Title

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Double Umbilical Cord Blood Transplantation (dUCB) is effective therapy for relapsed or refractory Hodgkin Lymphoma.

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Abstract

Background.—A sub-group of patients with Hodgkin Lymphoma (HL) who relapse after autologous stem cell transplantation can achieve long-term disease-free-survival after allogeneic stem cell transplantation (alloSCT). There is limited information regarding the tolerability and efficacy of double umbilical cord blood transplantation (dUCBT) for relapsed/refractory HL.

Methods.—We analysed 27 consecutive, heavily pre-treated patients receiving dUCBT for relapsed/refractory HL at two centers from 2003–2014. The majority of patients relapsed <6 months after autologous stem cell transplant. 15 patients received myeloablative (most commonly melphalan, fludarabine, thiotepa and anti-thymocyte globulin [ATG]) and 12 non-myeloablative conditioning regimens (fludarabine, cyclophosphamide, 200cGy total body irradiation +/− ATG)

Results.—All patients engrafted; median time to neutrophil and platelet engraftment was 17 and 37 days, respectively. Overall response rate was 68%; 58% achieved complete remission. Median progression-free survival (PFS) was 12.2 months; median overall survival was 27 months. Cumulative incidences of relapse and of non-relapse mortality at 5 years were 30% and 37.9%, respectively;5-year PFS was 31.3% (95% CI 10.1–52.5). There was a trend toward inferior PFS in patients with lymph node size ≥2cm at the time of alloSCT (p=0.07) and toward inferior survival in patients with chemorefractory disease pre-alloSCT (p=0.12).

Conclusions.—dUCBT is feasible in patients with heavily pre-treated HL and can achieve long-term disease-free survival in approximately 30% of patients.

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Introduction.

Hodgkin lymphoma (HL) has a generally excellent prognosis, with long-term disease-free survival achieved with frontline therapy in over 90% of patients with low-risk, early-stage disease and approximately 60% in patients with high-risk, advanced stage disease. Patients who relapse after initial therapy can be salvaged by high dose chemotherapy and autologous stem cell transplantation (autoSCT) in approximately 50% of cases.[1–4] Prognoses for patients relapsing after autoSCT, however, are poor, with an OS of approximately 32% at 5 years; patients relapsing within 6 months of autoSCT, with bulky or advanced stage disease and with advanced age or poor performance status, have particularly poor outcomes.[5] The optimal salvage treatment in this setting is not well-established. Allogeneic stem cell transplantation with myeloablative conditioning in HL has mainly been performed in patients who have not previously undergone autoSCT and is associated with excessive treatment-related mortality (TRM) of 43–61% at 3–4y,[6–10] reflecting both the high-risk patient populations and the intrinsic toxicity of the procedure.[11] A European Group for Blood and Bone Marrow Transplantation (EBMT) study demonstrated significantly better outcomes in relapsed patients receiving autologous transplant than allogeneic transplant, largely due to the higher TRM with allogeneic transplant.[8] Few patients relapsing post-autologous transplant are able to tolerate this procedure. In contrast, reduced-intensity conditioned (RIC) alloSCT has been used post-autologous transplant failure with an acceptable TRM of <25%.[11–18] One retrospective analysis which compared patients treated with RIC alloSCT with a historical control treated without alloSCT suggested a survival benefit for alloSCT.[19] A clinically-exploitable graft-vs-lymphoma (GVL) effect likely exists in HL, as evidenced by the association of graft versus host disease (GVHD) with lower relapse rates[20] and responses to donor lymphocyte infusion (DLI).

Only approximately 30% of patients who require allogeneic stem cell transplantation (alloSCT) will have a matched sibling donor.[21] Many patients without a matched sibling will have an adult MUD, but this is often not the case in patients from ethnic minorities.[22] HLA matching criteria are less stringent in UCBT, allowing suitable cord blood units to be found in most patients.[23] However, there are several challenges associated with UCBT: the low numbers of hematopoietic progenitors present within a cord blood unit leads to slower engraftment than with other stem cell transplant sources and a higher risk of failed engraftment;[23] infection risk is particularly high in UCBT due to delayed immune reconstitution; immunosuppression persists beyond the period of neutropenia, with ongoing risk of bacterial, viral and fungal infection.[24]

Adult patients treated for AML or ALL have lower relapse rates with UCBT compared to other stem cell sources, but higher TRM. Survival outcomes are similar.[25] However, there is relatively limited experience with UCBT in HL. A large SFGM-TC study reported results on allogeneic stem cell transplantation for 191 patients with relapsed or refractory (R/R) HL (92% with prior autoSCT). The 17 patients who had dUCBT had inferior survival to patients with adult donors due to higher rates of both relapse and NRM. In contrast, a small comparative study showed similar results for nine patients receiving RIC dUCBT compared to 12 patients receiving RIC sibling donor transplants[16] and a recent large CIBMTR study

(which included 39 patients with HL having UCBT) showed similar results for patients receiving UCBT to those receiving other alternative donor transplants.[26]

We report our experience of dUCBT for relapsed and refractory HL.

Patients and methods.

We studied 27 consecutive patients treated with dUCBT at the University of Texas M.D. Anderson Cancer Center (n=21) or The Royal Melbourne Hospital, Australia (n=6) for relapsed/refractory HL. Patients treated on clinical studies gave informed consent and studies were conducted according to the Declaration of Helsinki. Data were reviewed retrospectively after approval from both local institutional review boards.

Patients were staged according to the Ann Arbor system[27] and responses assessed according to the Cheson criteria.[28] Patients were considered chemoresistant if they had progressive disease or stable disease and chemosensitive if they achieved partial response (PR) or complete response (CR) prior to dUCBT. Relapse was defined as the appearance of any new lesion, enlargement of an existing lesion or reappearance of bone marrow disease. Progression-free survival (PFS) was defined as time from dUCBT to progression, death from any cause or initiation of subsequent salvage treatment and overall survival (OS) defined as time from transplant to death from any cause. TRM was defined as death in absence of documented disease progression.

Time-to-event outcomes with competing risks (TRM and relapse, death and acute- (aGVHD) or chronic-GVHD (cGVHD)) were estimated using the cumulative incidence method. PFS and OS were estimated using the Kaplan-Meier method and dichotomous variables compared using the log-rank test. Small numbers limited analysis of prognostic factors and precluded multivariable analysis. Statistical analysis was performed with SPSS version 22 (IBM Corp, Armonk, New York) and Graphpad Prism 6 (La Jolla, California).

Results.

Patients were treated consecutively between August 2003 and May 2014. Baseline patient characteristics are shown in table 1. The patient group represented a high-risk population: they were heavily pre-treated (median number of prior therapies 4, range 2–6); all but 2 patients had relapsed post-ASCT; the 2 patients who had not received autoSCT both had primary refractory disease and were also refractory to salvage therapy; they were thus thought to be unlikely to benefit from autoSCT; the majority of patients relapsed <6 months post-autoSCT with advanced stage disease; bulky lymphadenopathy, however was uncommon. The most recent therapy received prior to transplant was heterogeneous and era-dependent; patients transplanted prior to 2007 had predominantly received combination chemotherapy or radiotherapy, while patients transplanted after 2007 had frequently received the CD30 immunoconjugate brentuximab vedotin or another investigational regimen. Fifteen patients received myeloablative conditioning and 12 non-myeloablative (NMA) conditioning; regimens were chosen according to clinical studies available at the time of transplant; myeloablative regimens were melphalan 140mg/m^2, thiotepa 10mg/kg, fludarabine 160mg/m^2 and rabbit anti-thymocyte globulin (ATG) 3mg/kg[29] or busulfan

(pharmacokinetically monitored to achieve AUC of 5000 micromol/min for 4 days after an initial test dose of 32mg/m^2), fludarabine 160mg/m^2, clofarabine 120mg/m^2, 200cGy total body irradiation (TBI) and ATG 3mg/kg.[30] Non-myeloablative regimens were fludarabine 160mg/m^2, cyclophosphamide 50mg/kg, TBI 200cGy[31] +/− ATG 3mg/kg (n=5) or fludarabine 132mg/m^2, melphalan 140mg/m^2 and ATG 3mg/kg (n=2). 22 of 27 patients received antithymocyte globulin; median total nucleated cell dose was 4×10^7/kg (range 1.2–59.4); where available, patients were treated on *ex vivo* expansion/manipulation protocols with liquid culture media (N=8), mesenchymal stromal cells (N=3) or fucosylation (N=3), in part accounting for the very wide range of cell doses given. Only one patient received post-alloSCT radiotherapy to a site of bulky disease. No patient received post-transplant maintenance therapy with novel agents, such as brentuximab.

Engraftment.

Median time to neutrophil recovery (ANC > 500/mm^3) was 17 days (range: 5–38). Median time to platelet recovery (plt >20,000/mm^3 in the absence of transfusions for a week) was 37 days (range 21–105 days); 5 patients, all of whom died prior to day 100, did not achieve platelet engraftment. One patient, who received myeloablative conditioning, experienced secondary graft failure and hematopoiesis was rescued with stored autologous stem cells. There was no significant difference in engraftment times between patients who did and did not receive *ex vivo* graft manipulation; however, this analysis was confounded by the fact that patients who received manipulated grafts were significantly more likely to have had myeloblative conditioning.

Response to treatment, progression-free survival and overall survival.

Twenty-four patients were evaluable for post-transplant response; 3 were not evaluable due to early death prior to day 30. Of 24 evaluable patients, 19 were not in CR prior to transplant. Of these patients, 13/19 (68%) improved their response post-transplant: 11 (1 with stable disease [SD], 3 with progressive disease [PD] and 7 with partial response [PR]) achieved CR, while two patients with PD improved to PR. . Median progression-free survival (PFS) was 12 months (range 1.8–87.6 months) and median survival was 27 months (range 1.8–109.3 months) for the whole cohort, figure 1A. Actuarial progression-free survival at 5 years was 31.3 +/− 21.2%) Small numbers limited our ability to perform detailed subgroup analysis. However, we were interested in exploring the impact of chemorefractory disease pre-transplant as a prognostic variable given its importance in several series of patients with Hodgkin Lymphoma transplanted from adult donors.[32–34] No statistically-significant difference was seen in PFS (p=0.26), figure 1B, likely due to small numbers, but there was a suggestion of inferior survival (median 7.4mo vs not reached, p=0.12) in patients with chemorefractory disease, figure 1C In addition, others have shown that the presence of gross residual disease ≥2cm in diameter is associated with inferior PFS and survival in the setting of myeloablative alloSCT for HL.[35] In our cohort, there was a suggestion of inferior PFS (median PFS 7.4 months vs not reached, p=0.07), figure 1D, in patients with gross residual disease compared to those without, but there was no difference in survival (p=0.46), figure 1E. Finally, there was no difference in PFS (p=0.96), figure 1F or survival (p=0.27), data not shown, between patients receiving myeloablative vs non-myeloablative conditioning.

Incidence of graft-vs-host disease.

Median follow-up after transplant was 14 months. Cumulative incidences of grade II acute GVHD and extensive chronic GVHD were 33.5% (95% CI 18.8–52.4) and 40.5% (24.7–59.6), respectively. No patient developed grade III-IV acute GVHD.

Cumulative incidences of relapse and non-relapse mortality.

Cumulative incidences of relapse and non-relapse mortality are shown in figure 2. Cumulative incidence of non-relapse mortality was 26% at 100 days and 37.9% at 5 years. Cumulative incidence of relapse was 30% at 5 years and occurred at a median time of 7.4 months (range 4.1–36.0 months) Only one relapse occurred beyond 12 months. Treatment of relapsed disease post-dUCBT was heterogeneous: no patients received donor lymphocyte infusions due to lack of availability; one patient achieved a partial remission with the combination of sirolimus and vorinostat and subsequently remains in CR 12 months post-salvage haploidentical transplant. There was no statistically-significant difference in TRM or relapse according to whether patients received myeloablative conditioning or not.

Causes of death.

Causes of death prior to day 100 were predominantly infection-related: 2 patients died from bacterial pneumonia, 2 from viral infection (1 CMV pneumonitis and 1 adenovirus pneumonia) and 1 from aspergillus pneumonia; 1 patient died from acute interstitial pneumonia and another from a central nervous system event of unclear etiology. Two patients died after day 100 from disease relapse. The two treatment-related deaths post-day 100 both occurred in patients with extensive chronic GVHD, one from fungal pneumonia and another from unknown causes.

Notable proven opportunistic infections.

Several other notable infections occurred: one patient developed CMV retinitis before dying from aspergillus pneumonia; another patient developed rituximab-refractory EBV-driven post-transplant lymphoproliferative disease and achieved long-term complete remission after treatment with EBV-specific cytotoxic T-cells.

Discussion.

We have shown here that dUCBT is feasible in selected patients with relapsed/refractory Hodgkin Lymphoma. This was a very high-risk, heavily pre-treated population, who had predominantly relapsed early post-autoSCT, with advanced stage disease. In addition, 12 of 27 were refractory to their most recent salvage treatment prior to transplant, including 7 with progressive disease, a feature associated in studies of alloSCT for HL in the adult donor setting with poor transplant outcomes. Despite these high-risk features, long-term disease-free survival was achieved in a proportion of patients, including in 3 patients who had progressive disease during their most recent salvage therapy, who subsequently achieved durable complete remission post-transplant.

The major barriers to successful outcomes were TRM prior to day 100 and relapse prior to one year. In contrast, severe GVHD was not seen in our patient cohort, likely as a result of

the frequent use of preparative regimens containing ATG for *in vivo* T-cell depletion of the graft. The predominant cause of TRM was infection; there was a high incidence of life-threatening viral infection, with two patients dying from viral pneumonia (adenovirus and CMV) and a 3rd patient requiring EBV-specific 3rd-party CTLs to treat rituximab-refractory EBV-driven PTLD. A 4th patient developed CMV retinitis. All of these infections occurred in patients given ATG as part of their conditioning regimen. There were no issues with engraftment or mixed chimerism seen in the 5 patients conditioned with fludarabine, low-dose cyclophosphamide and 2Gy TBI, without ATG; although this was not a randomized study and numbers were small, this does suggest that the use of ATG in this patient population may not be necessary and could lead to deleterious side effects, particularly viral infection. In addition, myeloablative conditioning was used in 15 of 27 patients. Myeloablative regimens have been shown in the adult donor setting to be associated with a prohibitively high TRM in R/R HL; we did not see an excess mortality rate in patients conditioned with myeloablative regimens, but our numbers were likely insufficient to see a difference. Patients conditioned with NMA regimens in this study demonstrated adequate engraftment and all had full donor myeloid and lymphoid chimerism at D100 with or without the use of ATG.

Development of novel strategies to reduce early TRM is a priority for such patients. Prolonged neutropenia post-transplantation is a major risk factor for both bacterial and fungal infection.[25] There are now several methods available to promote more rapid neutrophil engraftment post-dUCBT: one strategy is to expand one cord unit *ex vivo* to yield increased numbers of CD34+ progenitors; this can be achieved by culture *ex vivo* in a GMP facility, utilizing mesenchymal stem cells,[36] with NOTCH1 ligand[37] or with nicotinamide;[38] alternatively, techniques to enhance homing of infused cord blood HPCs to niches within the marrow can be utilized, such as incubating cord blood *ex vivo* with fucosyltransferase VI[39] or with dmPGE2.[40] These techniques have all been shown to considerably shorten the duration of neutropenia post-dUCBT. This may, in turn, reduce the incidence of bacterial and fungal infection. Several of these methods, notably expansion using MSCs or NOTCH1 ligand, result in predictable long-term engraftment occurring from the non-expanded cord, potentially as a result of the expansion process resulting in infusion of a high-proportion of lineage-committed HPCs.[36] Opportunistic viral infections remain a major cause of morbidity and mortality post-dUCBT.[24] The development of viral-specific cytotoxic T-cells (CTLs) to treat these infections represents a major advance; approximately 70% of patients with chemorefractory CMV, EBV or adenoviral (ADV) infections respond to infusions of CTLs. Tri-virus specific CTLs targeting CMV, EBV and ADV can be generated from cord blood;[41] these could be prospectively generated pre-transplant from a small aliquot of cord blood and infused prophylactically post-dUCBT. If cord-blood expansion using MSCs is undertaken, the CTLs should be generated from the non-expanded cord, which is anticipated to produce long-term engraftment. Alternatively, banked 3rd-party VSTs could be infused to treat identified infection.[42] We anticipate that a combination of these strategies has the capacity to significantly reduce early TRM from dUCBT These strategies, however, remain to be proven in large-scale clinical studies, and simplified for broader applicability. Until they are, use of preparative regimens which do not contain T-cell

depleting antibodies and meticulous attention to anti-fungal prophylaxis may reduce the early TRM seen in this population.

Stategies to reduce early relapse are also needed to improve results of dUCBT for R/R HL. Although our numbers were too small to determine this in a statistically-significant way, it is likely that pre-treatment chemoresponsiveness has a major impact on post-transplant survival, as has been shown in several other studies in R/R HL.[32–34] In addition, there was a suggestion that the presence of gross residual disease pre-transplant is also associated with inferior outcomes. Our study included patients transplanted prior to the availability of more active salvage treatments, such as the CD30 immunoconjugate brentuximab vedotin.[43] More recently, impressive activity in patients with HL relapsed post-autoSCT has been seen with the PD1 inhibitor nivolumab;[44] the combination of the mTOR inhibitor sirolimus and the HDAC inhibitor vorinostat also shows promising activity.[45] Utilization of one of these novel regimens at the time of relapse post-autoSCT may achieve superior responses to conventional chemotherapy; given the association between depth of pre-transplant response and post-transplant survival, this could be predicted to result in enhanced post-transplant results. Additionally, minimization of cytotoxic salvage chemotherapy pre-alloSCT may potentially improve the tolerability of the procedure. Finally, development of post-transplant maintenance strategies may be beneficial to reduce relapse rates and allow longer-term disease control through the GVL effect. Others have shown that the use of brentuximab vedotin in combination with DLI to treat relapsed disease post-alloSCT may enhance the development of a HL-specific alloimmune response;[46] use of this agent for maintenance post-alloSCT may therefore be beneficial in reducing relapse rates. The safety and efficacy of these novel agents for post-transplant maintenance will need to be established by carefully designed studies; in particular, use of PD1 inhibitors post-transplant could potentially induce GVHD.

Treatment of relapse post-alloSCT in our cohort was heterogeneous and no conclusions can be drawn about the safety and relative efficacy of different treatment options in this setting from our data. One patient did achieve prolonged disease control after a haploidentical transplant. Patients have responded to DLI given for relapsed disease in the adult donor setting for HL relapsed post-alloSCT;[20] the majority of responses to DLI for relapse in the setting of T cell-replete, adult-donor alloSCT are transient. In contrast, DLI appears more efficacious after T-cell-depleted alloSCT, with the majority of patients treated for overt relapse showing durable responses and very few patients treated prophylactically for mixed chimerism relapsing.[20] Previously, in the setting of dUCBT, DLI has been unavailable; recently, however, the technology has become available to generate sufficient T-cells for DLI through *ex vivo* expansion using CD3/28 beads, from a 5% aliquot of cord blood set aside prior to transplantation.[47] This may prove to be a useful method to treat relapsed disease or persistent mixed chimerism in the setting of relapse post-dUCBT.

In summary, we have shown that dUCBT can provide long-term progression-free survival in a substantial fraction of patients with advanced HL. A number of techniques to optimize the cord blood graft and cellular therapies to treat viral infections will likely make the procedure safer in the future. Additionally, the availability of more active novel pharmacologic

therapies has the potential to improve transplant results through achieving more robust pre-transplant remissions and/or being utilized as post-transplant maintenance.

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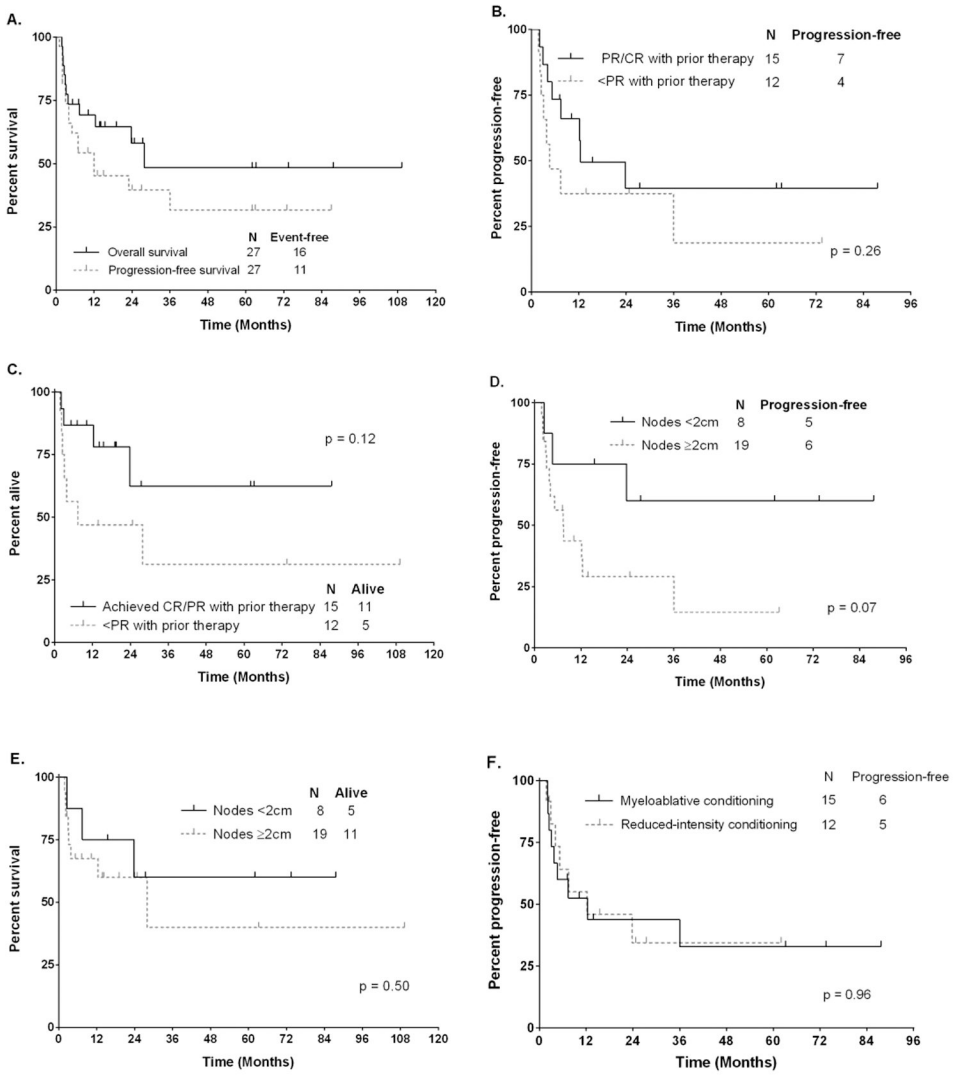

Figure 1.

A. PFS and survival in the whole cohort. B: PFS according to pre-transplant chemosensitivity. C: Survival according to pre-transplant chemosensitivity. D: PFS according to the presence of residual nodal disease ≥2cm in diameter. E: Survival according to the presence of residual nodal disease ≥2cm in diameter.

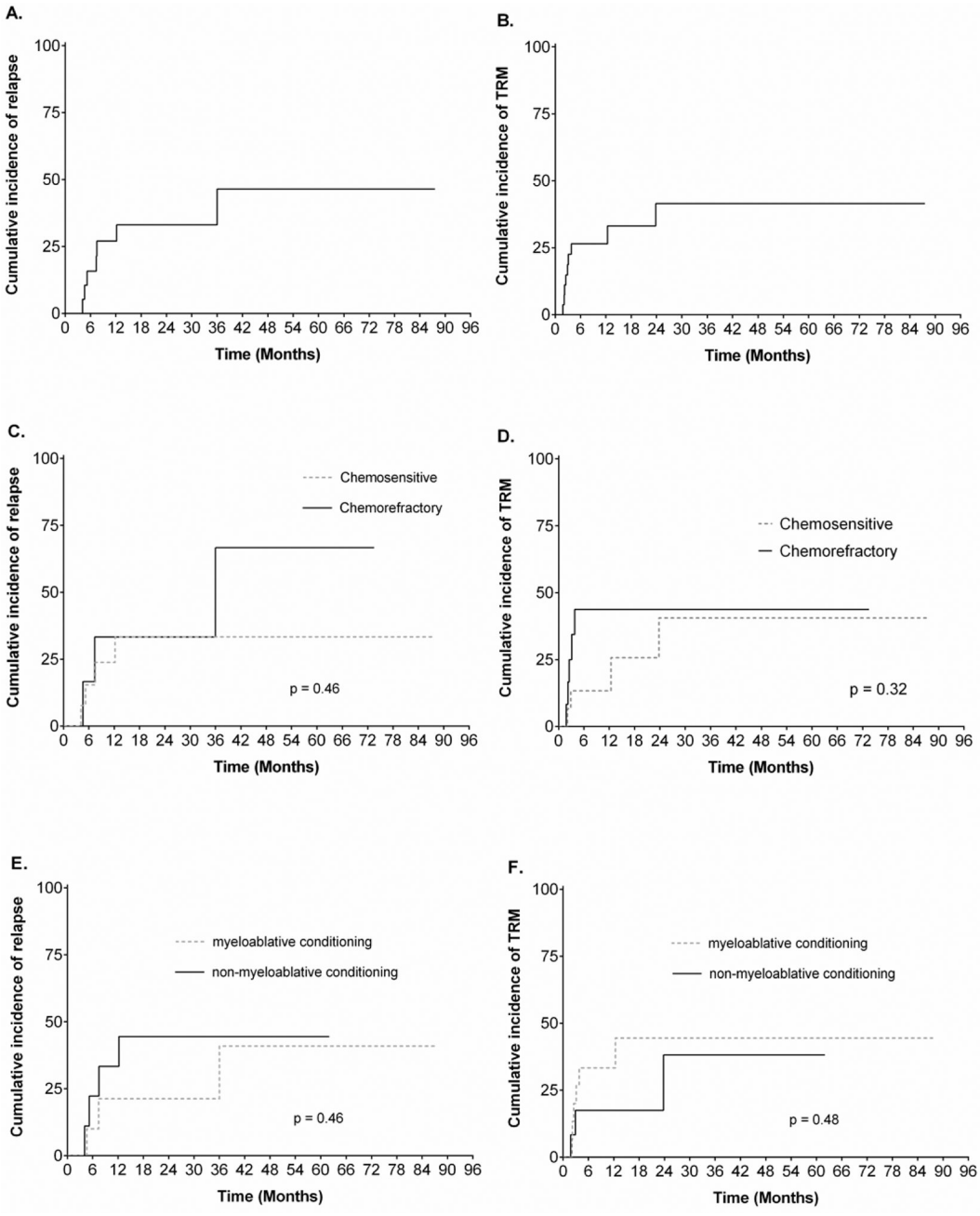

Figure 2.

A: Cumulative incidence of relapse in the whole cohort. B: Cumulative incidence of TRM in the whole cohort. C: Cumulative incidence of relapse according to chemosensitivity. D: Cumulative incidence of TRM according to chemosensitivity.

Table 1.

Characteristics of the patients (N = 27).

Characteristic, N = 27	n (%) unless stated
Male gender	16 (59.0)
Age at dUCBT, median (range)	29 (17–61)
Prior autologous transplant	25 (92.5)
Time to relapse post-autologous transplant, median (range)	5 months (1–61)
Response prior to dUCBT	
Complete Remission	6 (22.2)
Partial Remission	9 (33.3)
Stable Disease	5 (18.5)
Progressive Disease	7 (26.0)
Ann Arbor stage III-IV at relapse, n=24	15 (62.5)
Most recent prior therapy	
Combination chemotherapy	12 (44.4)
Brentuximab vedotin	7 (25.9)
Radiotherapy	4 (14.8)
Other	4 (14.8)
Bulky lymphadenopathy ≥5cm	2 (8)
Conditioning Regimen – non-myeloablative	
Fludarabine/low-dose cyclophosphamide/TBI 2Gy	5 (18.5)
Fludarabine/low-dose cyclophosphamide/TBI 2Gy + ATG	4 (14.8)
Fludarabine/Melphalan/ATG	2 (7.5)
Conditioning regimen - myeloablative	
Melphalan/Thiotepa/Fludarabine/ATG	12 (44.5)
Fludarabine/Clofarabine/Busulfan/ATG/TBI 2 Gy	3 (11.0)
Total Nucleated Cell Dose ($x10^7$/kg)	4.0 (range 1.2–59.4)
HLA match	
4/6, 4/6	15 (55.6)
4/6, 5/6	6 (22.2)
5/6, 5/6	5 (18.5)
6/6, 6/6	1 (3.7)