients remain suboptimal consistent with published data [12, 13]. Recently, new techniques for haplo-identical transplants [14, 15] have achieved improved results and these may represent a better alternative for FA patients with an indication to transplant but no available matched donor.

Our multivariate analysis identified pre-transplant bone marrow status, source of stem cells, CMV serostatus and use of fludarabine-based conditioning as predictors for OS, consistent with previous reports [3, 4, 8]. Interestingly, the use of Alemtuzumab lead to a very significant improvement on 5y-OS (91.2% *vs* 53.8%, p<0.0001) and 5y GVHD free EFS (87.7% *vs* 46.4%, p<0.0001) in univariate analysis but failed to achieve significance in the multivariate model. This might be explained by low numbers and also a strong co-linearity between use of

Alemtuzumab and source of stem cells (Fisher's test, p<0.0001). Although its use has scarcely been reported [10], Alemtuzumab could have a role to play in FA similar to what was described in acquired aplastic anaemia [16, 17]. The incidence of GVHD was too low in our cohort to study risk factors but the use of serotherapy with Alemtuzumab or ATG in almost all patients (including MSD) probably accounts for the decreased acute and chronic GVHD rates in comparison to previous registry studies [4, 7]. Viral infections can be a major concern with the use of Alemtuzumab. In this cohort, only viral infections leading to death were reported and occurred in both cases after a second haplo-identical transplant without Alemtuzumab. Further studies are needed to assess the risk of viral reactivations in FA patients receiving Alemtuzumab.

An important remaining concern in HSCT for FA patients is late mortality due mainly to cGVHD and malignancies. Both issues can be related as cGVHD was shown to be a risk factor for secondary malignancies [4]. Using Alemtuzumab as serotherapy could be a strategy to lower cGVHD, and thus decrease secondary malignancies and late mortality. Secondary malignancies in our study were not frequent although longer follow-up is required to draw any conclusion, as frequencies increase with time after HSCT [4, 18].

Due to the limited number of patients in the context of a rare disease, only risk factors significantly influencing survival in the univariate analysis were selected for the multivariate analysis. With this approach we may have omitted some of the risk factors. Also, owing to the limited number of events, the results of our multivariate analysis should be taken cautiously and has to be considered as an exploratory analysis.

Our study provides real-life data confirming the excellent outcome of matched related or unrelated HSCT in children with FA but disappointing results in mismatched HSCT. Very low rates of aGVHD and cGVHD were reported and specific benefit of the use of Alemtuzumab in this disease should be further evaluated with very long follow-up.

Acknowledgements

F.B. designed the study, analysed the data and wrote the paper. C.R.S.U. analysed the data and revised the manuscript. S.M., K.P., B.J., R. S., S.T., B.C., R. W. collected the data and revised the manuscript. P.V. and P. A. designed the study and revised the manuscript.

References

1. Auerbach AD. Fanconi anemia and its diagnosis. Mutat Res. 2009;668(1-2):4-10.
2. Fiesco-Roa MO, Giri N, McReynolds LJ, Best AF, Alter BP. Genotype-phenotype associations in Fanconi anemia: A literature review. Blood Rev. 2019;37:100589.
3. Ebens CL, MacMillan ML, Wagner JE. Hematopoietic cell transplantation in Fanconi anemia: current evidence, challenges and recommendations. Expert Rev Hematol. 2017;10(1):81-97.
4. Peffault de Latour R, Porcher R, Dalle JH, Aljurf M, Korthof ET, Svahn J, et al. Allogeneic hematopoietic stem cell transplantation in Fanconi anemia: the European Group for Blood and Marrow Transplantation experience. Blood. 2013;122(26):4279-86.
5. Przepiorka D, Weisdorf D, Martin P, Klingemann HG, Beatty P, Hows J, et al. 1994 Consensus Conference on Acute GVHD Grading. Bone Marrow Transplant. 1995;15(6):825-8.
6. Gray RJ. A Class of K-Sample Tests for Comparing the Cumulative Incidence of a

Competing Risk. The Annals of Statistics. 1988;16(3):1141-54.
7. Smetsers SE, Smiers FJ, Bresters D, Sonnevelt MC, Bierings MB. Four decades of stem cell transplantation for Fanconi anaemia in the Netherlands. Br J Haematol. 2016;174(6):952-61.
8. MacMillan ML, DeFor TE, Young JA, Dusenbery KE, Blazar BR, Slungaard A, et al. Alternative donor hematopoietic cell transplantation for Fanconi anemia. Blood. 2015;125(24):3798-804.
9. Ebens CL, DeFor TE, Tryon R, Wagner JE, MacMillan ML. Comparable Outcomes after HLA-Matched Sibling and Alternative Donor Hematopoietic Cell Transplantation for Children with Fanconi Anemia and Severe Aplastic Anemia. Biol Blood Marrow Transplant. 2018;24(4):765-71.
10. Chao MM, Kuehl JS, Strauss G, Hanenberg H, Schindler D, Neitzel H, et al. Outcomes of mismatched and unrelated donor hematopoietic stem cell transplantation in Fanconi anemia conditioned with chemotherapy only. Ann Hematol. 2015;94(8):1311-8.
11. Mehta PA, Davies SM, Leemhuis T, Myers K, Kernan NA, Prockop SE, et al. Radiation-free, alternative-donor HCT for Fanconi anemia patients: results from a prospective multi-institutional study. Blood. 2017;129(16):2308-15.
12. Chaudhury S, Auerbach AD, Kernan NA, Small TN, Prockop SE, Scaradavou A, et al. Fludarabine-based cytoreductive regimen and T-cell-depleted grafts from alternative donors for the treatment of high-risk patients with Fanconi anaemia. Br J Haematol. 2008;140(6):644-55.
13. Zecca M, Strocchio L, Pagliara D, Comoli P, Bertaina A, Giorgiani G, et al. HLA-haploidentical T cell-depleted allogeneic hematopoietic stem cell transplantation in children with Fanconi anemia. Biol Blood Marrow Transplant. 2014;20(4):571-6.
14. Bertaina A, Merli P, Rutella S, Pagliara D, Bernardo ME, Masetti R, et al. HLA-haploidentical stem cell transplantation after removal of alphabeta+ T and B cells in children with nonmalignant disorders. Blood. 2014;124(5):822-6.
15. Bonfim C, Ribeiro L, Nichele S, Loth G, Bitencourt M, Koliski A, et al. Haploidentical Bone Marrow Transplantation with Post-Transplant Cyclophosphamide for Children and Adolescents with Fanconi Anemia. Biol Blood Marrow Transplant. 2017;23(2):310-7.
16. Marsh JC, Pearce RM, Koh MB, Lim Z, Pagliuca A, Mufti GJ, et al. Retrospective study of alemtuzumab vs ATG-based conditioning without irradiation for unrelated and matched sibling donor transplants in acquired severe aplastic anemia: a study from the British Society for Blood and Marrow Transplantation. Bone Marrow Transplant. 2014;49(1):42-8.
17. Samarasinghe S, Clesham K, Iacobelli S, Sbianchi G, Knol C, Hamladji RM, et al. Impact of T-cell depletion strategies on outcomes following hematopoietic stem cell transplantation for idiopathic aplastic anemia: A study on behalf of the European blood and marrow transplant severe aplastic anemia working party. Am J Hematol. 2019;94(1):80-6.
18. Risitano AM, Marotta S, Calzone R, Grimaldi F, Zatterale A, Contributors R. Twenty years of the Italian Fanconi Anemia Registry: where we stand and what remains to be learned. Haematologica. 2016;101(3):319-27.

Figure 1 : OS (A) and cGVHD EFS (B) according to reason for transplant

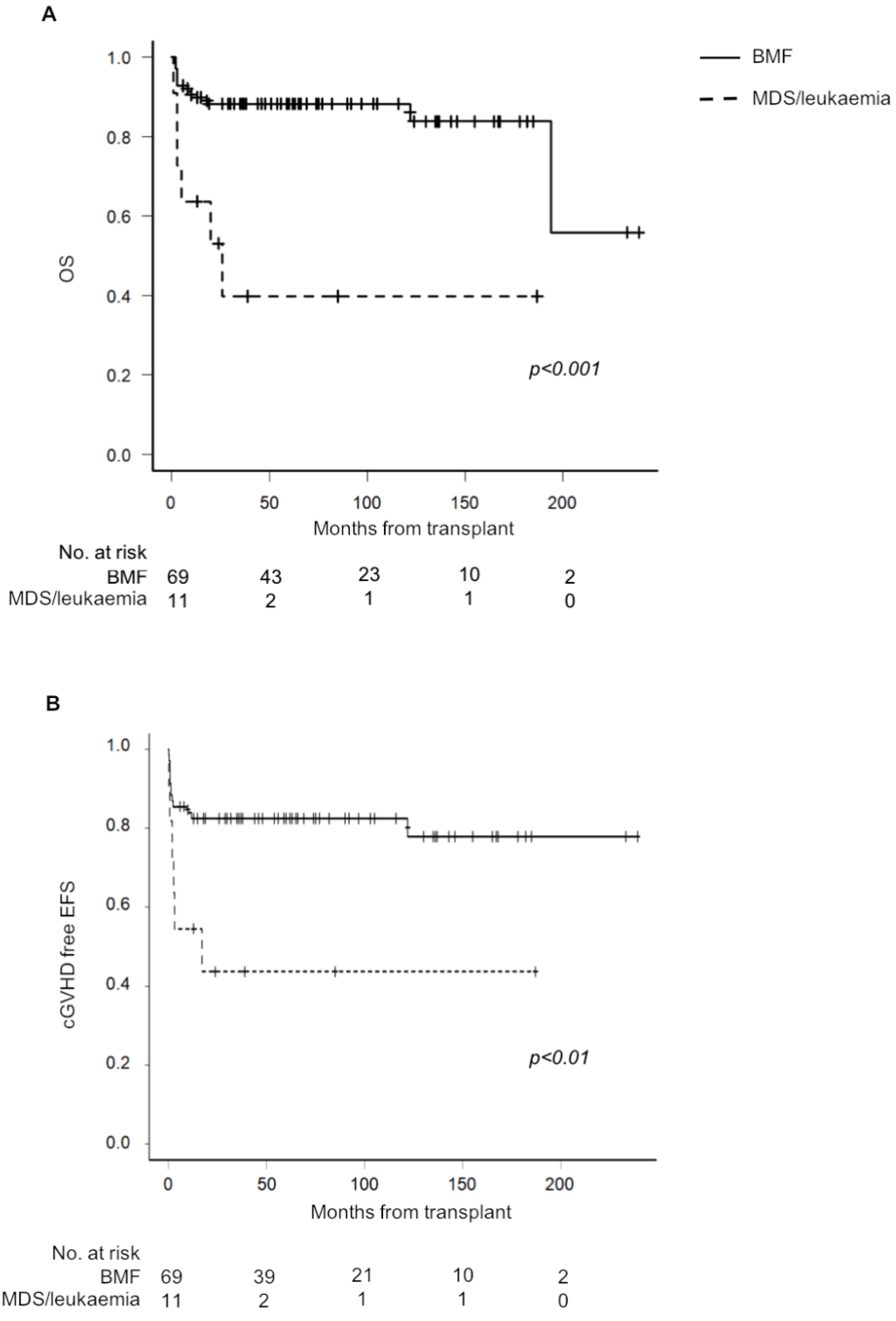


Figure 2 : OS (A, C) and cGVHD EFS (B, D) according to donor type and stem cell source

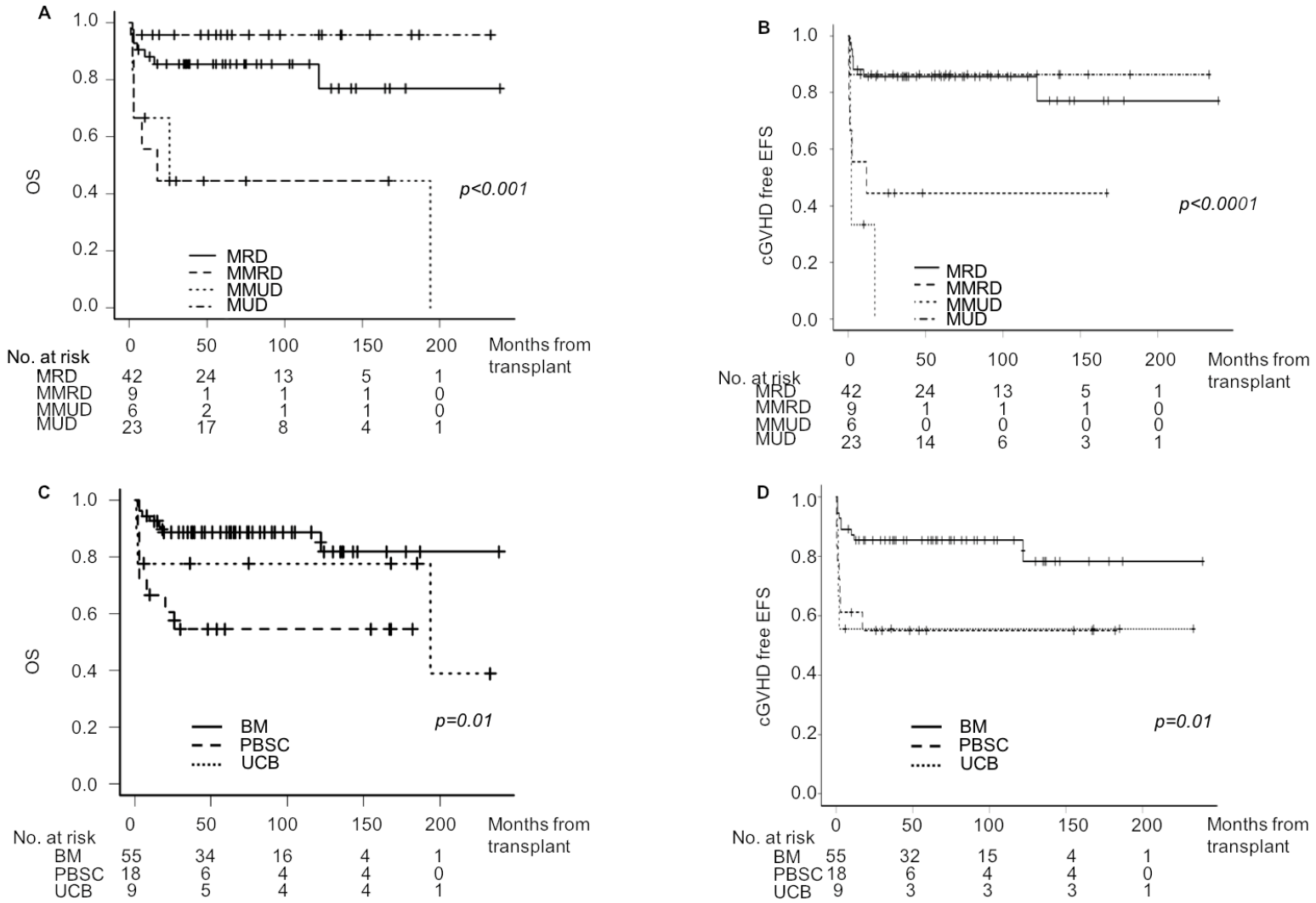
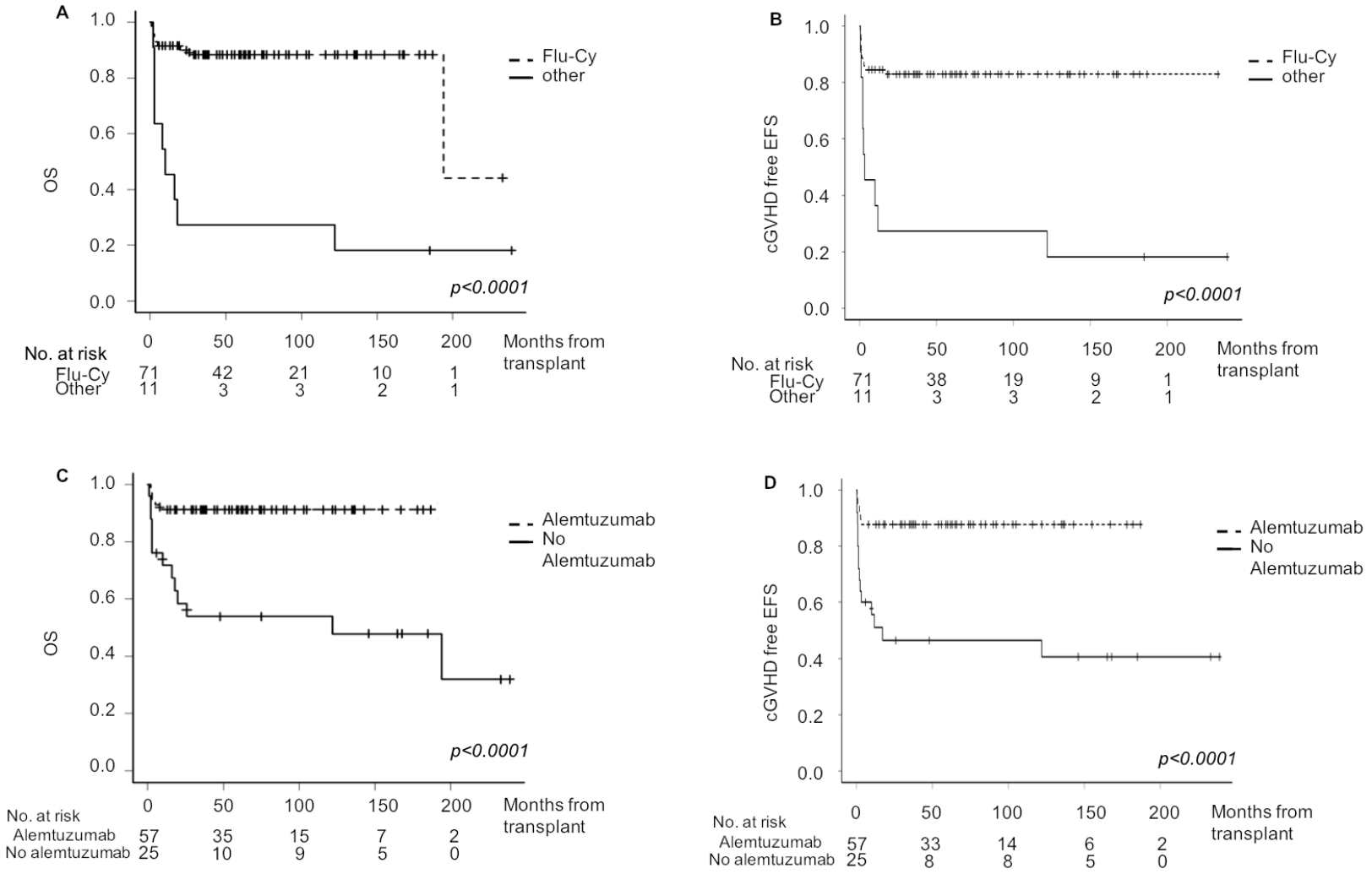


Figure 3 : OS (A, C) and cGVHD EFS (B, D) according to conditioning regimen and use of alemtuzumab



<u>Figure 4</u> : Cumulative incidence of non-relapse and relapse mortality