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# Matched unrelated donor stem cell transplant in 131 patients with follicular lymphoma: an analysis from the Lymphoma Working Party of the European Group for Blood and Marrow Transplantation

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## Summary

Matched unrelated donor stem cell transplantation (MUD-SCT) provides the only curative option for patients with follicular lymphoma (FL) who fail conventional therapies and do not have a sibling donor. The purpose of this study was to analyse the outcome of patients with FL treated with MUD-SCT included in the European Group for Blood and Marrow Transplantation registry. 131 patients treated with reduced-intensity conditioning (RIC, $n = 87$) or conventional myeloablative (CONV, $n = 44$) MUD-SCT between 2000 and 2005 were included. Median time from diagnosis to MUD-SCT was 47 months and the median number of previous therapeutic regimens was 4 (previous autograft: 47%). RIC recipients were significantly older, with a longer interval from diagnosis to MUD-SCT and had failed a previous autograft more frequently than CONV recipients. Non-relapse mortality (NRM) was 24% and 30% at 100-d and 1-year, respectively. After a median follow-up of 36 months, 17% of the patients developed disease progression, the 3-year progression-free survival (PFS) being 47%. Three-year overall survival (OS) for the whole series was 51%. On multivariate analysis, RIC regimens were associated with at lower NRM and a significantly longer PFS and OS. This retrospective study demonstrated that MUD-SCT results, even in heavily pre-treated populations, in a meaningful PFS and OS.

**Keywords:** matched unrelated donor transplant, conditioning regimen, follicular lymphoma.

 

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The number of available treatment options for patients with follicular lymphoma (FL) has expanded considerably in recent years and has translated into an improved outcome (Fisher *et al*, 2005; Swenson *et al*, 2005; Liu *et al*, 2006). Autologous stem cell transplantation (ASCT) has been reported to prolong progression-free survival (PFS) and overall survival (OS)(Schouten *et al*, 2003), particularly if performed early in the course of the disease(Lenz *et al*, 2004; Deconinck *et al*, 2005; Sebban *et al*, 2006; Montoto *et al*, 2007; Rohatiner *et al*, 2007; Kornacker *et al*, 2009). However, considerable proportions of patients eventually relapse and die of their disease. In contrast, allogeneic stem cell transplantation (allo-SCT) is recognized as a potentially curative approach, providing the graft-versus-lymphoma (GVL) effect required for complete eradication of the malignant clone(Marks *et al*, 2002; van Besien *et al*, 2003; Hosing *et al*, 2003; Peniket *et al*, 2003). Unfortunately, this advantage is offset by a high mortality rate, which has been observed particularly with conventional conditioning (CONV) allografts (van Besien *et al*, 2003; Hosing *et al*, 2003; Peniket *et al*, 2003). The introduction of reduced-intensity conditioning (RIC) regimens has been shown to decrease non-relapse mortality (NRM) in different studies(Niederwieser *et al*, 2003; Faulkner *et al*, 2004; Morris *et al*, 2004; Corradini *et al*, 2007; Khouri *et al*, 2008), including mostly matched sibling allografts. However, whether a matched unrelated allograft is a reasonable option for patients with advanced FL without a matched sibling donor remains an open question (Izutsu *et al*, 2004; Rezvani *et al*, 2008). The aim of this study was to assess the outcome of matched unrelated donor stem cell transplantation (MUD-SCT) in FL and to define the prognostic parameters in this setting.

## Patients and methods

### *Study design*

The European Group for Blood and Marrow Transplantation (EBMT) is a voluntary organization comprising 525 transplant centres, mainly from Europe. Participating centres register basic information on all consecutive SCT to the EBMT Central Registry Office. All EBMT centres were invited to contribute their data on patients treated with a CONV or RIC MUD-SCT for FL. No patients with histological transformation were included. Data from 60 participating centres were derived from the EBMT database and from questionnaires distributed among the centres. Additional follow-up questionnaires were sent to obtain missing data, update disease status and record the presence of graft-*versus*-host disease (GVHD). Patients receiving a MUD transplant from January 2000 until July 2005 were included in the study. Histological diagnosis was based on local review.

### *Definitions*

According to established EBMT criteria (Table S1; http://www.ebmt.org/4Registry/Activity/As05/ReducedIntensity2005.pdf), CONV conditioning regimens included: (i) cyclophosphamide plus total body irradiation (TBI), (ii) cyclophosphamide plus busulphan, with or without other cytotoxic agents and/or antithymocyte globulin (ATG) or alemtuzumab, and (iii) BEAM (carmustine, etoposide, cytarabine, melphalan) regimen. RIC protocols included fludarabine plus one or two alkylating agents, or a low-dose TBI (2–4 Gy), with or without ATG or alemtuzumab. Alkylating agents consisted of busulphan, melphalan, cyclophosphamide or thiotepa.

Within the EBMT registry, fully matched donor-recipients pairs are categorised as MUD; cases with a single mismatch, as determined either by low- or high-resolution testing at human leucocyte antigen (HLA)-A, -B, -C or -DRB1, are categorised as mismatched unrelated donors. High-resolution (allele) typing using molecular methodology has become increasingly used for the selection of unrelated SCT donors. Since the year 2000, the period considered in the current study, current policies at most European centres have included high-resolution testing at HLA-A, -B, -C and -DRB1, with or without -DBQ1 level (8/8 or 10/10)(http://www.ebmt.org/4Registry/Registry_docs/Forms%20and%20manuals/HLA%20MANUAL%2003_2004.pdf; European School of Haematology (ESH)-EBMT 2008).

Grades II-IV acute GVHD (aGVHD) were defined according to accepted criteria (EBMT 2009). Chronic GVHD (cGVHD) was evaluated in patients who engrafted and survived ≥100 d, and did not present disease progression. Thus, patients in whom cGVHD might be caused by cessation of immunosuppressive drugs or donor-lymphocyte infusion (DLI) due to disease progression were excluded from the analyses for cGVHD and only spontaneous cGVHD is presented. Performance status (PS) was defined according to the Eastern Cooperative Oncology Group (ECOG) scale.

Complete response (CR), partial response (PR) and very good partial response (VGPR) were defined according to the EBMT guidelines (EBMT 2009). For the purpose of this analysis, PR and VGPR were grouped together. Recurrence was defined as the occurrence of new sites of disease after a CR lasting ≥3 months and progression when CR had lasted <3 months, or when PR, rather than CR, had been previously achieved. Recurrence/progression was considered to be 'chemosensitive' if at least PR was achieved after salvage treatment, otherwise it was deemed to be 'chemoresistant'. Recurrence/progression was deemed 'untested' if the patient had no further treatment after recurrence (EBMT 2009).

Overall survival (OS) was defined as the time from transplant to death from any cause, with surviving patients censored at last follow-up. Progression-free survival (PFS) was defined as time from transplant to recurrence, progressive disease, or death, with surviving patients without disease progression censored at last follow-up. Both recurrence and progression were defined as disease progression with non-relapse deaths considered a competing event. Non-relapse mortality (NRM) was defined as death due to any cause

which occurred without previous disease progression after transplant.

### *Statistical analysis*

The probabilities of PFS and OS were estimated from the time of transplant, using Kaplan-Meier curves, and compared by the two-tailed log-rank test. $P = 0{\cdot}05$ was used to define statistical significance. The occurrence of neutrophil recovery, aGVHD, cGVHD, NRM, and disease progression after MUD-SCT was calculated using cumulative incidence (CI) estimates, taking into account the competing risk structure. In addition to the type of conditioning regimen used before SCT, the following covariates were analysed in univariate analyses: recipient age and sex, time interval between diagnosis and SCT, number of prior lines of therapy, prior autologous transplant, time to relapse following autologous transplant, PS and disease status at transplant, stem cell source, *ex vivo* T-cell depletion, *in vivo* T-cell depletion, ATG/antilymphocyte globulin (ALG) administration, GVHD prophylaxis (ciclosporin A with methotrexate vs ciclosporin A alone vs other), donor/recipient sex match (female donor to male recipient vs others), ABO compatibility and cytomegalovirus (CMV) risk group (donor and recipient seronegative vs other). All factors showing a significant impact or a trend to an impact in univariate analyses ($P < 0{\cdot}15$) together with some additional variables of clinical interest were

**Table I.** Patient characteristics and treatment.

| | Conventional myeloablative conditioning (CONV) $n = 44$ | Reduced-intensity conditioning regimens (RIC) $n = 87$ | |
|---|---|---|---|
| | No./no. assessable (%) | No./no. assessable (%) | *P* value |
| Male | 30 (68%) | 50 (57%) | NS |
| Age at SCT, median (range) | 42 (30–55) | 51 (30–66) | **<0·001** |
| Age ≥50 years | 13 (29%) | 47 (54%) | **0·009** |
| Previous treatment lines | | | |
| 1–3 | 22/41 (54%) | 30/82(37%) | **0·08** |
| ≥4 | 19/41 (46%) | 52/82(63%) | |
| Disease status at SCT | | | |
| CR | 11 (25%) | 24 (27%) | NS |
| Sensitive recurrence | 18 (41%) | 43 (50%) | |
| Refractory recurrence | 15 (34%) | 20 (23%) | |
| Previous autograft | 10 (23%) | 51 (59%) | **<0·001** |
| Poor PS (ECOG ≥2) | 3/38 (8%) | 6/77 (8%) | NS |
| Interval diagn-MUD-SCT (median) | 32 months | 55 months | **0·005** |
| CMV seropositivity (DON or REC) | 24/35 (69%) | 51/69 (74%) | NS |
| ABO major incompatibility | 10/29 (35%) | 21/61 (35%) | NS |
| Stem cell source | | | |
| BM | 20 (45%) | 27 (31%) | NS |
| PBSC | 24 (55%) | 60 (69%) | |
| *Ex vivo* T-cell depletion | 13/40 (33%) | 3/87 (3%) | **<0·001** |
| *In vivo* T-cell depletion | 9/37 (24%) | 26/79 (33%) | NS |
| ATG/ALG | 21/36 (58%) | 25/72 (35%) | **0·02** |
| Conditioning regimen | | | |
| TBI-containing | 25(57%) | – | – |
| Bu-Cy | 3 (7%) | – | |
| BEAM | 11 (25%) | – | |
| Other chemotherapy | 5 (11%) | 14 (17%) | |
| Low dose TBI-containing | – | 23 (26%) | |
| Fludarabine-Melphalan | – | 31 (36%) | |
| Fludarabine-Busulphan | – | 9 (10%) | |
| Fludarabine-Cy+-Thiotepa | – | 10 (11%) | |
| Follow-up (median) | 38 months | 34 months | NS |

MUD-SCT, matched unrelated donor stem cell transplant; CR, complete response; PS, performance status, ECOG, Eastern Cooperative Oncology Group; CMV, cytomegalovirus; DON, donor; REC, recipient; BM, bone marrow; PBSC, peripheral blood stem cells; ATG, antithymocyte globulin; ALG, antilymphocyte globulin; TBI, total-body irradiation; Bu-Cy, busulphan-cyclophosphamide; BEAM, carmustine, etoposide, cytarabine, melphalan; NS, not significant.

entered into the multivariate models. Thus, the following variables were included: recipient age, donor/recipient sex match, time interval between diagnosis and SCT, number of prior lines of therapy, prior autologous transplant, PS and disease status at transplant, type of conditioning regimen, use of ATG/ALG, stem cell source, T-cell depletion, ABO compatibility and cytomegalovirus (CMV) risk group. Covariates were first entered into the Cox proportional hazards model; those covariates found not to be significant at the 0·10 level were removed from model step by step (conditional backward method). Potential interactions between the covariate type of conditioning regimen and the other remaining covariates were tested. To avoid loss of information, a category for 'unknown' was included in the Cox model for those risk factors with more than 10% of missing values. In each model, the assumption of proportional hazards was tested for each variable using a time-dependent covariate. If a deviation from the proportionality assumption was found, a stratified Cox Model was used. The impact of aGVHD was investigated introducing aGVHD as a time-dependent variable, whereas a landmark analysis approach was used to analyse the influence of cGVHD. The Statistical package for the Social Sciences (SPSS) software, version 13.0 (SPSS Inc., Chicago, IL, USA) was used for all statistical analyses with the exception of the cumulative incidence analyses, which were performed with NCSS97 (Number Cruncher Statistical System, Kaysville, UT, USA).

## Results

### *Patient population*

One hundred and thirty-one patients with FL, treated with a MUD-SCT between 2000 and 2005 and reported to the EBMT registry, were included in the study. Characteristics of the patients according to the intensity of the conditioning regimen are presented in Table I. Median age at the time of MUD-SCT for the whole series was 49 years. The median time from diagnosis to transplant was 47 months. The median number of previous therapeutic regimens was 4. Sixty-one patients (47%) had failed a prior autograft.

### *Transplant characteristics*

The characteristics of the procedures are detailed in Table I. Forty-four patients (34%) were treated with a CONV regimen and 87 (66%) with a RIC regimen. RIC regimens included low-dose TBI in 26% of the cases and fludarabine plus alkylating agents in 74%, the latter being melphalan in 48% of the cases. Data on T-cell depletion was available in 111 patients: *ex vivo* T-cell depletion was performed in 16 and *in vivo* T-cell depletion, using alemtuzumab, in 35. GVHD prophylaxis included ciclosporin A with methotrexate in 33% of the cases, ciclosporin A alone in 50% and other combinations in 17%. All donors were fully matched unrelated, confirmed serologically and/or molecularly (8/8 matched, high resolution at HLA-A, -B, -C and -DRB1) according to established criteria (EBMT 2004, ESH-EBMT 2008).

### *Engraftment*

Considering death without recovery as a competing event, the CI of neutrophil recovery at 100 d was 95%, with no differences between RIC and CONV regimens. The CI of neutrophil recovery was 96% and 93% in patients transplanted with peripheral blood stem cells (PBSC) and bone marrow (BM), respectively ($P = 0{\cdot}01$). Three patients died before day +16 after MUD-SCT. Engraftment was otherwise achieved in 122 of the remaining 128 patients (95%). The median times for neutrophil and platelet recovery ($>50 \times 10^9$/l) were 15 and 20 d, respectively. Engraftment was significantly quicker in patients transplanted with PBSC than in patients transplanted with BM (13 vs. 19 d for neutrophil $P < 0{\cdot}001$, and 13 vs. 29 d for platelet recovery, $P < 0{\cdot}001$). Six patients were reported as not engrafting: 4 following a RIC transplant and 2 after a CONV procedure ($P$ = not significant, NS). Four of six patients without engraftment died of NRM causes before day +50 after transplant.

### *GVHD*

Seventy-three patients (56%) developed aGVHD [grade I, 23 patients (18%), grade II-IV, 49 patients (37%) and unknown grade, 1 case] at a median time of 22 d (range: 5–98). The CI of grade II-IV aGVHD at 100 d was 38% for the whole series; 40% in patients receiving a RIC transplant and 36% in the CONV group ($P$ = NS). There was a trend for patients in the CONV group to develop aGVHD earlier after MUD-SCT than patients in the RIC group (median time: 18 vs. 24 d, $P = 0{\cdot}1$). Introducing grade II-IV aGVHD as a time-dependent variable, this event was associated with a shorter PFS ($P = 0{\cdot}01$) and OS ($P = 0{\cdot}005$), due to a higher NRM $P = 0{\cdot}007$).

Data on cGVHD were available for 77 patients of 92 at risk (84%). Thirty-seven patients (48%) developed cGVHD (limited, 18–23%, extensive, 16–21%, and unknown, three cases). The CI of cGVHD at 1 year post-transplant was similar for patients receiving a CONV regimen (42%) to those in the RIC group (48%, $P$ = NS).

Introducing cGVHD as a time-dependent variable, the development of cGVHD was related to a higher NRM ($P = 0{\cdot}03$) and a trend to a lower risk of disease progression ($P = 0{\cdot}1$), with no significant effect on PFS or OS.

### *Disease progression and progression-free survival (PFS)*

After a median follow-up for surviving patients of 36 months (range: 6–99), 22 patients (17%) developed disease progression (median time: 4·2 months, range: 1–33) after MUD-SCT; 17 died from disease progression. Only two patients presented disease progression after 2 years. The CI of disease progression after MUD was 20% at 3 years, with no differences according

  

**Table II.** Multivariate analysis for the risk of disease progression, progression-free survival (PFS), overall survival (OS) and non-relapse mortality (NRM).

| | Relative risk (95%CI) | *P* value |
|---|---|---|
| Adverse prognostic factors for recurrence or progression | | |
| Interval diagnosis to MUD-SCT <3 years | 2·5 (1·02–6·2) | 0·04 |
| ≥4 previous treatment lines | 2·8 (1·02–7·9) | 0·04 |
| Adverse prognostic factors for PFS | | |
| Age ≥50 years | 2·5 (1·4–4·4) | 0·001 |
| Poor PS (ECOG ≥2) | 4·7 (1·9–11·8) | 0·001 |
| Previous ASCT | 2·3 (1·3–4·0) | 0·002 |
| Interval diagnosis to MUD-SCT <3 years | 2·4 (1·3–4·5) | 0·007 |
| CONV regimen | 2·2 (1·2–3·9) | 0·01 |
| Adverse prognostic factors for OS* | | |
| Age ≥50 years | 2·4 (1·4–4·3) | 0·002 |
| Poor PS (ECOG ≥2) | 6·9 (2·8–16·9) | <0·001 |
| Previous ASCT | 2·1 (1·2–3·8) | 0·01 |
| Interval diagnosis to MUD-SCT <3 years | 1·9 (1·02–3·7) | 0·04 |
| CONV regimen | 2·2 (1·2–3·9) | 0·01 |
| Adverse prognostic factors for NRM | | |
| Poor PS (ECOG ≥2) | 6·5 (2·4–17·2) | <0·001 |
| CONV regimen | 2·5 (1·2–5·1) | 0·01 |
| Age ≥ 50 years | 2·2 (1·1–4·2) | 0·02 |

MUD-SCT, matched unrelated donor stem cell transplant; ASCT, autologous stem cell transplant; CONV, conventional myeloablative conditioning; PS, performance status; ECOG, Eastern Cooperative Oncology Group.

*Causes of death: disease progression ($n$ = 17), infection ($n$ = 18), GVHD (with or without concomitant infection) ($n$ = 13), pneumonitis ($n$ = 5), lymphoproliferative disorder ($n$ = 3), other malignancies ($n$ = 1), haemorrhage ($n$ = 1), cardiac toxicity ($n$ = 1), and ARDS in one patient.

to the conditioning regimen. No variables were found to predict the risk of disease progression after MUD-SCT on univariate analysis. On multivariate analysis (Table II), an interval from diagnosis to MUD-SCT <3 years and ≥4 therapy lines prior to transplant were associated with an increased risk of progression.

PFS at 3 years for the overall series was 47% (Fig. 1A); 43% for patients receiving a CONV regimen and 49% for those treated with a RIC regimen ($P$ = NS). PFS was adversely affected on univariate analysis by refractory disease and poor PS (ECOG ≥2) at MUD-SCT. A previous autograft, ≥4 therapy lines prior to MUS-SCT, age at transplant ≥50 years, seropositivity for CMV (either donor or recipient) and major ABO incompatibility showed a trend to a worse PFS by univariate analysis. The variables with a prognostic significance in the multivariate analysis were an interval from diagnosis to MUD-SCT <3 years, age at MUD-SCT ≥50 years, CONV regimen (Fig. 2), a prior autograft and poor PS at MUD-SCT (Table II).

### *Overall survival (OS)*

Sixty patients (46%) died at a median of 3 months (range 0·4–40) after MUD-SCT, 43 without evidence of disease progression. The median time to death was 10 months for patients dying of disease progression and 2 months (range: 0·5–24) for those dying of NRM. The estimated OS at 3 years was 51% (Fig. 1B); OS at 3 years was 47% for patients in the CONV group and 53% for the RIC group ($P$ = NS), and was adversely influenced on univariate analysis by older age, refractory disease, a poor PS and ABO incompatibility, with a trend for a worse OS for patients who had received ≥4 lines of therapy or a prior autograft. On multivariate analysis, the same factors with significant impact on PFS were identified: an interval from diagnosis to MUD-SCT <3 years, age at MUD-SCT ≥50 years, CONV regimen, having failed a prior autograft and a poor PS (Table II).

### *Non-relapse mortality (NRM)*

Forty-three patients (33%) died without evidence of disease progression, 29 of them before day +100 after MUD-SCT. The causes of death are detailed in Table II.

The CI of NRM was 24% at 100 d, 30% at 1 year, and 33% at 3 years. The variables associated with a higher NRM on univariate analysis were age at MUD-SCT ≥50 years, refractory disease and poor PS, with a trend for a higher NRM for a prior autograft and CMV-seropositivity. NRM at 3 years for patients receiving a CONV procedure and those treated with a RIC regimen were 37% and 33%, respectively ($P$ = NS). On

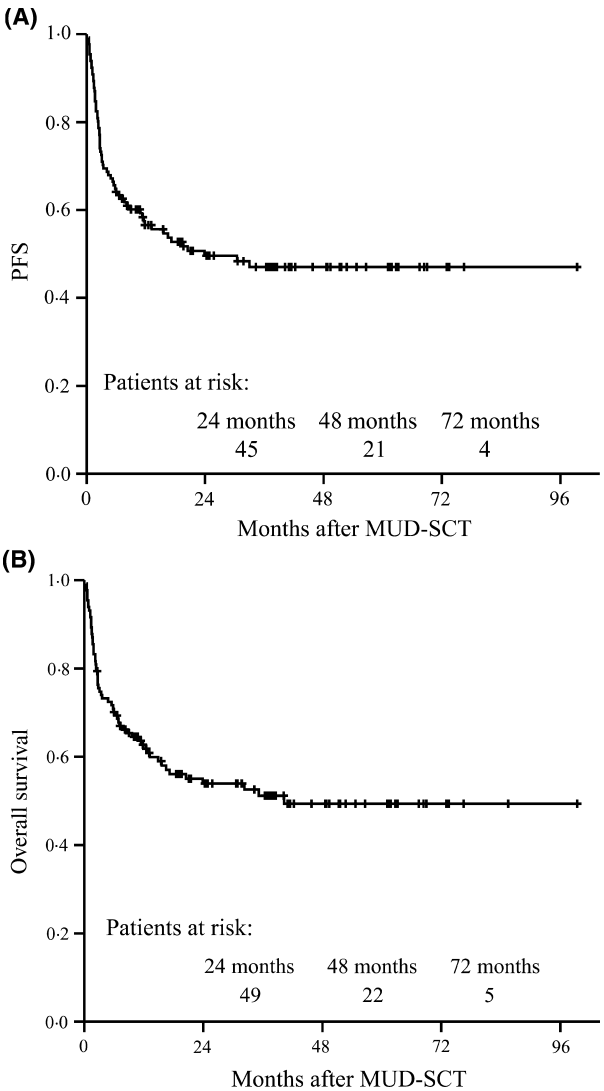


**Fig 1.** (A) Progression-free survival (PFS) in 131 patients who received a MUD-SCT for FL. (B) Overall survival (OS) in 131 patients who received a MUD-SCT for FL.

multivariate analysis, the factors associated with a higher NRM were age at MUD-SCT ≥50 years, a poor PS status at MUD-SCT and having received a CONV regimen (Table II).

### *Outcome of patients who had a MUD-SCT after failing a previous autograft*

Sixty-one patients (42M/19F, median age at the time of MUD-SCT: 48 years) underwent a MUD-SCT after failing a previous autograft. The median time from autograft to disease recurrence was 13 months and the median time from autograft to MUD-SCT, 26 months (range: 4–138). 64% patients had received ≥4 therapeutic regimens before MUD-SCT. Patients who received a RIC-MUD (N: 51, 84%) were older (median age: 48, vs. 42, $P = 0{\cdot}2$) and had received more therapy regimens before MUD (four or more: 68% vs. 44%, $P = 0{\cdot}2$)

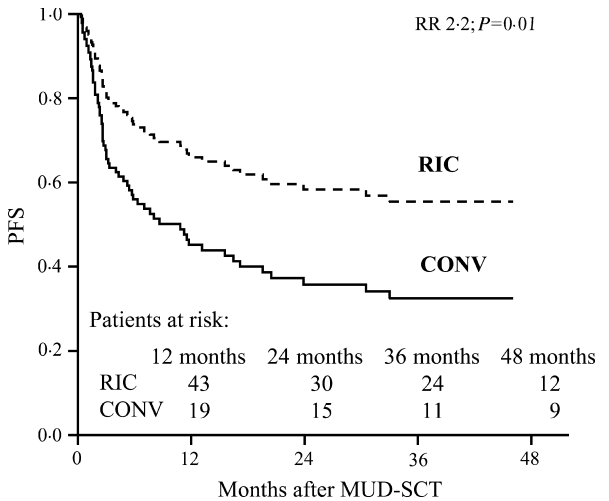


**Fig 2.** PFS in 131 patients who received a MUD-SCT for FL according to the conditioning regimen (CONV vs. RIC) after adjusting for other variables in the multivariate analysis.

but were transplanted less frequently with refractory disease (17% vs. 50%, $P = 0{\cdot}04$) than the remainder. The CI of disease progression at 3 years for patients having a MUD-SCT after a previous autograft was 19% with a 3-year PFS of 39%. The corresponding figures for patients having a MUD-SCT as the first transplant were 19% for risk of progression and 54% for PFS ($P = 0{\cdot}06$). Thirty-three patients who received a MUD-SCT after an autograft died, due to disease progression in eight cases and due to treatment toxicity in the remainder (infection, 11 patients; GVHD –with or without concomitant infection-, 8; interstitial pneumonitis, 2; and cardiac toxicity, lympho-proliferative disorder, central nervous system bleeding and acute myeloid leukaemia, one each). Three-year OS was 42% in patients having failed a previous autograft, in comparison with 60% in the remainder ($P = 0{\cdot}1$), whereas 3-year NRM was 42% when MUD-SCT was performed after an autograft and 27% for patients in whom MUD-SCT was the first transplant ($P = 0{\cdot}07$). On multivariate analysis, having failed a previous autograft was associated with a shorter PFS and OS (Table II).

## Discussion

This study reports the outcome of 131 patients with FL treated with MUD-SCT. Allogeneic SCT provides the only curative option for patients with FL but is accompanied by a prohibitively high NRM. The use of RIC regimens decreases the NRM observed with conventional allograft, expanding the indications of this strategy in patients with FL, a population that is relatively old and, frequently, heavily pretreated. RIC regimens may be especially effective in FL, a slowly evolving disease, as they seem to be sufficient to control the disease until an adequate GVL effect develops and eliminates residual disease, leading to prolonged remissions, and potential cure (Khouri *et al*, 2001, 2008; Robinson *et al*, 2002; Morris *et al*,

2004; Corradini *et al*, 2007; Vigouroux *et al*, 2007; Rezvani *et al*, 2008). As the majority of patients do not have a matched sibling donor, a crucial question is whether a MUD SCT is a reasonable option for these individuals(Izutsu *et al*, 2004; Rezvani *et al*, 2008).

The current study, though retrospective and affected by the caveats inherent in a registry study (mainly selection biases, heterogeneous management of patients in terms of treatment and follow-up, lack of central histological review precluding the analysis of the potential impact of histological grade and missing data), demonstrates that MUD-SCT can provide a long term PFS for a considerable number of patients with otherwise incurable, advanced FL. The results here reported are not easily comparable with those of previous papers, as most of them include only a small proportion of patients receiving an unrelated transplant. Not surprisingly, the outcome in the present study is inferior to that reported in series including mainly sibling donors(Morris *et al*, 2004; Khouri *et al*, 2008) with a higher NRM and a shorter PFS. However, given that half of the patients in this study had received at least four previous chemotherapy regimens before MUD-SCT and 47% had failed a prior autograft, a PFS of 47% at 3 years-post transplant should be regarded as highly promising.

As mentioned above, RIC regimens have been shown to decrease NRM, and the current study supports this observation. Although no differences were found in NRM in the univariate analysis according to the conditioning regimen, the population that underwent a RIC had significantly poorer prognostic features than patients who received a CONV. Thus, the relative risk (RR) of NRM was 2·5 for patients receiving a CONV regimen in comparison with those treated with a RIC regimen ($P = 0{\cdot}01$) after adjusting for other variables in the multivariate analysis. The relatively high NRM observed with RIC-MUD in the current series is likely to reflect the poor-risk characteristics of the patients: a relatively old (median age: 48 years) and heavily pre-treated population (half the patients had received ≥4 therapeutic regimens, and 47% had progressed after an autograft, the response after autograft lasting less than 13 months in half the patients). Nonetheless, despite these poor-risk features, patients undergoing a RIC-MUD did not present an increased progression rate compared with those receiving a CONV transplant (Table II). The retrospective nature of this study prevented the analysis of the response rate after DLI, as these data are not routinely collected and it was not one of the objectives of the study. Although no significant differences in PFS or OS were found on univariate analysis according to the conditioning regimen, CONV regimens appeared as an adverse prognostic factor in the multivariate analysis (RR of 2·2 for both PFS and OS, Table II), after adjusting for other variables. Given the controversy regarding the inclusion of BEAM as a myeloablative regimen(Robinson *et al*, 2002; Sureda *et al*, 2008), as defined by the EBMT criteria, the multivariate analyses were repeated including BEAM as non-myeloablative and the conditioning regimen retained its predictive value for both PFS and OS (data not shown). Of note, an increased risk of disease progression following RIC was recently reported in another registry study comparing CONV *versus* RIC(Hari *et al*, 2008) including only sibling donors. This result, together with the results reported here, suggest a stronger GVL effect evoked by MUD. However, the present results should be interpreted with caution, as this was a retrospective analysis, therefore patients having a RIC or a CONV-MUD were not matched for any biological or clinical parameters that might have affected their outcome. In addition, the median follow-up was relatively short, thus a longer follow-up is required to confirm the persistence of the differences in outcome.

The role, or rather, the appropriate timing for an allo-SCT in patients with relapsed FL is still a matter of debate. It is generally accepted that ASCT should be done earlier rather than later in the course of the disease, as an increased number of therapeutic regimens before ASCT influences adversely the outcome (Rohatiner *et al*, 1994; Bierman *et al*, 1997). Thus, a sibling or MUD allo-SCT is generally reserved for patients with disease progression after ASCT(Baron *et al*, 2006). It could, however, be argued to the contrary, as the PFS is significantly shorter for patients having a MUD-SCT after an autograft than for those having it as the first transplant. The former is clearly a more toxic procedure (with a 3-year NRM for patients receiving a RIC-MUD after a previous autograft of 42%), so it might be better to spare such toxicity in heavily pre-treated patients. The results here reported are worse than those published for RIC-allo after failing a previous autograft. However, it has to be mentioned that this study reports a larger group of patients with lymphoma receiving an unrelated transplant after an autograft, whereas in previous series either the percentage of patients with lymphomas was rather small(Baron *et al*, 2006) or the percentage of patients having a MUD-SCT was small(Morris *et al*, 2004; Khouri *et al*, 2008). Nevertheless, the goal of the present study was not to define the role of a MUD-SCT in the therapeutic algorithm of FL, as the nature of a retrospective registry study limits the availability of important data such as prognostic factors (i.e. the Follicular Lymphoma International Prognostic Index score) or previous treatment (i.e. previous rituximab). Notwithstanding this, it should be noted that this series benefits from one of the main advantages derived from a registry study: a large number of patients. Thus, this is, to the best of our knowledge, the largest series on unrelated SCT in FL and, as such, enabled some simple, but important conclusions to be drawn.

In this sense, MUD-SCT provides a 'good chance' of controlling the disease with an acceptable toxicity, considering the poor-risk characteristics of the treated population, This study demonstrates that RIC-MUD is a feasible option in selected patients with FL without a family donor. Nonetheless, the present study does not support that CONV regimens offer any advantage over RIC regimens, suggesting that CONV regimens might have a limited role in this setting.

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## Authorship and Disclosures

IA was the principal investigator and takes primary responsibility for the paper. JM, HAA, GJM, JF, AS, RF, JJC, JPV, NR, YB, KT, LFV, GK, HT and GS contributed vital data. CC performed statistical analysis. IA, SM and AS coordinated the research and analysed data. IA and SM wrote the paper. The authors reported no potential conflicts of interest.

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## Appendix

Listed are the transplantation centres and responsible co-investigators who included patients in this study; each centre's EBMT Centre Identification Code (CIC) is shown in brackets and is followed by the number of patients included in the study: Gratwohl A., University Hospital, Basel, Switzerland [202], 2; Bunjes D., Klinik fuer Innere Medzin III, Ulm, Germany [204], 2; Socié G., Hopital St. Louis, Paris, France [207], 3; Maertens J., University Hospital Gasthuisberg, Leuven, Belgium [209], 8; Ljungman P., Karolinska University Hospital, Huddinge, Sweden [212], 2; Carreras E., Hospital Clinic, Barcelona, Spain [214], 1; Mackinnon S., Royal Free Hospital and School of Medicine, London, UK [216], 1; Bacigalupo A., Ospedale San Martino, Genova, Italy [217], 1; Potter M., Royal Marsden Hospital, London, UK [218], 1; Thomson K., University College London Hospital, London, UK [224], 4; Remes K., Turku University, Turku, Finland [225], 1; Greinix H., Medizinische Universitaet Wien, Vienna, Austria [227], 1; Falda M., Azienda Ospedaliera S. Giovanni, Torino, Italy [231], 2; Ferrant A., Cliniques Universitaires St. Luc, Brussels, Belgium [234], 1; Schattenberg LF., Radboud University - Nijmegen Medical Centre, Nijmegen, Netherlands, The [237], 6; Verdonck LF., University Medical Centre, Utrecht, Netherlands, The [239], 4; McQuaker G., Glasgow Royal Infirmary, Glasgow, UK [244], 1; Cornelissen JJ., Erasmus MC-Daniel den Hoed Cancer Centre, Rotterdam, Netherlands, The [246], 5; Di Bartolomeo P., Ospedale Civile, Pescara, Italy [248], 1; Cordonnier C., Hôpital Henri Mondor, Creteil, France [252], 1; Cook G., St James' University Hospital, Leeds, UK [254], 2; Littlewood T., The Oxford Radcliffe Hospital, Oxford, UK [255], 1; ''Gramatzki M., UKSH, Campus Kiel, Kiel, Germany [256], 1; ''Vernant J-P., Groupe Hospitalier Pitié-Salpêtrière, Paris, France [262], 5; Guilhot F., Hopital La Miletrie, Poitiers, France [264], 1; Milpied N., CHU Bordeaux, Pessac, France [267], 1; Cahn J-Y., Hopital A. Michallon, Grenoble, France [270], 2; Milligan D., Birmingham Heartlands Hospital, Birmingham, UK [284], 3; Blasczyk R., Hannover Medical University, Hannover, Germany [295], 1; Bosi A., Ospedale di Careggi, Firenze, Italy [304], 1; Schwerdtfeger R., Deutsche Klinik für Diagnostik, Wiesbaden, Germany [311], 2; Marks D., Bristol Royal Hospital for Children, Bristol, UK [386], 2; Craddock C., Centre for Clinical Haematology, Birmingham, UK [387], 2; Niederwieser D., University Hospital Leipzig, Leipzig, Germany [389], 7; Kobbe G., Heinrich Heine Universität, Düsseldorf, Germany [390], 4; Scimè R., Ospedale V. Cervello, Palermo, Italy [392], 1; Ruutu T., Helsinki University Central Hospital, Helsinki, Finland [515], 3; Fassas A., George Papanicolaou General Hospital, Thessaloniki, Thessaloniki, Greece [561], 1; Crawley C., Addenbrookes Hospital, Cambridge, UK [566], 1; Indrák K., University Hospital, Olomouc, Czech Republic [574], 1; ''Liu Yin J., Manchester Royal Infirmary, Manchester, UK [601], 1; Zander A., University Hospital Eppendorf, Hamburg, Germany [614], 3; Vitek A., Institute of Hematology and Blood Transfusion, Prague, Czech Republic [656], 1; Lamy T., Centre Hospitalier Universitaire de Rennes, Rennes, France [661], 1; Kienast J., University of Münster, Münster, Germany [680], 3; Fanin R., University Hospital, Udine, Italy [705], 6; Cannell P., RP Group Royal Perth Hospital, Perth, Australia [710], 2; Hunter AE., Leicester Royal Infirmary, Leicester, UK [713], 2; Russell NH., Nottingham City Hospital, Nottingham, UK [717], 5; Koza V., Charles University Hospital, Pilsen, Czech Republic [718], 1; Beguin Y., University of Liege, Liege, Belgium [726], 5; Wahlin A., Umea University Hospital, Umeå, Sweden [731], 1; Nagler A., Chaim Sheba Medical Center, Tel-Hashomer, Israel [754], 1; Mufti GJ., GKT School of Medicine, London, UK [763], 7; Liakopoulou E., Christie NHS Trust Hospital, Manchester, UK [780], 1; Ehninger G., Universitaetsklinikum Dresden, Dresden, Germany [808], 2; Finke J., University of Freiburg, Freiburg, Germany [810], 7; Ciceri F., Istituto Scientifico H.S. Raffaele, Milano, Italy [813], 1; Tilly H., Centre Henri Becquerel, Rouen, France [941], 4;

## Supporting information

Additional Supporting Information may be found in the online version of this article:

**Table S1.** Transplant conditioning regimens.

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