Non-myeloablative Allogeneic Hematopoietic Stem Cell Transplantation for Adults with Relapsed and Refractory Mantle Cell Lymphoma: A Single Center Analysis in the Rituximab Era

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Abstract

Relapsed and refractory (rel/ref) mantle cell lymphoma (MCL) portends a dismal prognosis. Allogeneic hematopoietic stem cell transplantation (allo-HSCT) represents the only potentially curative therapy in this setting. We analyzed survival outcomes of 29 recipients of non-myeloablative allo-HSCT for rel/ref MCL, and studied possible prognostic factors in this setting. The cumulative incidence of disease progression and non-relapse mortality at 3 years were 28% (95% confidence interval [CI]: 13-46%) and 29% (95%CI: 13-47%), respectively. The cumulative incidence of grade II-IV acute graft-versus-host disease (GVHD) at days +100 and +180 were 34% (95%CI: 18-52%) and 45% (95%CI: 26-62%), respectively. With a median follow-up in survivors of 53 (range 24-83) months, the 3-year overall survival (OS) and progression-free survival (PFS) were 54% (95%CI: 38-76%) and 41% (95%CI: 26-64%), respectively. *In vivo* T-cell depletion with alemtuzumab (n=6) was associated with inferior 3-year PFS (0% vs. 51%, p=0.007) and OS (17% vs. 64%, p=0.014). Conversely, a second line international prognostic

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index (sIPI) at transplantation equal to 0 (no risk factors) was associated with an improved 3-year PFS (52% vs. 22%, p=0.020) and OS (71% vs. 22%, p=0.006) compared to sIPI 1. Performing an allo-HSCT before 2007 was associated with a decreased 3-year OS (25% vs. 76%, p=0.015) but not with a significantly inferior PFS (17% vs. 59%, p=0.058). In this single center series, we report encouraging results with allo-HSCT for patients with rel/ref MCL. High alemtuzumab doses should probably be avoided in this context.

INTRODUCTION

Mantle cell lymphoma (MCL) comprises approximately 6% of all non-Hodgkin lymphoma (NHL) and typically portends a poor long-term prognosis. Recent advances in the treatment of MCL have resulted in improved survival. Sequential high-dose chemotherapy followed by autologous stem cell transplantation or hyper-fractionated chemotherapy have lead to higher complete remission (CR) rates and remission duration exceeding 5 years in recent series.[1-4] Additionally, the introduction of novel drugs in the relapsed setting now offers effective therapeutic options.[5-11] Despite these improvements, patients with MCL have the worst long-term prognosis of any B cell NHL. Patients who relapse after intensive first line therapy have limited options to achieve durable disease control with conventional and novel therapies.[12, 13] Allogeneic hematopoietic stem cell transplantation (allo-HSCT) remains the only potentially curative treatment, with the predominant mechanism of action attributed to potential graft-versus-lymphoma (GVL) effects.[14-18] Retrospective studies, most of them from registry data, have shown a mean progression-free (PFS) and overall (OS) survival of 25-40% and 30-50% at 3 years, respectively,[19-22] with more favorable results observed in single-center studies,[23-25] Transplant-related mortality (TRM) has ranged from 25 to 40% at 3 years.[19-22] We sought to identify potential prognostic factors for patients with relapsed and refractory (rel/ref) MCL undergoing non-myeloablative (NMA) or reduced intensity conditioning (RIC) allo-HSCT in the post-rituximab era.

METHODS

Patients

In this retrospective single center study, we analyzed 29 patients with rel/ref MCL who underwent non-myeloablative (NMA) or reduced intensity conditioning (RIC) allo-HSCT at Memorial Sloan Kettering Cancer Center (MSKCC) between April 1999 and May 2013. Written informed consent for treatment was obtained from all patients and donors. Approval for this retrospective analysis was obtained from the MSKCC Institutional Review and Privacy Board. All patients had biopsy proven MCL as defined by the World Health Organization criteria including immunohistochemical analysis for cyclin D1 and/or cytogenetic analysis by either conventional karyotyping or fluorescence in situ hybridization (FISH) for t(11;14)(q13;q32).

Eligibility criteria for transplant included availability of a human leukocyte antigen (HLA)-matched or single-allele-mismatched donor or appropriate cord blood (CB) graft. Double-unit CB (DUCB) grafts were 4-6/6 HLA-A,-B antigen, −DRB1 allele matched to the recipient with a cryopreserved total nucleated cell (TNC) dose > 1.5×10^7/kg/unit as

previously described.[26] Unit-unit HLA-match was not considered in unit selection. Additional criteria included absence of active infection, lack of cardiac, pulmonary, hepatic or renal dysfunction that would preclude administration of the cytoreductive regimen. HLA matching was performed with DNA sequence-specific oligonucleotide typing for HLA-A, -B, -C, DRB1 and –DQB1 loci.

Conditioning and transplantation procedure

All patients received a NMA or RIC regimen. The predominant NMA regimen consisted of cyclophosphamide 50 mg/kg (day -6), fludarabine 25 mg/m^2 for 5 days (from day -6 to -2) and TBI 200 Gy (day -1). In recipients of DUCB, the dose of fludarabine was 30 mg/m^2 for 5 days. In 17 patients, rituximab was administered at 375 mg/m^2 day -8 or -7 and weekly for 4 doses beginning from day +21. In this NMA regimen group, recipients of MRD or MUD were treated on (n=8) or as per (n=7) a prospective phase II clinical trial (clinicaltrials.gov NCT00425802),[27] while recipients of DUCB (n=5) were treated on a parallel prospective phase II clinical trial (NCT00387959).

The RIC regimen consisted of fludarabine 25 mg/m^2 for 5 days (day -8 to -4) followed by melphalan 70 mg/m^2 for 2 days (from day -3 to -2), with (n=6) or without (n=2) alemtuzumab (20 mg flat dose for 4 days (day -8 to -5). Six patients were treated on (n=5) or as per (n=1) a prospective phase II clinical trial (NCT00027560).[28] One patient received cyclophosphamide 750 mg/m^2 and fludarabine 30 mg/m^2 for 3 (day -7 to -5). Donor stem cells were infused at day 0 after at least 24-48 hours from the completion of chemotherapy.

GVHD prophylaxis and supportive care

For patients receiving PBSC grafts, GVHD prophylaxis consisted in cyclosporine alone (n=6),[28] or in association with methotrexate (n=1) or mycophenolate (n=4). The other patients received tacrolimus-based prophylaxis with mycophenolate mofetil (MMF, n=1) or methotrexate plus sirolimus (n=12).[29] All recipients of DUCB grafts (n=5) received cyclosporine and MMF, as previously described.[30] Equine (30mg/kg total dose) or rabbit (5mg/kg total dose) antithymocyte globulin (ATG) was used in 1 recipient of a matched related donor, 5 recipients of matched unrelated donors and 2 recipients of a mismatched related donor. Recipient of DUCB and patients receiving alemtuzumab did not receive ATG. Patients were managed clinically according to standard institutional guidelines, including antimicrobial prophylaxis. Monitoring of cytomegalovirus (CMV) reactivation in peripheral blood initially by CMV pp65 antigenemia assay, and later by CMV PCR assay (beginning in November 2011), was performed regularly through day 100 when either the patient or donor was CMV seropositive. Preemptive therapy was instituted in patients with documented CMV viremia per institutional standard.

Study definitions

Mantle Cell Prognostic Index (MIPI), second line international prognostic index (sIPI) and Hematopoietic Stem Cell Transplant Comorbidity Index (HCT-CI) were calculated retrospectively according to published methods.[22, 31-33] Second line IPI was calculated assigning 1 point for each of the following risk factors: age >60; serum LDH >1 normal value; performance status (ECOG score) 2; Ann Arbor stage 3; extranodal involvement

> 1 site. Remission quotient was calculated as the number of months from diagnosis to allo-HSCT divided by the number of previous lines of therapy.[34] Standard definitions were used to assess disease response to therapy.[35] Time to neutrophil recovery was defined as the first of 3 consecutive days post transplant with an absolute neutrophil count (ANC) 500/μl. Platelet engraftment was defined as the first of 3 consecutive days at platelet count > 20.000/μl and at least 7 days without platelet transfusion support. GVHD was diagnosed clinically with histologic confirmation when appropriate. Acute and chronic GVHD were graded according to the International Bone Marrow Transplant Registry and the National Institutes of Health consensus criteria, respectively.[36, 37]

Study endpoints and statistical analysis

Analyses were performed as of December 31th, 2014. OS was defined from the date of transplant to death from any cause. PFS was defined from the date of transplant to disease progression or relapse, death, or last follow-up, whichever came first. Non-relapse mortality (NRM) comprised all deaths not related to disease progression or relapse. The following variables were assessed for their effects on OS and PFS: sIPI, time from diagnosis to allo-HSCT, age at transplant, prior lines of therapy, remission quotient, prior auto-HSCT, remission status before allo-HSCT, Positron Emission Tomography (PET) status pre allo-HSCT, HCT-CI, type of donor, use of alemtuzumab, and use of ATG. Ki-67 proliferation index was available only in a small fraction of patients, and was therefore not included in the analysis. Univariate analyses were performed using the log-rank test. Kaplan-Meier (KM) survival and a permutation-based logrank test were used to compare PFS and OS based on alemtuzumab use and sIPI. The cumulative incidence of aGVHD and of cGVHD, progression of disease (POD) and non-relapse mortality (NRM) incidence were calculated using the competing risk method. All analyses were conducted using the R statistical package (version 3.1.1).

RESULTS

Engraftment and GVHD

All patients had previously received rituximab. Twenty-four patients received peripheral blood stem cells (PBSC) from an HLA-matched or single-allele-mismatched sibling (n=12) or unrelated donor (n=12). Double unit cord blood grafts were used in 5 patients. Complete pretransplant characteristics of the 29 patients are described in Table 1. All but one DUCB patient engrafted. The median times to neutrophil and platelet engraftment were 11 days (range 0-60 days) and 16 days (range 0-152 days), respectively. The cumulative incidence of grade II-IV aGVHD for the entire cohort at day +100 and +180 were 34% (95%CI: 18-52%) and 45% (95%CI: 26-62%), respectively. One patient developed grade IV aGVHD. Median time to onset of aGVHD was 74 days (range 17-400 days). The cumulative incidence of cGVHD at 1 and 3 years was 24% (95%CI: 10-41%) and 35% (95%CI: 17-53%), respectively. Three patients experienced severe cGVHD by NIH criteria. The sub-type of cGVHD was classic in 3 patients and overlap syndrome in 8 patients.

Reactivation of cytomegalovirus and EBV

In patients at risk (donor and/or host CMV seropositive), CMV reactivation was documented in 9 of 19 patients. All 6 patients treated with alemtuzumab were CMV seropositive and 3 had CMV reactivation. No patients developed CMV end-organ disease. None of the patients reactivated EBV.

Non relapse mortality

The NRM of the entire cohort at 3 years was 29% (95% CI:13-47%). Five of 9 deaths were attributed to GVHD while the remaining deaths were secondary to: *Enterobacter cloacae spp.* septicemia, Pseudomonas aeruginosa septicemia, probable progressive multifocal leukoencephalopathy and one acute ischemic stroke.

Progression of disease and survival

The cumulative incidence of POD at 3 years was 28% (95%CI: 13-46%). Of the 10 patients who progressed, 7 died of MCL. The median time to POD was 12 months after allo-HSCT (range 1-85 months). Two patients received donor leukocyte infusion (DLI) for POD without response. One patient died of aGVHD following DLI. With a median follow up in survivors of 53 months (range 24-83 months), the 3-year PFS and OS are 41% (95%CI: 26-64%) and 54% (95%CI: 38-76%), respectively (Figure 1). At last follow up, 10 patients were alive.

Analysis of pre-transplant factors revealed that *in vivo* T-cell depletion with alemtuzumab was associated with inferior 3-year PFS (0% vs. 51%, p=0. 0.007) (Figure 2A). Additionally, a sIPI at transplant equal to 0 was associated with an improved 3-year PFS (52% vs. 22%, p=0.020) compared to higher sIPI values (Figure 3A). Similarly, 3-year OS was significantly reduced with alemtuzumab (17% vs. 64%, p= 0.014) (Figure 2B) and also observed for patients with sIPI ≥ 1 (22% vs. 71%, p=0.006) (Figure 3B). Performing an allo-HSCT before 2007 was associated with a decreased 3-year OS (25% vs. 76%, p=0.015) but not with a significantly inferior PFS (17% vs. 59%, p=0.058). Of note, the use of ATG did not influence survival outcomes (3-year PFS 50% vs. 36%, p=0.671; 3-year OS 60% vs. 51%, p=0.579). The other factors analyzed were not significant on PFS and OS (Table 2).

DISCUSSION

In this study we report the MSKCC experience of NMA/RIC allo-HSCT for MCL and demonstrate a 3-year OS and PFS of 53% and 46%, respectively. This compares favorably with previous studies.[19-22] We also observed a 3-year incidence of NRM of 26% and 3-year incidence of POD of 30%, similar to previously reported series.[19-22]

Analysis of prognostic factors revealed interesting results. We found that *in vivo* T-cell depletion with alemtuzumab was associated with inferior PFS and OS, mostly attributable to POD. This can be explained by a reduced GVL effect with *in vivo* T-cell depletion. The importance of a GVL effect in MCL is demonstrated indirectly by the relapse risk associated with allografts performed with T-cell depletion. Morris et al. reported a relapse incidence of 50% at 3 years in a small cohort of patients with MCL treated with an alemtuzumab-based RIC regimen.[38] A recent study from the British Society for Blood and Marrow Transplant

reported a significantly increased incidence of POD in 51 patients receiving an alemtuzumab-based conditioning regimen versus 17 non-alemtuzumab treated patients.[20] Perez-Simon et al. reported that patients treated with an alemtuzumab-based regimen required additional immunotherapy with DLI to achieve disease control compared to patients treated without alemtuzumab.[39] Alemtuzumab is a monoclonal antibody directed against the CD52 antigen present not only on lymphocytes but also on monocytes, offering explanation for more potent immunosuppressive properties compared to other methods of *in vivo* T-cell depletion. Alemtuzumab impairs not only the activity of lymphocytes but also dendritic cells,[40] and cell-mediated cytotoxicity of natural killer (NK) cells.[41] This likely compounds impairment of the GVL effect.[42, 43] It should be noted that we used a higher dose of alemtuzumab compared to other centers, potentially contributing a dose-dependent effect on the incidence of POD.[20]

In contrast, we did not observe an effect of ATG on PFS or OS. Le Gouill et al. reported a trend toward higher relapse rate when ATG was used in this setting; however the difference was not statistically significant.[19] The existence of a GVL effect in lymphoid malignancies has been previously demonstrated, at least for indolent histology lymphoma such as follicular lymphoma,[44, 45] and chronic lymphocytic leukemia.[46, 47] In MCL, DLI has been effective in reducing the incidence of POD after allo-HSCT in some series.[14, 38, 48, 49] Moreover, reduction of immunosuppressive therapy and presence of cGVHD have also been associated with disease control in this setting.[50] Tam et al. reported a reduced disease progression in MCL patients developing cGVHD after allo-HSCT (5% versus 46% at 6 years). A recent multicenter study from CIBMTR showed a significantly decreased risk of POD in patients with evidence of cGVHD after RIC allo-HSCT.[51]

Moreover, we observed a statistically significant association between PFS, OS and a sIPI equal to 0 before allo-HSCT. Second-line IPI has never been tested in MCL patients undergoing allo-HSCT; nonetheless a possible role of this prognostic factor in the context of allo-HSCT for lymphoma has already been reported.[32] Interestingly, a positive PET pre allo-HSCT was not associated with a worse PFS or OS compared to a negative PET. This is in line with a prior report from our group regarding pre allo-HSCT PET for indolent and aggressive lymphomas.[52] Finally, performing an allo-HSCT before 2007 was associated with a lower OS but not with an inferior PFS. This is probably associated with a general improvement in supportive care for allo-HSCT patients as already reported in literature.[53]

CMV reactivation, monitored with antigenemia before November 2011 and PCR thereafter, was similar to the incidence reported for conventional grafts. None of the patients developed CMV disease, including those treated with alemtuzumab where a higher risk is expected. A low EBV reactivation rate was consistent with what is observed in conventional grafts. Rituximab could have further reduced this incidence.

Considering the retrospective nature of the study we should consider the presence of potential biases. The small patient population likely impaired the ability to detect outcome difference in characteristics that have demonstrated significance in other studies such as MIPI,[54] blastic morphology,[55] Ki67 proliferative index.[54] The heterogeneity and the small size of the study population limited the power of the analysis. Interestingly, the majority of

patients had a low MIPI or sIPI score suggesting a possible patient selection. Nevertheless, this is one of the largest single center studies evaluating MCL and allo-HSCT.

In conclusion, our study showed that RIC allo-HSCT is an effective curative strategy in patients with relapsed and refractory MCL. These findings would support other studies suggesting a GVL effect in MCL, and furthermore that T-cell depletion should be probably avoided. Moreover, considering that disease relapse after allo-HSCT is a major cause of death for patients affected by MCL, prospective studies should focus on safely decreasing the incidence of POD. This goal is potentially achievable with the growth of pathway specific targeted agents that could be used as post-allograft maintenance therapy.[5-10]

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENTS

References

1. Romaguera JE, Fayad LE, Feng L, Hartig K, Weaver P, Rodriguez MA, et al. Ten-year follow-up after intense chemoimmunotherapy with Rituximab-HyperCVAD alternating with Rituximab-high dose methotrexate/cytarabine (R-MA) and without stem cell transplantation in patients with untreated aggressive mantle cell lymphoma. Br J Haematol. 2010; 150:200–208. [PubMed: 20528872]

2. Vandenberghe E, Ruiz de Elvira C, Loberiza FR, Conde E, Lopez-Guillermo A, Gisselbrecht C, et al. Outcome of autologous transplantation for mantle cell lymphoma: a study by the European Blood and Bone Marrow Transplant and Autologous Blood and Marrow Transplant Registries. Br J Haematol. 2003; 120:793–800. [PubMed: 12614212]

3. Geisler CH, Kolstad A, Laurell A, Jerkeman M, Raty R, Andersen NS, et al. Nordic MCL2 trial update: six-year follow-up after intensive immunochemotherapy for untreated mantle cell lymphoma followed by BEAM or BEAC + autologous stem-cell support: still very long survival but late relapses do occur. Br J Haematol. 2012; 158:355–362. [PubMed: 22640180]

4. Gianni AM, Magni M, Martelli M, Di Nicola M, Carlo-Stella C, Pilotti S, et al. Long-term remission in mantle cell lymphoma following high-dose sequential chemotherapy and in vivo rituximab-purged stem cell autografting (R-HDS regimen). Blood. 2003; 102:749–755. [PubMed: 12663455]

5. Robinson KS, Williams ME, van der Jagt RH, Cohen P, Herst JA, Tulpule A, et al. Phase II multicenter study of bendamustine plus rituximab in patients with relapsed indolent B-cell and mantle cell non-Hodgkin's lymphoma. J Clin Oncol. 2008; 26:4473–4479. [PubMed: 18626004]

6. Fisher RI, Bernstein SH, Kahl BS, Djulbegovic B, Robertson MJ, de Vos S, et al. Multicenter phase II study of bortezomib in patients with relapsed or refractory mantle cell lymphoma. J Clin Oncol. 2006; 24:4867–4874. [PubMed: 17001068]

7. Goy A, Sinha R, Williams ME, Kalayoglu Besisik S, Drach J, Ramchandren R, et al. Single-agent lenalidomide in patients with mantle-cell lymphoma who relapsed or progressed after or were refractory to bortezomib: phase II MCL-001 (EMERGE) study. J Clin Oncol. 2013; 31:3688–3695. [PubMed: 24002500]

8. Wang ML, Rule S, Martin P, Goy A, Auer R, Kahl BS, et al. Targeting BTK with ibrutinib in relapsed or refractory mantle-cell lymphoma. N Engl J Med. 2013; 369:507–516. [PubMed: 23782157]

9. Hess G, Herbrecht R, Romaguera J, Verhoef G, Crump M, Gisselbrecht C, et al. Phase III study to evaluate temsirolimus compared with investigator's choice therapy for the treatment of relapsed or refractory mantle cell lymphoma. J Clin Oncol. 2009; 27:3822–3829. [PubMed: 19581539]

10. Morschhauser FA, Cartron G, Thieblemont C, Solal-Celigny P, Haioun C, Bouabdallah R, et al. Obinutuzumab (GA101) monotherapy in relapsed/refractory diffuse large b-cell lymphoma or mantle-cell lymphoma: results from the phase II GAUGUIN study. J Clin Oncol. 2013; 31:2912–2919. [PubMed: 23835718]

11. Till BG, Jensen MC, Wang J, Qian X, Gopal AK, Maloney DG, et al. CD20-specific adoptive immunotherapy for lymphoma using a chimeric antigen receptor with both CD28 and 4-1BB domains: pilot clinical trial results. Blood. 2012; 119:3940–3950. [PubMed: 22308288]

12. Mussetti A, Kumar A, Dahi PB, Perales MA, Sauter CS. Lifting the mantle: Unveiling new treatment approaches in relapsed or refractory mantle cell lymphoma. Blood Rev. 2014

13. Dietrich S, Boumendil A, Finel H, Avivi I, Volin L, Cornelissen J, et al. Outcome and prognostic factors in patients with mantle-cell lymphoma relapsing after autologous stem-cell transplantation: a retrospective study of the European Group for Blood and Marrow Transplantation (EBMT). Ann Oncol. 2014; 25:1053–1058. [PubMed: 24585719]

14. Khouri IF, Lee MS, Romaguera J, Mirza N, Kantarjian H, Korbling M, et al. Allogeneic hematopoietic transplantation for mantle-cell lymphoma: molecular remissions and evidence of graft-versus-malignancy. Ann Oncol. 1999; 10:1293–1299. [PubMed: 10631455]

15. Khouri IF, Saliba RM, Giralt SA, Lee MS, Okoroji GJ, Hagemeister FB, et al. Nonablative allogeneic hematopoietic transplantation as adoptive immunotherapy for indolent lymphoma: low incidence of toxicity, acute graft-versus-host disease, and treatment-related mortality. Blood. 2001; 98:3595–3599. [PubMed: 11739162]

16. Kolb HJ. Graft-versus-leukemia effects of transplantation and donor lymphocytes. Blood. 2008; 112:4371–4383. [PubMed: 19029455]

17. Khouri IF. Reduced-intensity regimens in allogeneic stem-cell transplantation for non-hodgkin lymphoma and chronic lymphocytic leukemia. Hematology Am Soc Hematol Educ Program. 2006:390–397. [PubMed: 17124088]

18. Robinson S, Dreger P, Caballero D, Corradini P, Geisler C, Ghielmini M, et al. The EBMT/EMCL consensus project on the role of autologous and allogeneic stem cell transplantation in mantle cell lymphoma. Leukemia. 2015; 29:464–473. [PubMed: 25034148]

19. Le Gouill S, Kroger N, Dhedin N, Nagler A, Bouabdallah K, Yakoub-Agha I, et al. Reduced-intensity conditioning allogeneic stem cell transplantation for relapsed/refractory mantle cell lymphoma: a multicenter experience. Ann Oncol. 2012; 23:2695–2703. [PubMed: 22440229]

20. Cook G, Smith GM, Kirkland K, Lee J, Pearce R, Thomson K, et al. Outcome following Reduced-Intensity Allogeneic Stem Cell Transplantation (RIC AlloSCT) for relapsed and refractory mantle cell lymphoma (MCL): a study of the British Society for Blood and Marrow Transplantation. Biol Blood Marrow Transplant. 2010; 16:1419–1427. [PubMed: 20399879]

21. Fenske TS, Zhang MJ, Carreras J, Ayala E, Burns LJ, Cashen A, et al. Autologous or Reduced-Intensity Conditioning Allogeneic Hematopoietic Cell Transplantation for Chemotherapy-Sensitive Mantle-Cell Lymphoma: Analysis of Transplantation Timing and Modality. J Clin Oncol. 2013

22. Hamadani M, Saber W, Ahn KW, Carreras J, Cairo MS, Fenske TS, et al. Allogeneic hematopoietic cell transplantation for chemotherapy-unresponsive mantle cell lymphoma: a cohort analysis from the center for international blood and marrow transplant research. Biol Blood Marrow Transplant. 2013; 19:625–631. [PubMed: 23333532]

23. Tam CS, Bassett R, Ledesma C, Korbling M, Alousi A, Hosing C, et al. Mature results of the M. D. Anderson Cancer Center risk-adapted transplantation strategy in mantle cell lymphoma. Blood. 2009; 113:4144–4152. [PubMed: 19168784]

24. Baron F, Storb R, Storer BE, Maris MB, Niederwieser D, Shizuru JA, et al. Factors associated with outcomes in allogeneic hematopoietic cell transplantation with nonmyeloablative conditioning after failed myeloablative hematopoietic cell transplantation. J Clin Oncol. 2006; 24:4150–4157. [PubMed: 16896000]

25. Kruger WH, Hirt C, Basara N, Sayer HG, Behre G, Fischer T, et al. Allogeneic stem cell transplantation for mantle cell lymphoma--final report from the prospective trials of the East German Study Group Haematology/Oncology (OSHO). Ann Hematol. 2014; 93:1587–1597. [PubMed: 24782119]

26. Barker JN, Byam C, Scaradavou A. How I treat: the selection and acquisition of unrelated cord blood grafts. Blood. 2011; 117:2332–2339. [PubMed: 21149636]

27. Sauter CS, Barker JN, Lechner L, Zheng J, Devlin SM, Papadopoulos EB, et al. A phase II study of a nonmyeloablative allogeneic stem cell transplant with peritransplant rituximab in patients with B cell lymphoid malignancies: favorably durable event-free survival in chemosensitive patients. Biol Blood Marrow Transplant. 2014; 20:354–360. [PubMed: 24315843]

28. Sauter CS, Chou JF, Papadopoulos EB, Perales MA, Jakubowski AA, Young JW, et al. A prospective study of an alemtuzumab containing reduced-intensity allogeneic stem cell transplant program in patients with poor-risk and advanced lymphoid malignancies. Leuk Lymphoma. 2014

29. Ceberio I, Devlin SM, Sauter C, Barker JN, Castro-Malaspina H, Giralt S, et al. Sirolimus, tacrolimus and low-dose methotrexate based graft-versus-host disease prophylaxis after non-ablative or reduced intensity conditioning in related and unrelated donor allogeneic hematopoietic cell transplant. Leuk Lymphoma. 2014:1–8.

30. Ponce DM, Sauter C, Devlin S, Lubin M, Gonzales AM, Kernan NA, et al. A novel reduced-intensity conditioning regimen induces a high incidence of sustained donor-derived neutrophil and platelet engraftment after double-unit cord blood transplantation. Biol Blood Marrow Transplant. 2013; 19:799–803. [PubMed: 23416850]

31. Hoster E, Dreyling M, Klapper W, Gisselbrecht C, van Hoof A, Kluin-Nelemans HC, et al. A new prognostic index (MIPI) for patients with advanced-stage mantle cell lymphoma. Blood. 2008; 111:558–565. [PubMed: 17962512]

32. Perales MA, Jenq R, Goldberg JD, Wilton AS, Lee SS, Castro-Malaspina HR, et al. Second-line age-adjusted International Prognostic Index in patients with advanced non-Hodgkin lymphoma after T-cell depleted allogeneic hematopoietic SCT. Bone Marrow Transplant. 2010; 45:1408–1416. [PubMed: 20062091]

33. Moskowitz CH, Nimer SD, Glassman JR, Portlock CS, Yahalom J, Straus DJ, et al. The International Prognostic Index predicts for outcome following autologous stem cell transplantation in patients with relapsed and primary refractory intermediate-grade lymphoma. Bone Marrow Transplant. 1999; 23:561–567. [PubMed: 10217186]

34. Cassaday RD, Guthrie KA, Budde EL, Thompson L, Till BG, Press OW, et al. Specific features identify patients with relapsed or refractory mantle cell lymphoma benefitting from autologous hematopoietic cell transplantation. Biol Blood Marrow Transplant. 2013; 19:1403–1406. [PubMed: 23871782]

35. Cheson BD, Pfistner B, Juweid ME, Gascoyne RD, Specht L, Horning SJ, et al. Revised response criteria for malignant lymphoma. J Clin Oncol. 2007; 25:579–586. [PubMed: 17242396]

36. Rowlings PA, Przepiorka D, Klein JP, Gale RP, Passweg JR, Henslee-Downey PJ, et al. IBMTR Severity Index for grading acute graft-versus-host disease: retrospective comparison with Glucksberg grade. Br J Haematol. 1997; 97:855–864. [PubMed: 9217189]

37. Filipovich AH, Weisdorf D, Pavletic S, Socie G, Wingard JR, Lee SJ, et al. National Institutes of Health consensus development project on criteria for clinical trials in chronic graft-versus-host disease: I. Diagnosis and staging working group report. Biol Blood Marrow Transplant. 2005; 11:945–956. [PubMed: 16338616]

38. Morris E, Thomson K, Craddock C, Mahendra P, Milligan D, Cook G, et al. Outcomes after alemtuzumab-containing reduced-intensity allogeneic transplantation regimen for relapsed and refractory non-Hodgkin lymphoma. Blood. 2004; 104:3865–3871. [PubMed: 15304395]

39. Perez-Simon JA, Kottaridis PD, Martino R, Craddock C, Caballero D, Chopra R, et al. Nonmyeloablative transplantation with or without alemtuzumab: comparison between 2 prospective studies in patients with lymphoproliferative disorders. Blood. 2002; 100:3121–3127. [PubMed: 12384408]

40. Buggins AG, Mufti GJ, Salisbury J, Codd J, Westwood N, Arno M, et al. Peripheral blood but not tissue dendritic cells express CD52 and are depleted by treatment with alemtuzumab. Blood. 2002; 100:1715–1720. [PubMed: 12176892]

41. Condiotti R, Nagler A. Campath-1G impairs human natural killer (NK) cell-mediated cytotoxicity. Bone Marrow Transplant. 1996; 18:713–720. [PubMed: 8899185]

42. Ruggeri L, Capanni M, Urbani E, Perruccio K, Shlomchik WD, Tosti A, et al. Effectiveness of donor natural killer cell alloreactivity in mismatched hematopoietic transplants. Science. 2002; 295:2097–2100. [PubMed: 11896281]

43. Kohrt HE, Thielens A, Marabelle A, Sagiv-Barfi I, Sola C, Chanuc F, et al. Anti-KIR antibody enhancement of anti-lymphoma activity of natural killer cells as monotherapy and in combination with anti-CD20 antibodies. Blood. 2014; 123:678–686. [PubMed: 24326534]

44. Marks DI, Lush R, Cavenagh J, Milligan DW, Schey S, Parker A, et al. The toxicity and efficacy of donor lymphocyte infusions given after reduced-intensity conditioning allogeneic stem cell transplantation. Blood. 2002; 100:3108–3114. [PubMed: 12384406]

45. van Besien K, Loberiza FR Jr. Bajorunaite R, Armitage JO, Bashey A, Burns LJ, et al. Comparison of autologous and allogeneic hematopoietic stem cell transplantation for follicular lymphoma. Blood. 2003; 102:3521–3529. [PubMed: 12893748]

46. Rondon G, Giralt S, Huh Y, Khouri I, Andersson B, Andreeff M, et al. Graft-versus-leukemia effect after allogeneic bone marrow transplantation for chronic lymphocytic leukemia. Bone Marrow Transplant. 1996; 18:669–672. [PubMed: 8879640]

47. Schetelig J, Thiede C, Bornhauser M, Schwerdtfeger R, Kiehl M, Beyer J, et al. Evidence of a graft-versus-leukemia effect in chronic lymphocytic leukemia after reduced-intensity conditioning and allogeneic stem-cell transplantation: the Cooperative German Transplant Study Group. J Clin Oncol. 2003; 21:2747–2753. [PubMed: 12860954]

48. Sohn SK, Baek JH, Kim DH, Jung JT, Kwak DS, Park SH, et al. Successful allogeneic stem-cell transplantation with prophylactic stepwise G-CSF primed-DLIs for relapse after autologous transplantation in mantle cell lymphoma: a case report and literature review on the evidence of GVL effects in MCL. Am J Hematol. 2000; 65:75–80. [PubMed: 10936869]

49. Corradini P, Dodero A, Farina L, Fanin R, Patriarca F, Miceli R, et al. Allogeneic stem cell transplantation following reduced-intensity conditioning can induce durable clinical and molecular remissions in relapsed lymphomas: pre-transplant disease status and histotype heavily influence outcome. Leukemia. 2007; 21:2316–2323. [PubMed: 17597807]

50. Grigg A, Bardy P, Byron K, Seymour JF, Szer J. Fludarabine-based non-myeloablative chemotherapy followed by infusion of HLA-identical stem cells for relapsed leukaemia and lymphoma. Bone Marrow Transplant. 1999; 23:107–110. [PubMed: 10197793]

51. Urbano Ispizua A, Pavletic SZ, Flowers MED, Zhang M-J, Carreras J, Smith SM, et al. Association Of Graft Vs. Host Disease (GVHD) With a Lower Relapse/Progression Rate After Allogeneic Hemopoietic Stem Cell Transplantation (HSCT) With Reduced Intentsity Conditioning In Patients With Follicular and Mantle Cell Lymphoma: A Cibmtr Analysis. Blood. 2013; 122:2093–2093. [PubMed: 23926305]

52. Sauter CS, Lechner L, Scordo M, Zheng J, Devlin SM, Fleming SE, et al. Pretransplantation Fluorine-18-Deoxyglucose-Positron Emission Tomography Scan Lacks Prognostic Value in Chemosensitive B Cell Non-Hodgkin Lymphoma Patients Undergoing Nonmyeloablative Allogeneic Stem Cell Transplantation. Biol Blood Marrow Transplant. 2014

53. Gooley TA, Chien JW, Pergam SA, Hingorani S, Sorror ML, Boeckh M, et al. Reduced mortality after allogeneic hematopoietic-cell transplantation. N Engl J Med. 2010; 363:2091–2101. [PubMed: 21105791]

54. Salek D, Vesela P, Boudova L, Janikova A, Klener P, Vokurka S, et al. Retrospective analysis of 235 unselected patients with mantle cell lymphoma confirms prognostic relevance of Mantle Cell Lymphoma International Prognostic Index and Ki-67 in the era of rituximab: long-term data from the Czech Lymphoma Project Database. Leuk Lymphoma. 2014; 55:802–810. [PubMed: 23772666]

55. Tiemann M, Schrader C, Klapper W, Dreyling MH, Campo E, Norton A, et al. Histopathology, cell proliferation indices and clinical outcome in 304 patients with mantle cell lymphoma (MCL): a clinicopathological study from the European MCL Network. Br J Haematol. 2005; 131:29–38. [PubMed: 16173960]

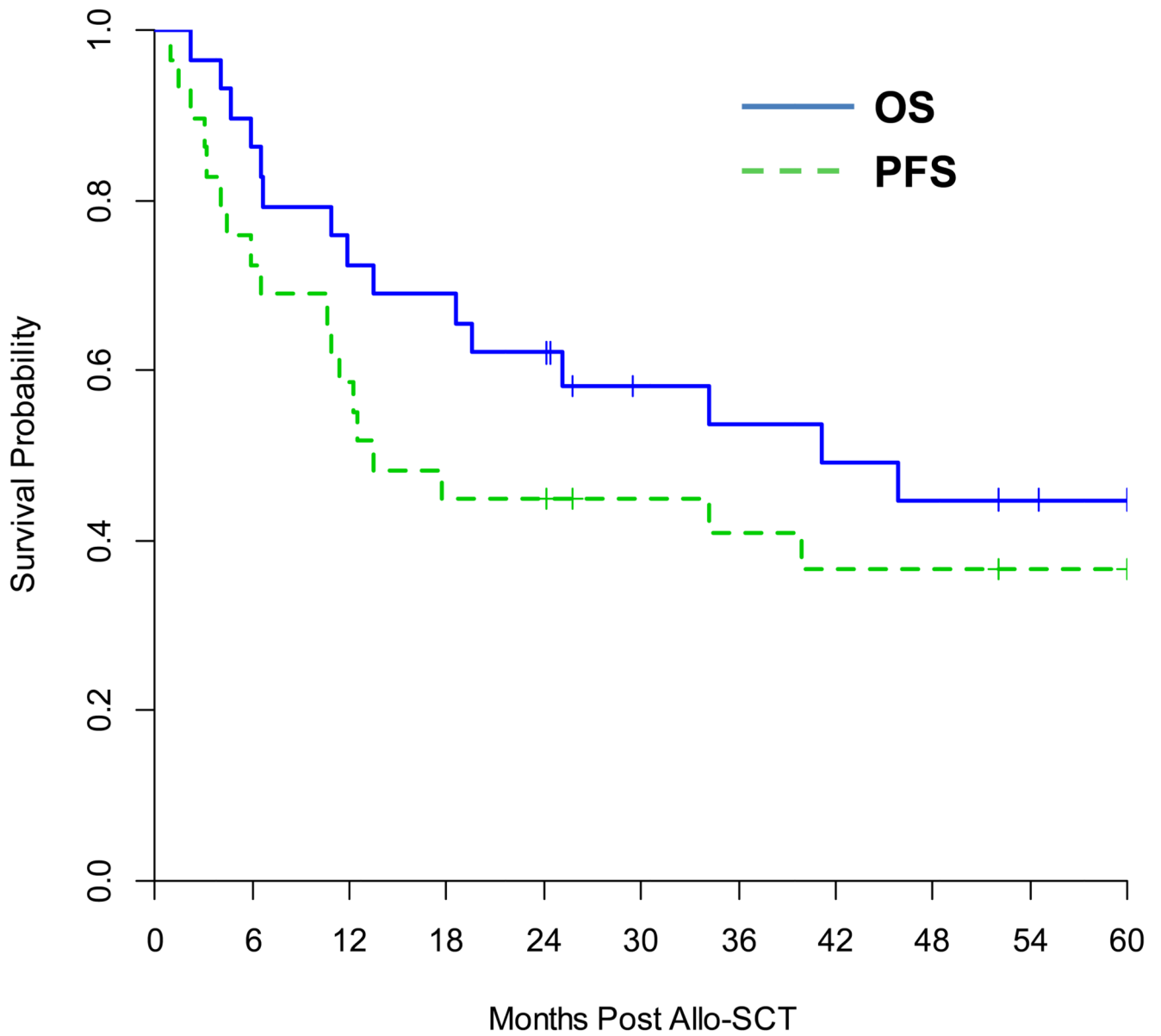**Figure 1.**
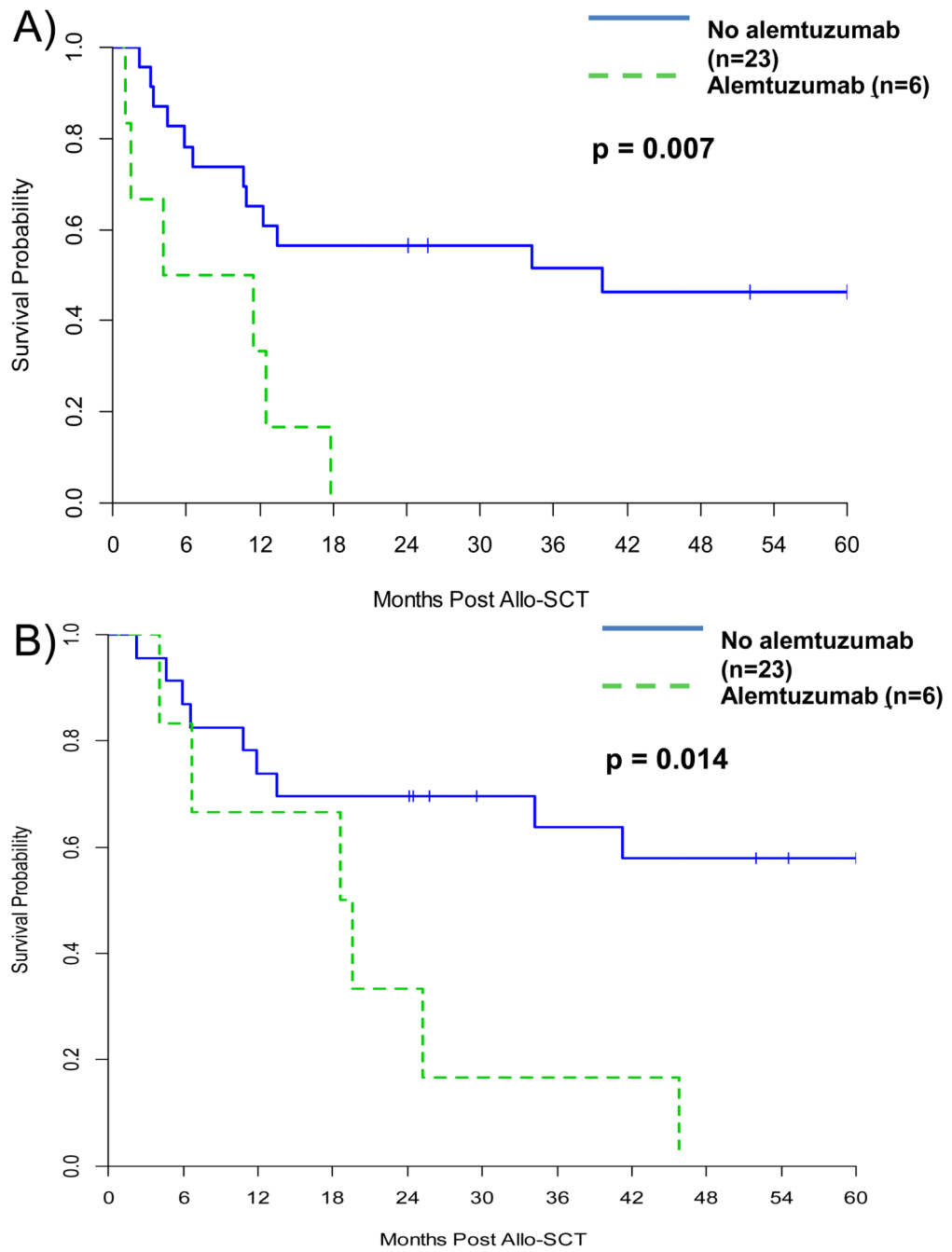Kaplan-Meier estimate of OS and PFS of the study cohort (n=29).

Figure 2.
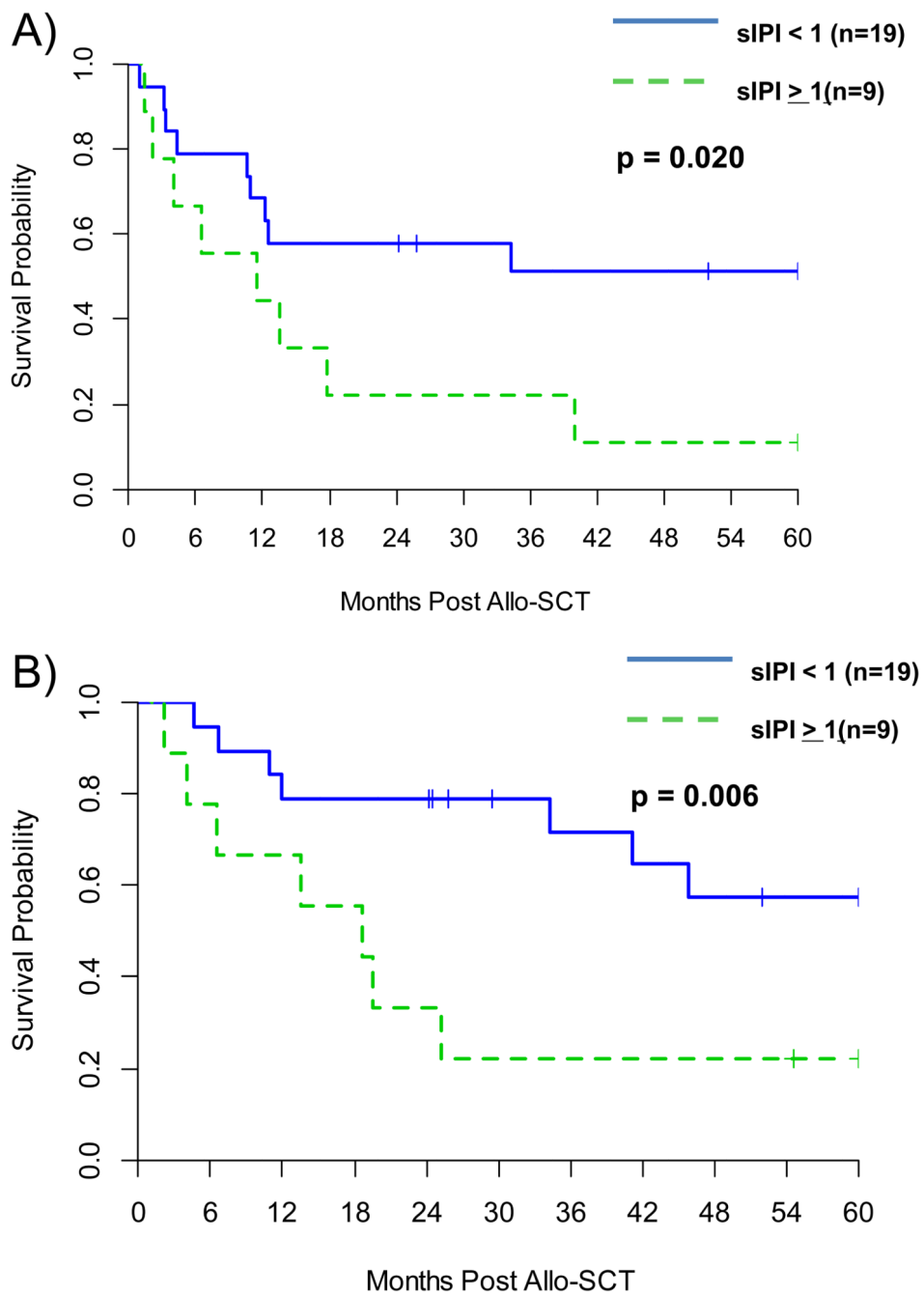Kaplan-Meier estimate of PFS (A) and OS (B) according to alemtuzumab use.

Figure 3.
Kaplan-Meier estimate of PFS (A) and OS (B) according to sIPI.

Table 1

Patients characteristics (N=29)

Patient Characteristic	N (%)
Male, n (%)	25 (86%)
Median age, y (range)	37 (34-71)
Stage 3 at diagnosis, n (%)	28 (96%)
Blastic variant	2 (7%)
Extranodal involvement, n (%)	26 (90%)
MIPI at SCT	
low risk, n (%)	22 (81%)
intermediate risk, n (%)	4 (16%)
high risk, n (%)	1 (1%)
IPI score at SCT (sIPI)	
0 no risk factors, n (%)	19 (68%)
>= 1 risk factor, n (%)	9 (32%)
Median time from initial diagnosis, mo (range)	53 (6-200)
Median no. of prior lines of chemotherapy SCT (range)	5 (1-6)
LDH elevated at SCT (%)	12 (41%)
Remission Quotient *<11, n (%)	13 (45%)
Extranodal sites at SCT, n (%)	4 (14%)
Previous autoSCT, n (%)	13(45%)
PET positive before SCT, n (%)	9 (37%) (Missing data, n = 5)
Disease status at SCT	
CR, n (%)	17 (59%)
PR, n (%)	9 (31%)
SD, n (%)	3 (10%)
Chemosensitive disease beforeSCT, n (%)	26 (90%)
HCT-CI 3, n (%)	5 (17%)
Source of cells (PBSC), n (%)	24 (83%)
Source of cells (DUCB), n (%)	5 (17%)
Rituximab during conditioning, n (%)	18 (62%)
ATG, n (%)	10 (34%)
Campath, n (%)	6 (21%)
Conditioning regimen	
Fludarabine/Melphalan/ Alemtuzumab	6 (21%)
Fludarabine/Melphalan	2 (7%)
Cyclophosphamide/Fludarabine/TBI	20 (69%)
Cyclophosphamide/Fludarabine	1(3%)

MIPI: Mantle Cell International Prognostic Index; SCT: Stem Cell Transplantation; IPI: International Prognostic Index; sIPI: second line International Prognostic Index; LDH: Lactate Dehydrogenase; PET: Positron Emission Tomography; CR: Complete Remission; PR: Partial Remission; SD: Stable Disease; HCT-CI: Hematopoietic Stem Cell Transplantation Comorbidity Index; PBSC: Peripheral Blood Stem Cells; DUCB: Double Umbilical Cord Blood; ATG: Anti-thymocyte Globulin; TBI: Total Body Irradiation.

Table 2

Univariate analysis of PFS and OS risk factors.

Variable	Value	Number of patients	PFS 3-year estimate	P-value	OS 3-year estimate	P-value
Age	<60	17	0.51 (0.32-0.83)	0.054	0.51 (0.31-0.83)	0.464
	60	12	0.25 (0.09-0.67)		0.58 (0.36-0.94)	
Alemtuzumab use	No	23	0.51 (0.34-0.77)	0.007	0.64 (0.46-0.88)	0.014
	Yes	6	0		0.17 (0.03-0.99)	
ATG or alemtuzumab	No	13	0.53 (0.31-0.89)	0.231	0.67 (0.45-0.99)	0.248
	Yes	16	0.31 (0.15-0.65)		0.43 (0.24-0.76)	
HCT-CI	<3	24	0.45 (0.29-0.71)	0.576	0.53 (0.36-0.78)	0.68
	3	5	NA		0.6 (0.29-0.99)	
PET positive before allo-HSCT	No	15	0.37 (0.19-0.75)	0.826	0.63 (0.41-0.97)	0.692
	Yes	9	0.44 (0.21-0.92)		0.44 (0.21-0.92)	
Prior auto-SCT	No	16	0.5 (0.31-0.82)	0.629	0.61 (0.41-0.91)	0.363
	Yes	13	0.29 (0.12-0.7)		0.43 (0.22-0.84)	
Prior lines of therapy	<3	17	0.4 (0.22-0.73)	0.435	0.56 (0.35-0.87)	0.459
	3	12	0.42 (0.21-0.81)		0.50 (0.28-0.88)	
Remission quotient	<11	16	0.38 (0.2-0.71)	0.865	0.49 (0.3-0.82)	0.669
	11	13	0.46 (0.26-0.83)		0.62 (0.4-0.95)	
sIPI	0	19	0.52 (0.33-0.81)	0.020	0.71 (0.53-0.97)	0.006
	1	9	0.22 (0.07-0.75)		0.22 (0.07-0.75)	
Time from diagnosis to allo-HSCT	<2 years	12	0.5 (0.28-0.88)	0.867	0.67 (0.45-0.99)	0.394
	2 years	17	0.35 (0.19-0.67)		0.46 (0.28-0.78)	
Type of donor	Related	12	0.33 (0.15-0.74)	0.264	0.5 (0.28-0.88)	0.344
	Unrelated	17	0.45 (0.26-0.78)		0.56 (0.36-0.88)	
Year of allo-HSCT	< 2007	12	0.17 (0.05-0.59)	0.064	0.25 (0.09-0.67)	0.017
	2007	17	0.59 (0.4-0.88)		0.76 (0.59-0.99)	

PFS: Progression Free Survival; OS: Overall Survival; ATG: anti-thymocyte Globulin; HCT-CI: Hematopoietic Stem Cell Transplantation Comorbidity Index; PET: Positron Emission Tomography; HSCT: hematopoietic Stem Cell Transplantation; auto-SCT: autologous Stem Cell Transplantation; sIPI: second line International Prognostic Index;