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AUTOLOGOUS HAEMATOPOIETIC CELL TRANSPLANTATION FOR NON-HODGKIN LYMPHOMA WITH SECONDARY CNS INVOLVEMENT

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Contributions:

R.T.M. and P.N.H. designed the study and all other authors contributed to the design of the study. Z.W. and M.J.Z. assembled and analysed the data. All authors participated in the interpretation of the data. R.T.M. and P.N.H. wrote the first draft of the paper and all other authors contributed to the final version.

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SUMMARY

Pre-existing central nervous system (CNS) involvement may influence referral for autologous haematopoietic cell transplantation (AHCT) for patients with non-Hodgkin lymphoma (NHL). The outcomes of 151 adult patients with NHL with prior secondary CNS involvement (CNS⁺) receiving an AHCT were compared to 4688 patients without prior CNS lymphoma (CNS⁻).

There were significant baseline differences between the cohorts. CNS⁺ patients were more likely to be younger, have lower performance scores, higher age-adjusted international prognostic index scores, more advanced disease stage at diagnosis, more aggressive histology, more sites of extranodal disease, and a shorter interval between diagnosis and AHCT. However, no statistically significant differences were identified between the two groups by analysis of progression-free survival (PFS) and overall survival (OS) at 5 years. A matched pair comparison of the CNS⁺ group with a subset of CNS⁻ patients matched on propensity score also showed no differences in outcomes. Patients with active CNS lymphoma at the time of AHCT (n=55) had a higher relapse rate and diminished PFS and OS compared with patients whose CNS lymphoma was in remission (n=96) at the time of AHCT.

CNS⁺ patients can achieve excellent long-term outcomes with AHCT. Active CNS lymphoma at transplant confers a worse prognosis.

Keywords

CNS Involvement; Non-Hodgkin Lymphoma; Autologous transplantation; Outcomes

Introduction

Non-Hodgkin lymphomas (NHL) have the potential for extranodal involvement with predilection for bone marrow, central nervous system (CNS), testes, and other sites. In aggressive NHL subtypes, such as Burkitt lymphoma and lymphoblastic lymphoma, CNS involvement is reported as high as 30% whereas in diffuse large B cell lymphoma (DLBCL), CNS involvement is reported in 1–7% of patients at diagnosis or at relapse (Siegal & Goldschmidt, 2012). Low grade lymphomas also can involve the CNS, but with lower incidence. Irrespective of histological subtype, CNS involvement is therapeutically challenging and associated with worse outcomes.

Autologous haematopoietic stem cell transplantation (AHCT) is a standard of care for eligible patients with relapsed NHL. There are few series evaluating the impact of prior CNS lymphomatous involvement on the outcome of AHCT. CNS involvement by lymphoma has been associated with worse prognosis and is a therapeutic challenge. A registry analysis by the European Group for Blood and Marrow Transplant (EBMT) in 1994 of 62 patients reported that CNS remission at AHCT predicted better outcomes. Long-term progression-free survival (PFS) was 9% for those with active CNS disease versus 42% for those in CNS remission at transplant (Williams *et al*, 1994). Retrospective, single centre studies (van

Besien *et al*, 1998; van Besien *et al* 1996; Alvarnas *et al*, 2000; Kassamon *et al*, 2005) mostly confirm these results. However, many of the studies were performed in the era before rituximab and prior to the application of aggressive treatment regimens for patients with higher risk disease. However, even with more modern regimens incorporating rituximab and intrathecal and/or systemic methotrexate, the rate of CNS relapse post primary therapy for large cell lymphoma has only been slightly reduced (Boehme *et al*, 2009; Villa *et al*, 2010). The current study was designed to determine the outcomes of AHCT in patients with NHL and prior CNS involvement (excluding primary CNS lymphoma).

Patients and methods

Data sources

The Center for International Blood and Marrow Transplant Research (CIBMTR) is a combined research program of the Medical College of Wisconsin and the National Marrow Donor Program (NMDP). CIBMTR comprises a voluntary network of more than 450 transplantation centres worldwide that contribute detailed data on consecutive allogeneic and autologous haematopoietic cell transplants to a centralized Statistical Center. Observational studies conducted by the CIBMTR are performed in compliance with all applicable federal regulations pertaining to the protection of human research participants. Protected Health Information used in the performance of such research is collected and maintained in CIBMTR's capacity as a Public Health Authority under the Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule. Additional details regarding the data source are described elsewhere (Horowitz, 2008).

Patients

Outcomes of adult patients (>18 years) with systemic NHL with (151) or without (4688) CNS involvement, who underwent AHCT between 1990 and 2005 are reported. CNS involvement (CNS⁺) was defined and classified as NHL involvement of brain or spinal cord parenchyma or leptomeningeal involvement or both at any time prior to AHCT. Patients with primary CNS lymphoma were excluded.

Endpoints

Primary outcomes included non-relapse mortality (NRM), progression/ relapse, PFS, and overall survival (OS). NRM was defined as death from any cause in the first 28 days after AHCT or death without evidence of lymphoma progression/relapse. Progression was defined as an increase of ≥ 25% in the sites of lymphoma or development of new sites of lymphoma. Relapse was defined as recurrence of lymphoma after a complete response (CR). For PFS, patients were considered treatment failures at the time of relapse/progression or death from any cause. Patients alive without evidence of NHL relapse or progression were censored at last follow up and the PFS event was summarized by a survival curve. The OS interval variable was defined as the time from date of transplant to date of death or last contact and summarized by a survival curve.

Statistical Analysis

Patient-, disease- and transplant-related variables for the two study groups were compared using the chi-square statistic for categorical and the Kruskal-Wallis test for continuous variables. Univariate probabilities of PFS and OS were calculated using the Kaplan-Meier estimator. Probabilities of NRM and relapse/progression were calculated using cumulative incidence curves to accommodate competing risks.

Matched Pair Analysis

A matched pair comparison was performed on a subset of 135 CNS⁺ patients with follicular lymphoma, DLBCL, Burkitt lymphoma and lymphoblastic histology and a matched CNS⁻ control group. Propensity score method was used to match for pretransplant disease characteristics between the groups by fitting a logistic regression model (D'Agostino, 1998). Matching on propensity scores generated from the model addressed the imbalance between the 2 groups across major risk factors and allowed us to exclude control subjects in the non-overlapping ranges of the propensity score. This resulted in similar cohorts of CNS⁺ and CNS⁻ patients allowing comparison of AHCT outcomes between these groups (Supplemental Table 1).

A numeric propensity score for each CNS⁺ transplant was calculated using the following significant variables from the model: age at AHCT, histology (follicular vs. DLCL vs. lymphoblastic), second line age-adjusted International Prognostic Index (IPI) score, disease status at transplant, year of AHCT and time from diagnosis to transplant. For the CNS⁺ group, the median propensity score was 0.0417. For the pooled CNS⁻ sample, the median propensity score was 0.0343. The aim was to identify 4 matches from the CNS⁻ cohort for each CNS⁺ patient for the matched pair analysis. CNS⁺ transplant recipients (cases) were matched in random order to CNS⁻ transplant recipients (controls) with similar propensity scores. Any CNS⁻ (control) patient with a difference in the propensity score within one standard error from the pooled CNS⁺ sample was considered a potential matched control and a control patient with the smallest difference in propensity score from among all potential matched controls was selected. These steps were repeated among cases until 4 controls were identified for each of the cases.

For 135 CNS⁺ cases, 535 CNS⁻ controls were identified. Median follow-up and risk factor variables used for propensity score were confirmed to be similar between the 2 cohorts. Validation of the selected CNS⁻ control group (n= 535) was performed by confirming similar survival probability with the original CNS⁻ control group from which the cases were drawn. Baseline subject-, disease-, and transplant-related variables for the CNS⁺ and the CNS⁻ matched groups were compared. Multivariate analysis was performed by fitting a Cox model stratified on matched-pairs.

Results

Patient, disease, and transplant characteristics of subjects receiving an AHCT for NHL with or without pre-existing CNS involvement are shown in Table I. There were significant differences between these cohorts, as might be anticipated. Recipients with prior CNS lymphoma were younger, had a shorter interval between diagnosis and AHCT, lower performance scores, more advanced second line age-adjusted IPI scores at transplant, more aggressive histology, more advanced disease stage and a greater frequency of extranodal lymphoma. Univariate probabilities of outcomes of interest after AHCT between the CNS⁺ and CNS⁻ cohort are summarized in Table II. NRM, PFS, relapse risk and OS did not differ between the groups early after transplantation and at one, three and five years. The majority of relapses in either cohort were outside of the CNS compartment. Karnofsky score post AHCT (at last reported contact) was similar between cohorts and 90 in two-thirds of the patients in each cohort. Finally, the CNS⁺ cohort was examined to discern if there was an impact on survival of pre-transplant parenchymal versus leptomeningeal involvement. No difference in OS at 100 days, one year, three years or five years could be determined (p=0.41; data not shown).

The CNS⁺ cohort was further analysed and stratified by CNS remission status at the time of AHCT. Significantly inferior outcomes were observed for those with active CNS lymphoma

at AHCT (see Fig 1 and Table III). At 100 days, 1 year and 3 years post-AHCT, the cumulative incidence of relapse was 33% (95% confidence interval [CI]: 21–46%), 63% (95% CI 49–75%) and 72% (95% CI 59–83%) for those with active CNS lymphoma compared with 19% (95% CI 12–27%), 39% (95% CI 30–49%) and 49% (95% CI 38–59%) in those in CNS remission at the time of AHCT. PFS at 100 days, 1 and 3 years was lower in the cohort with active CNS disease at AHCT 58% (95% CI 45–71%), 28% (95% CI 17–41%) and 19% (95% CI 10–30%), versus 79% (95% CI 70–86%), 57% (95% CI 47–67%) and 46% (95% CI 36–56%) in those in a CNS remission. OS at 100 days, 1 year and 3 years was also inferior for those with active CNS disease at AHCT 78% (95% CI 66–88%), 49% (95% CI 35–62%), 31% (95% CI 19–44%) versus 88% (95% CI 81–94%), 73% (95% CI 64–82%) and 58% (95% CI 47–68%), for those in CNS remission at transplant.

As there were significant baseline differences between the overall CNS⁺ and CNS⁻ cohorts, a matched pair comparison was performed between 135 patients with follicular lymphoma, DLBCL, Burkitt lymphoma and lymphoblastic NHL with CNS disease and a subset (n=535) of closely matched patients that lacked CNS involvement. Advanced disease stage at diagnosis, marrow involvement and extranodal disease were more likely to be associated with the CNS⁺ cohort. Otherwise, the matched cohorts were well balanced with respect to age, sex, performance status, lymphoma stage, chemotherapy sensitivity, time from diagnosis, rituximab exposure (see Supplemental Table I.). Multivariate analysis was performed using Cox regression models stratified on matched pairs. There was no significant differences in relapse (p=0.5572), treatment-related mortality (p=0.8968), PFS (P=0.6152) or OS (P=0.2469) between these cohorts (Fig 2). The major cause of death (>75%) of patients within this analysis was relapse/progression of NHL.

Discussion

The outcomes of patients with CNS involvement of NHL are variable. There are subsets of highly aggressive lymphoma, which commonly are associated with involvement of the CNS early in the natural history, for which therapeutic regimens have been designed to provide CNS therapy as part of upfront management. However, for the vast majority of lymphoma patients, CNS involvement occurs late and can be associated with inferior outcomes. Multiple salvage modalities have been developed, including systemic and intrathecal/intraventricular chemotherapy, radiation therapy, and recently, intrathecal/intraventricular administration of therapeutic antibodies (Vilella *et al*, 2008; Jaime-Perez *et al* 2009). However, decision-making regarding therapy is influenced by the extent of CNS involvement - leptomeningeal or parenchymal relapse or a combination of both and also, on our diagnostic ability to determine persistent disease, recognizing the failure of radiological imaging to truly delineate remission status from ongoing disease, and as well the evolution of imaging technology over the past two decades.

AHCT is another therapeutic modality available to lymphoma patients with CNS involvement. Both autologous and allogeneic HCT have been performed, although in the latter circumstance, only small anecdotal reports exist. In contrast, prior experience with AHCT has demonstrated that this modality can be safe and efficacious.

From a cohort of 605 newly diagnosed patients with intermediate grade and immunoblastic lymphoma, the MD Anderson group identified 24 patients with CNS disease at relapse (van Besien *et al*, 1998). Those with CNS recurrence had worse prognosis and only four of the 20 patients with prior CNS involvement remained free of disease. Another retrospective evaluation of patients receiving high dose therapy with pre-existing CNS involvement for NHL at Stanford University Medical Center indicated that if disease control was achieved, better outcomes were obtained with an actuarial 5-year PFS and OS of 46% and 41%,

respectively, in the 15 AHCT recipients with CNS involvement (out of 481 NHL patients) (Alvarnas *et al*, 2000). This study confirmed that AHCT could provide extended PFS in patients with secondary CNS lymphoma and even possibly in patients with recurrent primary CNS lymphoma. Similar observations were reported from the Johns Hopkins Medical Center, where 37 lymphoma patients who had CNS involvement were treated into remission by the time of either autologous (59%) or allogeneic (41%) HCT (Kasamon *et al* 2005). Age ≥ 18 years, resistant systemic disease, busulfan and cyclophosphamide conditioning and lack of intrathecal consolidation were associated with inferior survival, as was CNS involvement at the time of relapse as opposed to time of diagnosis. Most notably, 5-year survival rates (actuarial OS = 39%) were not dissimilar to those seen in other high risk lymphoma patients without CNS disease undergoing HCT, suggesting that pre-existing CNS disease was not a contraindication to proceeding with transplantation efforts. Cote et al (2012) presented data on 16 patients with secondary CNS lymphoma of various histologies, demonstrating the efficacy of AHCT. The majority (13/16) of patients underwent AHCT at first response with 11 patients in CR, 4 in PR and 1 with stable/progressive disease at time of transplant (Cote *et al*, 2012). Excellent outcomes were reported with 93% OS and 90% PFS at one year. In a prospective phase II study, Korfel et al (2013) treated 24 patients with relapsed secondary CNS lymphoma with 3 cycles of induction therapy followed by AHCT. Survival at 2 years was 68% for AHCT recipients but 6 out of the 30 enrolled patients could not proceed to transplant.

Despite these promising published results there has been a reluctance to refer patients for transplantation, given the perceived poor outcomes for this lymphoma patient subpopulation. We recognize that many patients are never referred to transplant centres and this current study also represents patients who were young or healthy enough to be considered for and actually received AHCT. It is valuable to consider the outcomes of potentially eligible patients that do not pursue transplant. A retrospective study from the International Primary CNS Lymphoma Collaborative Group of 113 patients with isolated brain parenchymal relapse of NHL, suggested that the best outcomes were found in patients aged <60 years and who were treated with high-dose systemic methotrexate (Doolittle *et al*, 2008). Only ten patients in that cohort underwent AHCT and in this cohort treated primarily with chemotherapy and/ or radiotherapy, the median OS from date of CNS relapse was only 1.6 years. Another study from the same study group analysed 92 patients with secondary CNS lymphoma and reported a median OS of 7 months (Bromberg et al 2013). Only 29% of patients with CNS relapses underwent AHCT although patients were seen at transplant centres. For those who received AHCT, 2-year survival was 54% (vs. 17% in those treated with non-transplant therapy).

Our study is the largest analysis of outcomes after AHCT for patients with NHL and prior CNS lymphoma. We found no significant difference in NRM, progression/relapse, PFS or OS compared to patients with NHL, but without prior CNS lymphoma. A sub-analysis comparing those with CNS disease to a similar matched high risk NHL cohort without CNS involvement also showed no differences in these outcomes. Interestingly, the vast majority of the patients relapsed outside of the CNS, suggesting that the overall therapy for the CNS sanctuary site was adequate. Historically, total body irradiation (TBI) was thought to be a critical element of the conditioning for its CNS penetration, but this cohort (only 23% receiving TBI conditioning) do not substantiate this need. Overall, these data indicate that a history of pre-existing CNS involvement by NHL, by itself, should not exclude patients from AHCT. However, patients within the CNS⁺ cohort who had active disease at the time of AHCT had much worse outcomes. Achieving disease remission in the CNS compartment prior to transplantation is crucial to optimize the chance of long-term survival.

Our analysis was retrospective, with data collected from over 400 transplant programmes. Insufficient data were available from individual transplant centres regarding the utilization of post-transplantation adjuvant intrathecal or radiation therapy. Similarly, the outcomes of CNS⁺ patients who were unable to receive AHCT is beyond the scope of this analysis. Jahnke et al (2006) analysed their institutional experience of patients with systemic lymphoma involving the CNS at time of diagnosis or at relapse. Between 1982–2004, 43 patients were identified of which the vast majority were diagnosed with secondary CNS involvement at relapse. The median survival was 5 months and only 26 patients had significant response to treatment. Only three proceeded to autologous transplantation of which two patients were reported with long-term survival (Jahnke *et al*, 2006). Similarly, although only 29% of patients in the series reported by Bromberg et al (2013) were able to receive AHCT, there was a survival benefit for transplant recipients (estimated 3-year OS of 42%).

This study was also limited to adult patients, recognizing that lymphoblastic lymphoma and Burkitt lymphoma are far more common in the paediatric population. Despite this observation, approximately 25% of the study group included patients with these diagnoses of very aggressive lymphomas, recognizing that their behaviours and their treatments may vary from the indolent and less aggressive lymphomas that make up the bulk of the population. We would hope that these data would contribute to focus efforts in future large, randomized prospective lymphoma trials to collect additional data that would further enhance our understanding of these high-risk patients.

In summary, our data indicate that prior CNS involvement, by itself, should not preclude AHCT for otherwise eligible transplant candidates. Rather, aggressive pretransplant CNS disease management should be the therapeutic goal prior to AHCT as remission within the CNS was most predictive of PFS. These observations may also prove to be beneficial to in the setting of primary CNS lymphoma (Ferreri, 2011; Deckert *et al*, 2011), recognizing that AHCT is currently being evaluated as part of treatment schedules for early as well as late primary CNS lymphoma. A collaborative analysis of AHCT for this entity has been established between the EBMT and CIBMTR and is forthcoming.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Univariate analysis: Pre-transplant CNS Status Impacts Outcomes 3 Years Post AHCT

Figure 1.

Cumulative incidence of relapse, progression-free survival and overall survival comparing patients with active CNS disease at time of transplantation (dashed line) with patients with CNS remission status at AHCT (solid line).

REL, relapse; PFS, progression-free survival; OS, overall survival; AHCT, autologous haematopoietic stem cell transplantation; CNS, central nervous system; CI, cumulative incidence; Prob, probability.

Outcomes of Auto-HSCT for NHL with Pre-existing CNS Cases vs Matched Non-CNS Involvement Controls

Figure 2.

Comparison of patients from the CNS⁺ cohort (selected by disease histology) with a matched control group with no CNS involvement prior to AHCT. Cumulative incidence of relapse and non-relapse mortality, and Kaplan-Meier probabilities for PFS and OS shown. TRM, treatment-related mortality; REL, relapse, PFS, progression-free survival; OS, overall survival; AHCT, autologous haematopoietic stem cell transplantation; CNS, central nervous system; CNS⁺, prior central nervous system lymphoma; CI, cumulative incidence; Prob, probability.

Table 1
Comparison of Adult AHCT recipients for NHL with no CNS involvement vs. pre-existing CNS involvement

Variable	CNS ⁻		CNS ⁺		P-value
	N eval	N (%)	N eval	N (%)	
Patient related					
Number of patients		4688		151	
Age, median (range), years	4688	51 (18–82)	151	46 (18–72)	<0.001
Male sex	4688	2835 (60)	151	96 (64)	0.44
Karnofsky score pre-transplant	4541		142		<0.001
<80		320 (7)		27 (19)	
80–90		1133 (25)		35 (25)	
90–100		3088 (68)		80 (56)	
Disease related					
Second line age-adjusted International Prognostic Index (IPI) at transplant	3384		104		0.005
Low		1329 (39)		36 (35)	
Low-Intermediate		1407 (42)		38 (37)	
High-Intermediate		580 (17)		23 (22)	
High		68 (2)		7 (7)	
LDH>upper limit of normal at diagnosis	1922	1002 (52)	66	46 (70)	0.005
Disease stage at diagnosis	4688		151		<0.001
I		468 (10)		13 (9)	
II		889 (19)		14 (9)	
III		1115 (24)		14 (9)	
IV		2216 (47)		110 (73)	
Histological diagnosis	4688		151		<0.001
Follicular lymphoma		1301 (28)		22 (15)	
DLBCL		2413 (51)		83 (55)	
Lymphoblastic/Burkitt/Burkitt-like		189 (4)		39 (26)	
Mantle cell lymphoma		423 (9)		3 (2)	
Other		362 (8)		4 (3)	
Immunophenotype for NHL patients	4688		151		0.16

Variable	CNS ⁻		CNS ⁺		P-value
	N eval	N (%)	N eval	N (%)	
B-cell		4464 (95)		140 (93)	
T-cell		224 (5)		11 (7)	
B Symptoms at diagnosis	4389	1729 (39)	142	56 (39)	0.99
Non-CNS extranodal disease		3092 (66)		130 (86)	<0.001
HIV Positive		12 (<1)		2 (1)	0.02
Number of prior lines of therapy	4664		151		0.70
1		803 (17)		26 (17)	
2–3		2935 (63)		90 (60)	
4		918 (20)		35 (23)	
Unknown		8 (<1)		0	
CNS irradiation as part of therapy			151		
None				104 (69)	
Cranial-spinal				4 (3)	
Brain				23 (15)	
Spine				20 (13)	
Disease status at transplant	4670		151		0.84
Chemotherapy sensitive		3587 (77)		119 (79)	
Chemotherapy Resistant		454 (10)		13 (9)	
Unknown sensitivity PIF/Relapse		649 (13)		19 (13)	
Interval from diagnosis to transplant, median (range), months	4685	15 (1–389)	151	12 (3–137)	0.002
Interval from most recent relapse to transplant, median (range), months	3166	4(<1–89)	101	3 (<1–71)	0.10
Conditioning regimen	4688		151		0.20
TBI-based		1171 (25)		35 (23)	
BEAM and similar		2464 (53)		70 (46)	
CBV or similar		429 (9)		20 (13)	
BuMEL/BuCy		323 (7)		15 (10)	
Others ^e		301 (6)		11 (7)	
Radiation in conditioning regimen	4679	1225 (26)	151	43 (28)	0.65
Rituxan in conditioning regimen	4688	96 (2)	151	1 (1)	0.23
Planned radiation therapy post-transplant	4658	501 (11)	150	21 (14)	0.21

Variable	CNS ⁻			CNS ⁺		
	N eval	N (%)	N eval	N (%)	P-value	
Planned chemo therapy post-transplant	4658	168 (4)	150	12 (8)	0.005	
Site of post-transplant relapse	3153		90		<0.001	
No relapse		2065 (65)		57 (63)		
Relapsed at CNS		5 (<1)		1 (1)		
Relapsed at non-CNS site		1020 (32)		25 (28)		
CNS and Other sites		63 (2)		7 (8)		
Karnofsky score at last contact	3624		106		0.78	
<80		431 (12)		15 (14)		
80–90		751 (21)		21 (20)		
90–100		2442 (67)		70 (66)		
Median follow-up of survivors, months	2303	73 (<1–200)	64	77 (1–174)		

AHCT, autologous haematopoietic stem cell transplantation; CNS⁻, without prior central nervous system lymphoma; CNS⁺, prior central nervous system lymphoma; N eval, number evaluable; LDH, lactate dehydrogenase; DLBCL, diffuse large B cell lymphoma; NHL, non-Hodgkin lymphoma; HIV, human immunodeficiency virus; TBI, total body irradiation; BEAM, carmustine, etoposide, cytarabine, melphalan; CBV, cyclophosphamide, carmustine, etoposide; BuMeL, busulfan and melphalan; BuCy, busulfan and cyclophosphamide.

Table II

Outcomes of Adult AHCT recipients for NHL with no CNS involvement vs. pre-existing CNS involvement

Outcome	CNS ⁻		CNS ⁺		P-value
	N Eval	Probability (95% CI)	N Eval	Probability (95% CI)	
Relapse	4618		150		0.075
100-day	3513	20 (18–21)	106	24 (18–31)	
1 years	2407	39 (37–40)	68	48 (40–56)	
3 years	1483	52 (51–54)	46	57 (49–65)	
5 years	986	57 (55–58)	31	61 (53–69)	
Non-relapse mortality	4618		150		0.756
100-day	3513	4 (3–4)	106	5 (2–9)	
1 years	2407	5 (5–6)	68	5 (2–10)	
3 years	1483	7 (6–8)	46	7 (3–11)	
5 years	986	8 (8–9)	31	9 (5–14)	
Disease-free survival	4618		150		0.127
100-day	3513	77 (76–78)	106	71 (64–78)	
1 years	2407	56 (54–57)	68	47 (39–55)	
3 years	1483	41 (39–42)	46	36 (28–44)	
5 years	986	35 (33–36)	31	30 (23–38)	
Overall survival	4688		151		0.079
100-day	4167	90 (89–91)	126	85 (78–90)	
1 years	3111	71 (70–73)	92	64 (56–72)	
3 years	2074	57 (56–59)	59	48 (40–56)	
5 years	1396	49 (48–51)	43	42 (34–51)	

AHCT, autologous haematopoietic stem cell transplantation; CNS⁻, without prior central nervous system lymphoma; CNS⁺, prior central nervous system lymphoma; N eval, number evaluable; 95% CI, 95% confidence interval.

Table III
Outcomes of patients with pre-existing CNS involvement, by CNS disease status at AHCT

Outcome	CNS remission at AHCT		Active CNS disease at AHCT		P-value
	N Eval	Probability (95% CI)	N Eval	Probability (95% CI)	
Relapse	95		55		<0.001
100-day	74	19 (12–27)	32	33 (21–46)	
1 years	53	39 (30–49)	15	63 (49–75)	
3 years	36	49 (38–59)	10	72 (59–83)	
Non-relapse mortality	95		55		0.099
100-day	74	2 (0–6)	32	9 (3–18)	
1 years	53	3 (1–8)	15	9 (3–18)	
3 years	36	5 (2–11)	10	9 (3–18)	
Disease-free survival	95		55		<0.001
100-day	74	79 (70–86)	32	58 (45–71)	
1 years	53	57 (47–67)	15	28 (17–41)	
3 years	36	46 (36–56)	10	19 (10–30)	
Overall survival	96		55		<0.001
100-day	83	88 (81–94)	43	78 (66–88)	
1 years	66	73 (64–82)	26	49 (35–62)	
3 years	45	58 (47–68)	14	31 (19–44)	

AHCT, autologous haematopoietic stem cell transplantation; CNS, central nervous system; N eval, number evaluable; 95% CI, 95% confidence interval.