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Impact of Conditioning Regimen on Outcomes for Patients with Lymphoma Undergoing High-Dose Therapy with Autologous Hematopoietic Cell Transplantation

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Abstract

There are limited data to guide the choice of high-dose therapy (HDT) regimen prior to autologous hematopoietic cell transplantation (AHCT) for patients with Hodgkin (HL) and non-Hodgkin lymphoma (NHL). We studied 4,917 patients (NHL n=3,905; HL n=1,012) who underwent AHCT from 1995-2008 using the most common HDT platforms: BEAM (n=1730), CBV (n=1853), BuCy (n=789), and TBI-containing (n=545). CBV was divided into CBV^{high} and CBV^{low} based on BCNU dose. We analyzed the impact of regimen on development of idiopathic pulmonary syndrome (IPS), transplant-related mortality (TRM), progression free and overall survival (PFS and OS). The 1-year incidence of IPS was 3-6% and was highest in recipients of CBV^{high} (HR 1.9) and TBI (HR 2.0) compared to BEAM. 1-year TRM was 4-8% and was similar between regimens. Among patients with NHL, there was a significant interaction between histology, HDT regimen, and outcome. Compared to BEAM, CBV^{low} (HR 0.63) was associated with lower mortality in follicular lymphoma ($p<0.001$), and CBV^{high} (HR1.44) with higher mortality in diffuse large B-cell lymphoma ($p=0.001$). For patients with HL, CBV^{high} (HR1.54), CBV^{low} (HR1.53), BuCy (HR1.77) and TBI (HR 3.39) were associated with higher mortality compared to BEAM ($p<0.001$). The impact of specific AHCT regimen on post transplant survival is different depending on histology; therefore, further studies are required to define the best regimen for specific diseases.

Keywords

autologous transplant; lymphoma; idiopathic pneumonia syndrome

Introduction

High-dose therapy (HDT) with autologous hematopoietic cell transplantation (AHCT) has been a standard component of therapy for patients with Hodgkin[1] and non-Hodgkin lymphoma[2,3] for decades. The therapeutic rationale of HDT with AHCT relies on enhanced cytotoxicity through the delivery of myeloablative doses of chemotherapy or total body irradiation. The choice of HDT regimen has traditionally been based on institutional experience, and several regimens are considered standard and routinely used for patients with all histologies of lymphoma.[4]

Each HDT regimen is associated with its own unique toxicities, based on the individual agents or modalities used. One example is idiopathic pneumonia syndrome (IPS), which encompasses non-infectious pneumonitides caused by high dose alkylating chemotherapy (e.g., BCNU) or total body irradiation (TBI) and is the major pulmonary toxicity after HDT.[5] As prompt initiation of corticosteroids can often result in clinical improvement, early recognition of IPS is important, and the published risk factors for IPS after AHCT are variable.[6-12]

A large study of lymphoma patients undergoing AHCT in the modern era has not been performed to define the impact of conditioning regimens on overall outcomes, or to describe the incidence and risk factors for developing IPS and its impact on outcomes. To this end,

we undertook a large retrospective registry study to analyze the impact of several commonly used HDT regimens on clinical outcomes.

Methods

Data Source

The CIBMTR includes a voluntary working group of more than 450 transplantation centers worldwide that contribute detailed data on consecutive allogeneic and autologous hematopoietic cell transplantations to a statistical center at the Medical College of Wisconsin in Milwaukee and the National Marrow Donor Program (NMDP) Coordinating Center in Minneapolis. Participating centers are required to report all transplants consecutively; patients are followed longitudinally and compliance is monitored by on-site audits. Computerized checks for discrepancies, physicians' review of submitted data and on-site audits of participating centers ensure data quality. 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 HIPAA Privacy Rule.[13]

Patient Selection

All adult patients (≥18 years) reported to the CIBMTR who received AHCT using marrow or peripheral blood stem cells (PBSC) for NHL or HL between 1995 and 2008 were included in this analysis. Patients were excluded for: no post-transplant follow up information (n=138), BCNU given in a regimen other than BEAM (BCNU, etoposide, cytarabine, melphalan) [14] or CBV (cyclophosphamide, BCNU, etoposide [VP-16]) [15] (n=145), or date of development of IPS was prior to the transplant (n=23). Among recipients of BEAM, cases were excluded if the BCNU dose per body surface area was less than 10^{th} percentile (n=228), greater than the 90^{th} percentile (n=4) or if the dose was missing (n=166). Among recipients of CBV, patients were excluded if the BCNU dose per body surface area was less than 10^{th} percentile (n=137) or if the dose was missing (n=241). Among patients who received non-BCNU regimens, only patients who received BuCy (busulfan, cyclophosphamide[16] and TBI (total body irradiation) [17] were included to the final dataset. A total of 4,917 patients were identified from 204 centers. In order to address the impact of BCNU dose on outcomes, the total dose administered of BCNU was divided by the calculated body surface area from height and weight data reported to the CIBMTR. According to patterns of practice, the dose distribution of BCNU varied widely among recipients of CBV, clustering approximately around 300 mg/m^2 (median 296 mg/m^2, range 225-374 mg/m^2)and at 450mg/m^2(median 453 mg/m^2, range 376-807 mg/m^2), which were then separated into CBV^{low} and CBV^{high}, respectively. Among recipients of BEAM, the BCNU dose distribution was approximately around 300mg/m^2 (median 293 mg/m^2, range 227-347 mg/m^2).

Study Endpoints

The primary endpoint of this analysis was overall survival (OS) among the different conditioning regimens. Secondary endpoints included IPS, transplant-related mortality

(TRM), relapse or progression, and progression-free survival (PFS). TRM was defined as any death without recurrent lymphoma. Relapse or progression was defined as evidence of disease recurrence censored at the date of last contact and using death in remission as the competing hazard. PFS was defined as survival without death or relapse censored at the date of last contact.

Statistical Analysis

Patient-, disease- and transplant-related characteristics were described according to each conditioning regimen and compared using chi-square tests or Kruskal-Wallis tests as appropriate. The cumulative incidence function was used for calculating IPS, TRM, relapse or progression outcomes accounting for competing risks. OS and PFS were analyzed by the Kaplan-Meier method. Multivariable analysis for each outcome was performed using a Cox proportional hazards model. The effect of development of IPS on subsequent TRM, treatment failure (relapse progression or death) and overall mortality was performed by fitting a Cox model with a time-dependent effect for prior development of IPS. Preparative regimens were included in all models as the main effect. The proportional hazards assumption was checked using graphical approaches or time-dependent covariates. Stepwise model building was used to identify additional predictors besides preparative regimen, from among the following candidate variables included: age (18-39, 40-49, 50-59, ≥60), gender, body mass index (<18.5, 18.5-25, 25-30, > 30, unknown), Karnofsky performance status (<90, 90-100, unknown), disease status at AutoHCT, number of prior chemotherapy regimens received, year of AutoHCT (1995-1999, 2000-2004, 2005-2008), history of smoking, time from diagnosis to AutoHCT, prior use of rituximab in NHL patients and graft type (bone marrow vs. peripheral blood stem cells). Interactions between preparative regimen and other baseline characteristics were checked. Disease was tested in two ways, first separating on Hodgkin lymphoma (HL) and Non-Hodgkin lymphoma (NHL), and second separating NHL according to histologies. Both ways demonstrated a significant interaction between disease and conditioning on several outcomes. Details of the final model are shown for the four largest disease groupings: HL, follicular lymphoma (FL), diffuse large B-cell lymphoma (DLBCL) and mantle cell lymphoma (MCL). Considering multiple comparisons across conditioning regimens, only p-values≤0.01 were considered significant.

Results

Clinical Characteristics

Patient characteristics for each regimen are summarized in Table 1. The cohorts differed in age, distribution of disease, year of AHCT, Karnofsky performance score (KPS), prior chemotherapy, time from diagnosis to AHCT and prior use of rituximab in NHL patients. Recipients of AHCT with BEAM were older: age ≥ 54 years (BEAM 53%, CBV^{low} 38%, CBV^{high} 34%, BuCy 50% and TBI 40%, p<0.001). A lower proportion of BEAM and TBI patients had Hodgkin lymphoma: (BEAM 18%, CBV^{low} 23%, CBV^{high} 37%, BuCy 21% and TBI 4%, p<0.001). BEAM was used more frequently in later years of the study period: year of AHCT 2002 or later: (BEAM 70%, CBV^{low} 18%, CBV^{high} 26%, BuCy 49% and TBI 19%, p<0.001). For patients with NHL, prior rituximab use was different: (BEAM 67%, CBV^{low} 18%, CBV^{high} 29%, BuCy 43% and TBI 21%, p<0.001). Among patients with

available age adjusted IPI, the proportion of patients with low and low-intermediate IPI was in the range of 82% to 88% across the conditioning groups. The cohorts were similar in terms of gender and median follow-up for survivors.

Idiopathic Pneumonia Syndrome

The incidence of IPS by 1 year after AHCT was: BEAM (3% [2-4%]), CBV^{low} (3% [2-4%]), CBV^{high} (6% [4-8%]), BuCy (4% [2-5%]), and TBI (5% [3-7%]). Multivariate analysis showed that in comparison to BEAM, the risk of IPS for each regimen was: CBV^{low} (HR 1.07 [0.72-1.60], p=0.742), CBV^{high} (HR 1.88 [1.24-2.83], p=0.003), BuCy (HR 1.25 [0.82-1.92], p=0.30), and TBI (HR 2.03 [1.30-3.19], p=0.002) (Table 2). Additional risk factors associated with the development of IPS: 1) diagnosis of Hodgkin lymphoma (HR 2.33, [1.68-3.24], $p < 0.001$), 2) female gender (HR 1.39 [1.05-1.82], p=0.019), 3) chemotherapy-resistant disease at time of AHCT (HR 1.9 [1.29-2.79], p=0.001), and 4) age ≥ 55 (HR 1.54, [1.13-2.09], p=0.006). In the entire cohort, patients who developed IPS had a significantly higher rate of TRM (HR 4.02, [3.09-5.24], $p < 0.001$), shorter PFS (HR 1.85, [1.53-2.24], $p < 0.001$), and shorter OS (HR 2.50, [2.10-2.99], $p < 0.001$).

Transplant Related Mortality

There was no difference in TRM for patients with HL compared to those with NHL, and thus, the groups were combined for analysis. The incidence of TRM at 1 year for each cohort was as follows: BEAM (4% [3-5%]), CBV^{low} (7% [5-8%]), CBV^{high} (8% [6-11%]), BuCy (7% [6-9%]), and TBI (8% [6-10%]) and was not significantly different after multivariate analysis. While choice of high-dose regimen had no effect on TRM, the following factors were associated with increased TRM: older age, male gender, KPS < 90, chemo-resistant disease, higher number of previously received chemotherapy regimens, earlier year of AHCT, history of smoking, and use of bone marrow as source of progenitor cells (data not shown).

Relapse / Progression

The cumulative incidences of disease progression or relapse varied according to histologies and are shown in Table 3. Multivariate analysis of disease progression or relapse (Table 4) demonstrated that the effect of conditioning on outcome was significant for patients with MCL and HL. Among patients with MCL, the HR for disease progression or relapse for CBV^{low} was 0.55 (95% CI 0.34-0.88, p=0.014) compared to BEAM. Conversely, when testing all possible comparisons, the HR for CBV^{high} and TBI were 2.28 (95% CI, 1.29-4.04, $p<0.005$) and 2.28 (95% CI. 1.38-3.76, p=0.001) compared to CBV^{low}, respectively (Table 4). For patients with Hodgkin lymphoma, BuCy (HR 1.52 [1.13-2.05] compared to BEAM, p=0.006) and CyTBI (HR 1.94, [1.09-3.45] compared to BEAM, p=0.024) were associated with higher rates of progression compared to BEAM, CBV^{low} and CBV^{high}. Multivariate analysis also showed the following factors to be associated with increased relapse or disease progression: older age, chemo-resistant disease, higher number of prior regimens of chemotherapy, and shorter time from diagnosis to AHCT (data not shown).

PFS and OS

For patients with non-Hodgkin lymphoma, probabilities of three-year PFS were: BEAM (51% [48-53%]), CBV^{low} (52% [49-55]), CBV^{high} (41% [36-46%]), BuCy (49% [45-53%]), and TBI (50% [45-54]). Table 3 shows three-year PFS and OS probabilities for the three most common NHL histologies: FL, FLBCL and MCL. Multivariate analysis for treatment failure (1-PFS) showed no specific impact of conditioning regimen on this outcome in FL, DLBCL or MCL. (Table 3). Probabilities of three-year OS were: BEAM (64% [61-66]), CBV^{low} (60% [57-64%]), CBV^{high} (52% [47-57]), BuCy (59% [55-63]), and TBI (59% [55-63%]). . Multivariate analysis for overall mortality (Table 4) demonstrated that among patients with FL, CBV^{low} resulted in better outcomes compared to BEAM (HR 0.63, [0.45-0.87], p=0.006) and to CBV^{high} (HR 0.50 [0.33-0.78], p=0.002). Among patients with with DLBCL, CBV^{high} resulted in worse outcomes compared to BEAM (HR 1.44 [1.16-1.77], p=0.001) and CBV^{low} (HR 1.38 [1.11-1.70], p=0.003). All conditioning regimens resulted in similar overall survival among patients with MCL. Figure 1A-C shows overall survival for each NHL histology.

For patients with Hodgkin lymphoma, probabilities of three-year PFS were: BEAM (62% [56-67%]), CBV^{low} (60% [54-66%]), CBV^{high} (57% [50-64%]), BuCy (51% [43-59%]), and TBI (43% [24-63]). Multivariate analysis demonstrated that BuCy (HR 1.51 [1.15, 1.97], p=0.003) and TBI (HR 2.01, [1.21, 3.34], p=0.007) had worse PFS compared to BEAM (Table 4). Probabilities of three-year OS were: BEAM (79% [74-83]), CBV^{low} (73% [68-79]), CBV^{high} (68% [61-74]), BuCy (65% [58-73]), and TBI (47% [27-68%]) (Figure 1D). Multivariate analysis revealed that patients with HL receiving BEAM had superior overall survival compared to all other regimens (Table 4). Factors associated with inferior OS for all patients included older age, male gender, BMI < 18.5, KPS < 90, chemo-resistant disease, higher number of previous regimens of chemotherapy received, shorter time from diagnosis to AHCT, and use of bone marrow (data not shown).

Discussion

In this large retrospective registry study of patients with NHL and HL, we analyzed the impact of several commonly used high-dose therapy regimens (BEAM, CBV^{low}, CBV^{high}, BuCy and TBI) for AHCT on outcomes including IPS, TRM, relapse or progression, PFS, and OS. The results demonstrated clear differential outcomes according to the conditioning regimen utilized with NHL or HL. For all patients, the development of IPS significantly increases the risk of death after AHCT and the incidence of IPS was higher in patients receiving higher doses of BCNU and TBI-based regimens. For patients with NHL, the outcomes further differed by specific disease histologies, with CBV^{low} associated with better survival for FL, CBV^{high} being worse for DLBCL and no difference in survival according to the conditioning regimens studied among patients with MCL. Among patients with HL, BEAM was associated with better survival compared to all other regimens.

In this analysis, the development of IPS was most common after CBV^{high} (6%) or TBI-based (5%) regimens, and patients who developed IPS had much worse PFS and OS. The most recently published series investigating pulmonary toxicity following AHCT was a retrospective study on 222 patients with lymphoma receiving a CBV^{high} regimen at

Massachusetts General Hospital and Dana-Farber Cancer Institute. Clinical factors associated with pneumonitis included prior mediastinal radiation, total BCNU dose ≥ 1000 mg, and age < 54 years. Importantly, 3 of the 4 cases of TRM in their cohort were due to pneumonitis.[12] While the dose of BCNU was found to be a risk factor for IPS in the current study, mediastinal radiation could not be validated as this data was not comprehensively available. However, the fact that HL was associated with the diagnosis of IPS suggests that the treatment of HL, which commonly includes radiation, could be contributing to the increased risk. The association of older age (rather than younger) with an increased risk of pneumonitis may reflect patients with pre-existing pulmonary disease, however, routine pulmonary function data was also not available.

While the choice of specific HDT regimen did not influence the risk of TRM when adjusted for all clinical variables, several characteristics were associated with an increased risk of TRM, including older age, male gender, KPS < 90%, chemo-resistant disease, higher number of previously received chemotherapy regimens, earlier year of AHCT, history of smoking, and use of bone marrow. Most of these variables reflect patient co-morbidities or significant changes in supportive care and patient selection over time, and have previously been shown to be associated with TRM after AHCT.

Interestingly, the impact of HDT regimen on the risk of disease relapse or progression differed in NHL vs. HL. For example, patients with MCL who received CBV^{low} or TBI experienced lower rates disease progression. For patients with HL, those who received either BuCy or TBI-based regimens had a significantly increased risk of relapse compared to patients who received BEAM or either CBV regimen. Of greater interest, these effects translated into better overall survival outcomes in some subsets. For example, in FL the use of CBV^{low} was associated with better survival, but there was no effect on disease progression or TRM. One explanation is that there are few TRM events after AHCT which makes it challenging to observe differences within each disease histology. Progression after AHCT is a much more common event, and therefore if a conditioning regimen results in inferior disease control *and* is associated with higher toxicity this may translate into higher overall mortality.

These findings are noteworthy given that many practitioners are of the opinion that all standard HDT regimens yield similar outcomes across all lymphoma types as long as myeloablative doses are employed. This belief is supported by many single-arm series and the study by Vose et al from the Blood and Marrow Transplant Clinical Trials Network (BMT CTN) [18] describing outcomes of different regimens, all of which show comparable results but are impossible to directly compare to one another. Appropriately, in recent years, most centers have moved away from using TBI-based regimens given the long-term sequelae of TBI,[19-21] particularly the increased risk for secondary malignancies.[22] Moreover, retrospective studies have suggested improved efficacy with chemotherapy-alone regimens compared to those which are TBI-based.[23-25]

Recent studies support our finding of the superiority of BEAM for HL. The Nebraska Lymphoma Study Group performed a retrospective analysis on 225 patients with HL who received AHCT between 1984 and 2007. Importantly, they only included patients who were

alive after 2 years, and compared outcomes of BEAM vs. CBV. At 10 years, PFS was 79% for BEAM and 59% for CBV (p=0.01) and OS was 84% for BEAM vs. 66% for CBV (p=0.02).[26] More recently, investigators used a matched control analysis to compare outcomes of a cohort of 184 lymphoma patients enrolled on a multi-center phase II study of AHCT following BuCyE (intravenous Bu, cyclophosphamide, etoposide) to controls who received BEAM from the CIBMTR database. Toxicity and TRM appeared to be comparable between the groups. Outcomes for patients with NHL were equivalent between BuCyE and BEAM, however, for patients with HL, patients receiving BuCyE had a significantly higher rate of progression and much shorter PFS.[27] Recently, investigators have incorporated newer agents into traditional high-dose regimens. Visani et al. conducted a phase I/II study on 43 patients using BeEAM (bendamustine, etoposide, cytarabine, melphalan) conditioning for AHCT for relapsed / refractory lymphoma and showed an impressive CR rate of 81% at a median follow-up of 18 months.[28] Vose et al. have conducted several trials combining 131-Iodine tositumomab with BEAM for AHCT, but no clear advantage was observed in the phase III trial.[18,29,30] Other trials have studied Gem-Bu-Mel (gemcitabine, busulfan and melphalan)[31], Bu-Mel-TT (busulfan, melphalan and thiotepa)[32], and the additions of (90)Y-ibritumomab tiuxetan[33] or Bortezomib,[34] respectively, to BEAM conditioning. Clearly, prospective randomized trials will determine if incorporation of these newer agents into HDT regimens has significant value, but based on our results,the selection of the control needs to take into account the differences in outcomes based on histologies..

The limitations of our analysis are those inherent to any large registry study. For example, the patients who received BEAM were predominantly treated in a more recent era, and thus, any improvements observed could have been partly due to improved supportive care, patient selection, or salvage therapy. These variables may not be well adjusted for in our multivariate model, although year of transplant and source of stem cells were included and were not significantly associated with outcomes. In addition, the regimens were given heterogeneously, according to individual center standards, which includes the order and rate of chemotherapy administration, use of systemic corticosteroids as anti-emetics, and institution specific supportive care, all of which could influence toxicities such as the development of IPS. The method by which the diagnosis of IPS was made was based on the individual center's definition of IPS and the lack of pulmonary infection. Given the large number of patients treated at many centers over many years, individual cases could not be validated centrally. Furthermore, we were unable to analyze if pre-existing pulmonary dysfunction (as defined by standard pulmonary function tests) influenced the development of IPS given the incompleteness of available data. The study compare the most common high dose regimens used in lymphoma, however, in some subgroups, for example recipients of TBI for HL the numbers are too small. This needs to take into consideration when interpreting the results.

In summary, we have conducted the largest study to date on lymphoma patients undergoing AHCT, comparing outcomes of five commonly used HDT regimens. In this large cohort, IPS was a significant complication of all regimens, but more commonly observed after CBV^{high} or TBI-based regimens. The development of IPS had a profoundly negative effect on overall survival. In terms of overall survival, patients with FL appeared to do best with CBV^{low}, while patients with HL appeared to do best with BEAM. Regimens with higher

doses with BCNU were associated with higher incidences of IPS, and in DLBCL resulted in higher mortality. In conclusion, there is variability in toxicity and disease outcomes among specific AHCT regimens. Further analyses in specific lymphoma subtypes are important to understand the best regimen that maximizes disease control with lower toxicities.

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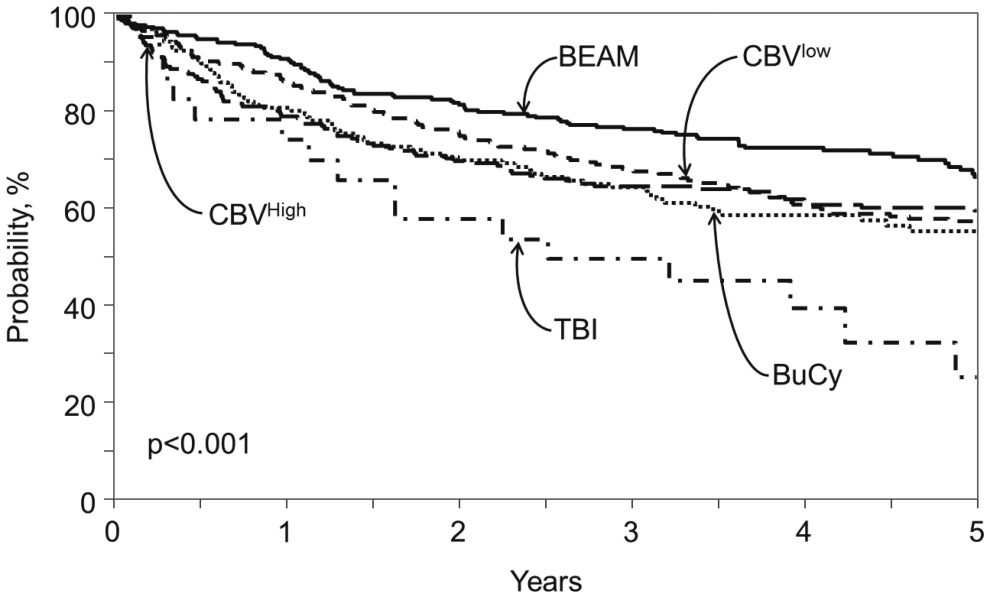
Key points

Different high-dose therapy regimens resulted in different outcomes based on Hodgkin vs. non-hodgkin lymphoma.

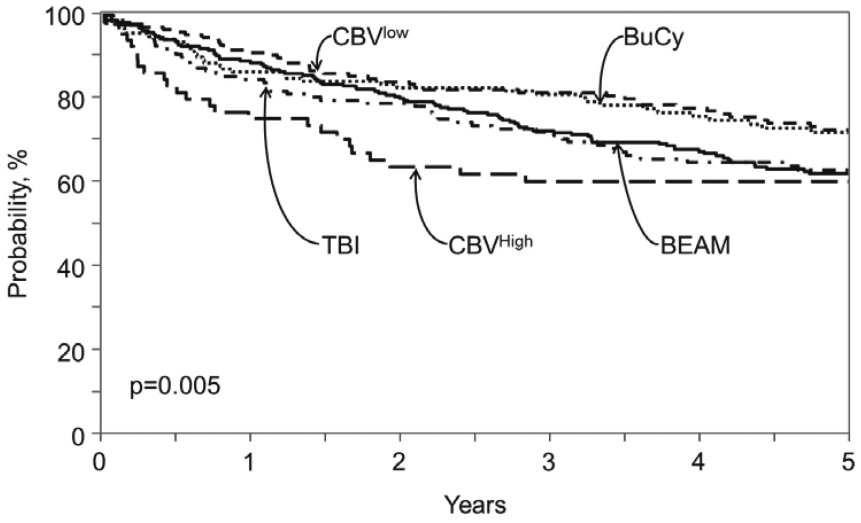
Compared to other high-dose therapy regimens, BEAM gives the best outcomes for patients with Hodgkin lymphoma.

Compared to BEAM, CBV^{low} results in better survival for patients with follicular lymphoma

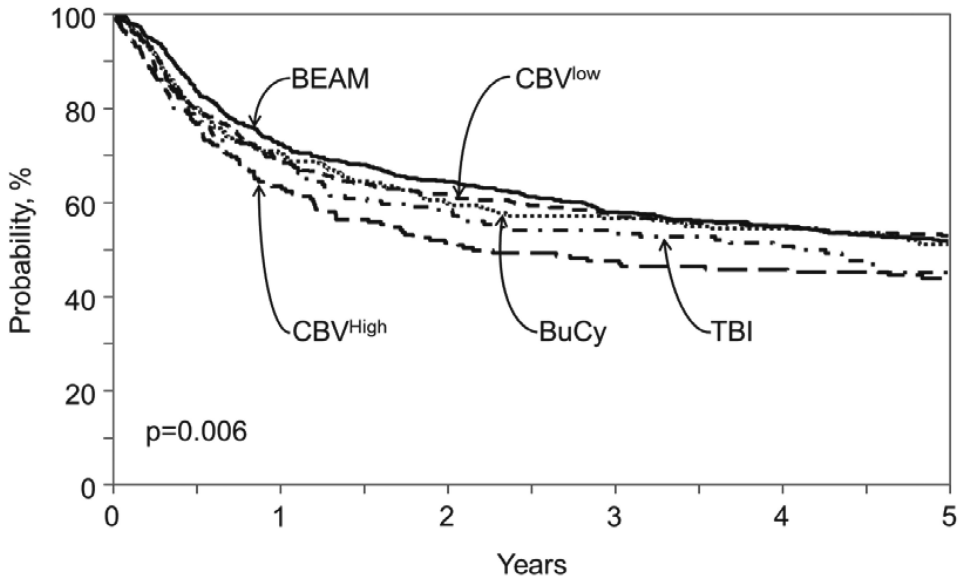
A) HL



B) FL



C) DLBCL



D) MCL

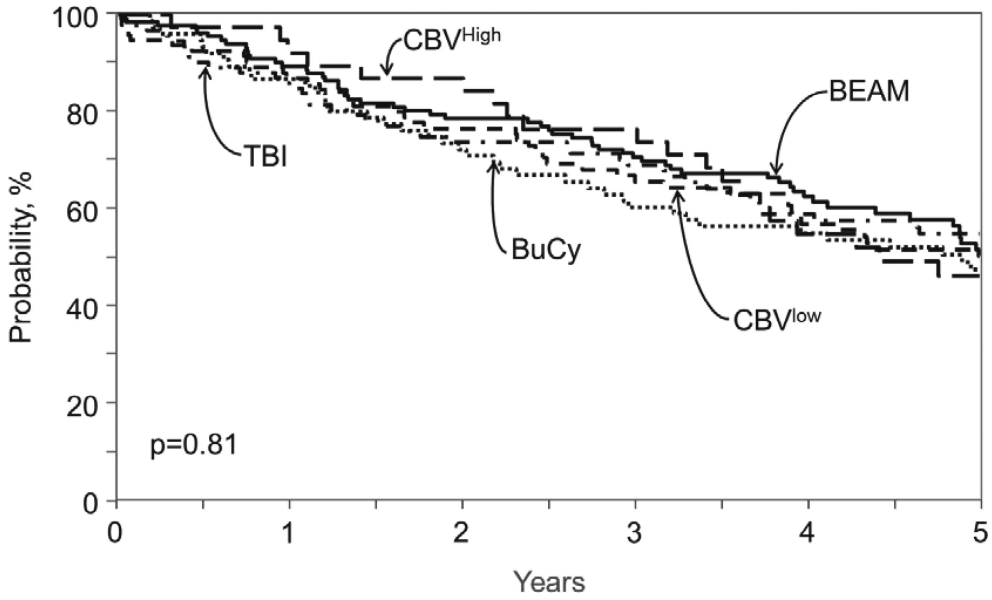


Figure 1.

Adjusted probability of overall survival after autologous hematopoietic cell transplant for (A) Hodgkin lymphoma, (B) follicular lymphoma, (C) diffuse large B-cell lymphoma and (D) mantle cell lymphoma according to conditioning regimen.

Table 1

Clinical characteristics of patients

Characteristic	BEAM	CBV^{low}	CBV^{high}	BuCy	TBI	p
Number of patients	1730	1249	604	789	545	--
Number of centers	126	106	92	54	68	--
Age						
Median (range)	55 (18-79)	49 (18-80)	46 (18-74)	54 (18-76)	51 (19-73)	<0.001
Age < 54, (%)	819 (47)	775 (62)	396 (66)	392 (50)	327 (60)	<0.001
Gender						0.57
Male (%)	1108 (64)	787 (63)	368 (61)	499 (63)	332 (60)	
Female (%)	622 (36)	462 (37)	236 (39)	290 (37)	213 (40)	
Karnofsky Score						<0.001
< 90 (%)	545 (32)	413 (33)	133 (22)	253 (32)	145 (27)	
90-100 (%)	1089 (63)	809 (65)	456 (75)	501 (63)	386 (71)	
Missing (%)	96 (6)	27 (2)	15 (2)	35 (4)	14 (3)	
Disease						<0.001
Hodgkin lymphoma	316 (18)	283 (23)	224 (37)	165 (21)	24 (4)	
Non-Hodgkin lymphoma	1414 (82)	966 (77)	380 (63)	624 (79)	521 (96)	
Follicular	254 (15)	171 (14)	60 (10)	126 (16)	152 (28)	
Diffuse large cell	735 (42)	472 (38)	190 (31)	279 (35)	161 (30)	
Lymphoblastic	64 (4)	34 (3)	18 (3)	26 (3)	24 (4)	
Burkitt's / Burkitt's like	19 (1)	29 (2)	13 (2)	9 (1)	14 (3)	
Mantle cell	162 (9)	96 (8)	47 (8)	77 (10)	91 (17)	
Other	180 (10)	164 (13)	52 (9)	107 (14)	79 (14)	
Disease status at AHCT						<0.001
PIF sensitive	304 (18)	218 (17)	109 (18)	142 (18)	90 (17)	
PIF resistant	58 (3)	45 (4)	30 (5)	36 (5)	28 (5)	
CR1	336 (19)	254 (20)	95 (16)	115 (15)	115 (21)	
REL sensitive	422 (24)	355 (28)	166 (27)	213 (27)	112 (21)	
REL resistant	104 (6)	70 (6)	45 (7)	49 (6)	35 (6)	
CR2+	430 (25)	217 (17)	104 (17)	149 (19)	70 (13)	
REL/PIF untreated/unknown	22 (1)	39 (3)	28 (5)	12 (2)	13 (2)	
Missing	54 (3)	51 (4)	27 (4)	73 (9)	82 (15)	
Age adjusted IPI score						<0.001
Low	415 (24)	398 (32)	147 (24)	172 (22)	159 (29)	
Low-Intermediate	386 (22)	328 (26)	171 (28)	195 (25)	150 (28)	
High-Intermediate	98 (6)	98 (8)	66 (11)	68 (9)	54 (10)	
High	12 (<1)	8 (<1)	1 (<1)	8 (1)	4 (<1)	
Undetermined	819 (47)	417 (33)	219 (36)	346 (44)	178 (33)	

Characteristic	BEAM	CBV^{low}	CBV^{high}	BuCy	TBI	p
Number of regimens of Chemotherapy received						<0.001
1-2	953 (55)	770 (62)	346 (57)	404 (51)	285 (52)	
≥ 3	769 (44)	469 (38)	250 (42)	379 (48)	251 (46)	
Use of rituximab in NHL						<0.001
Rituximab	949 (67)	177 (18)	110 (29)	266 (43)	109 (21)	
No rituximab	465 (33)	789 (82)	270 (71)	358 (57)	412 (79)	
Year of ASCT						<0.001
1995-1999	302 (17)	865 (69)	393 (65)	296 (37)	400 (74)	
2000-2004	446 (26)	288 (23)	104 (17)	218 (27)	74 (14)	
2005-2008	982 (57)	96 (7)	107 (17)	277 (35)	71 (13)	
Time from dx to AHCT, median (range), months	17 (2-383)	16 (3-259)	16 (3-362)	17 (3-282)	14 (3-272)	0.017
Graft type						<0.001
Bone marrow (%)	15 (<1)	84 (7)	36 (6)	48 (6)	79 (14)	
Peripheral blood (%)	1715 (99)	1165 (93)	568 (94)	741 (94)	466 (86)	
Dose of BCNU, median (range), mg/m^2	**293 (227 – 347)**	**296 (225 – 374)**	**453 (376 – 807)**	--	--	-
History of smoking						<0.001
Yes	764 (44)	491 (39)	257 (43)	347 (44)	242 (44)	
No	911 (53)	658 (53)	305 (50)	401 (51)	264 (48)	
Missing	55 (3)	100 (8)	42 (7)	41 (5)	39 (7)	
Median follow-up, median range), months	66 (1-193)	116 (1-217)	110 (1-216)	72 (1-194)	95 (3-206)	

Abbreviations: BEAM = BCNU, etoposide, cytarabine, melphalan; CBV = cyclophosphamide, BCNU, etoposide; BuCy = busulfan, cyclophosphamide; TBI = total body irradiation; AHCT = autologous hematopoietic cell; transplantation; PIF = primary induction failure; REL = relapsed; CR = complete remission; NHL = non-Hodgkin lymphoma

Table 2

Multivariate Analysis for IPS

Regimen	Reference	HR (95% CI)	p
CBV^{low}	BEAM	1.07 (0.72-1.6)	0.742
CBV^{high}	BEAM	1.88 (1.24-2.83)	0.003
BuCy	BEAM	1.25 (0.82-1.92)	0.299
TBI	BEAM	2.03 (1.30-3.19)	0.002
CBV^{high}	CBV^{low}	1.75 (1.14-2.70)	0.01
BuCy	CBV^{low}	1.17 (0.75-1.84)	0.489
TBI	CBV^{low}	1.90 (1.19-3.04)	0.008
BuCy	CBV^{high}	0.67 (0.42-1.06)	0.085
TBI	CBV^{high}	1.08 (0.67-1.76)	0.746
TBI	BuCy	1.62 (0.99-2.65)	0.055

Table 3

Univariate probabilities for treatment related mortality, disease progression or relapse, progression free survival and overall survival across different high dose regimens prior to autologous hematopoietic cell transplantation for Hodgkin lymphoma, follicular lymphoma, diffuse large B-cell lymphoma and mantle cell lymphoma.

Outcomes	BEAM (95% CI)	CBV^{low} (95% CI)	CBV^{high} (95% CI)	BuCy (95% CI)	TBI (95% CI)	P-values
Hodgkin Lymphoma						
Progression/Relapse						
Number of patients	313	279	219	162	23	
@ 3 years	32 (27-37)	32 (26-38)	30 (24-36)	41 (34-49)	57 (37-76)	0.026
Progression-free survival						
Number of patients	313	279	219	162	23	0.004
@ 3 years	62 (56-67)	60 (54-66)	57 (50-64)	51 (43-59)	43 (24-63)	0.110
Overall survival						
Number of patients	316	283	224	165	24	<0.001
@ 3 years	79 (74-83)	73 (68-79)	68 (61-74)	65 (58-73)	47 (27-68)	0.001
Follicular Lymphoma						
Progression/Relapse						
Number of patients	253	171	60	125	151	
@ 3 years	39 (33-46)	28 (21-35)	51 (38-63)	31 (23-39)	39 (31-47)	0.010
Progression free survival						
Number of patients	253	171	60	125	151	
@ 3 years	52 (45-58)	67 (59-74)	41 (28-54)	60 (52-69)	54 (45-62)	0.002
Overall survival						
Number of patients	254	171	60	126	152	
@ 3 years	73 (68-79)	81 (75-87)	55 (42-68)	79 (71-86)	71 (63-78)	0.004
Diffuse Large B-Cell Lymphoma						
Progression/Relapse						
Number of patients	731	465	187	273	156	
@ 3 years	44 (40-47)	40 (36-45)	47 (40-54)	41 (35-47)	42 (35-50)	0.599
Progression free survival						
Number of patients	731	465	187	273	156	
@ 3 years	47 (44-51)	47 (43-52)	39 (32-46)	45 (39-52)	42 (34-50)	0.273
Overall survival						
Number of patients	735	472	190	279	161	
@ 3 years	58 (55-62)	55 (50-59)	43 (36-51)	52 (46-58)	47 (40-55)	0.002
Mantle Cell Lymphoma						
Progression relapse						
Number of patients	162	96	47	77	90	

Outcomes	BEAM (95% CI)	CBV^{low} (95% CI)	CBV^{high} (95% CI)	BuCy (95% CI)	TBI (95% CI)	P-values
@ 3 years	27 (21-35)	22 (14-32)	44 (30-59)	44 (33-55)	24 (16-34)	0.006
Progression free survival						
Number of patients	162	96	47	77	90	0.611
@ 3 years	62 (54-70)	57 (47-68)	49 (35-64)	47 (36-58)	62 (51-72)	0.165
Overall survival						
Number of patients	162	96	47	77	91	0.127
@ 3 years	75 (68-82)	66 (56-76)	80 (68-90)	60 (49-71)	66 (56-76)	0.051

Table 4

Impact of high-dose therapy regimen on treatment related mortality, disease progression or relapse, treatment failure (death or disease progression) and overall mortality by each histology.

	Regimen	Disease Progression/Relapse (95% CI)	p	Treatment Failure HR (95% CI)	p	Overall Mortality HR (95% CI)	p
HL							
	BEAM	1.00	**0.008*1**	1.00	**<0.001*1**	1.00	**<0.001*1**
	CBV^{low}	1.12 (0.85-1.47)	0.41	1.27 (1.01-1.61)	0.04	1.53 (1.16-2.02)	0.003
	CBV^{high}	0.95 (0.71-1.28)	0.75	1.18 (0.92-1.51)	0.20	1.54 (1.15-2.05)	0.003
	BuCy	**1.52 (1.13-2.05)**	**0.006*1**	**1.51 (1.15-1.97)**	**0.003*1**	**1.77 (1.30-2.42)**	**<0.001*1**
	TBI	1.94 (1.09-3.46)	0.024	**2.01 (1.21-3.34)**	**0.007*1**	**3.38 (2.03-5.63)**	**<0.001*1**
	CBV^{high} vs. CBV^{low}	0.85 (0.63-1.15)	0.30	0.92 (0.73-1.18)	0.53	1.00 (0.77-1.30)	0.97
	BuCy vs CBV^{low}	1.35 (1.00-1.84)	0.05	1.19 (0.91-1.55)	0.21	1.16 (0.86-1.55)	0.32
	TBI vs. CBV^{low}	1.73 (0.97-3.09)	0.06	1.58 (0.95-2.62)	0.07	2.20 (1.34-3.63)	0.002*1*
	BuCy vs. CBV^{high}	**1.59 (1.15-2.21)**	**0.006*1**	1.28 (0.97-1.70)	0.08	1.16 (0.85-1.56)	0.35
	TBI vs. CBV^{high}	2.04 (1.13-3.69)	0.02	1.71 (1.03-2.86)	0.04	2.20 (1.33-3.64)	0.002*1*
	TBI vs. BuCy	1.28 (0.71-2.31)	0.42	1.33 (0.79-2.25)	0.28	1.91 (1.13-3.20)	0.015
FL							
	BEAM	1.00	0.105*	1.00	0.042*	1.00	**0.005*1**
	CBV^{low}	0.79 (0.58-1.08)	0.23	0.72 (0.55-0.94)	0.016	**0.63 (0.45-0.87)**	**0.006*1**
	CBV^{high}	1.34 (0.90-2.00)	0.12	1.16 (0.81-1.67)	0.42	1.24 (0.83-1.86)	0.30
	BuCy	0.82 (0.59-1.14)	0.35	0.77 (0.58-1.03)	0.08	0.69 (0.49-0.87)	0.035
	TBI	1.03 (0.76-1.41)	0.73	0.88 (0.66-1.16)	0.35	0.93 (0.68-1.28)	0.65
	CBV^{high} vs. CBV^{low}	1.70 (1.10-2.61)	0.02	1.62 (1.11-2.37)	0.01	**1.98 (1.28-3.06)**	**0.002*1**
	BuCy vs CBV^{low}	1.04 (0.72-1.50)	0.85	1.08 (0.79-1.48)	0.63	1.10 (0.74-1.62)	0.64
	TBI vs. CBV^{low}	1.31 (0.92-1.85)	0.16	1.22 (0.91-1.65)	0.19	1.48 (1.04-2.11)	0.03
	BuCy vs. CBV^{high}	0.61 (0.39-0.96)	0.04	0.67 (0.45-0.99)	0.05	**0.55 (0.35-0.97)**	**0.01*1**

	Regimen	Disease Progression/Relapse (95% CI)	p	Treatment Failure HR (95% CI)	p	Overall Mortality HR (95% CI)	p
	TBI vs. CBV^{high}	0.77 (0.50-1.19)	0.23	0.76 (0.51-1.11)	0.15	0.75 (0.49-1.15)	0.18
	TBI vs. BuCy	1.26 (0.87-1.83)	0.26	1.13 (0.82-1.56)	0.45	1.35 (0.93-1.97)	0.11
DLBCL							
	BEAM	1.00	0.30*	1.00	0.11*	1.00	**0.006*1**
	CBV^{low}	1.05 (0.89-1.25)	0.55	1.03 (0.88-1.21)	0.73	1.04 (0.88-1.24)	0.63
	CBV^{high}	1.25 (0.99-1.57)	0.06	1.26 (1.03-1.55)	0.02	**1.44 (1.16-1.77)**	**0.001**1
	BuCy	0.95 (0.77-1.17)	0.62	0.99 (0.83-1.19)	0.95	1.10 (0.91-1.33)	0.32
	TBI	1.09 (0.84-1.41)	0.52	1.19 (0.96-1.49)	0.12	1.29 (1.02-1.62)	0.03
	CBV^{high} vs. CBV^{low}	1.19 (0.93-1.51)	0.17	1.23 (1.00-1.51)	0.05	**1.38 (1.11-1.70)**	**0.003**1
	BuCy vs CBV^{low}	0.90 (0.72-1.13)	0.36	0.97 (0.80-1.17)	0.73	1.06 (0.86-1.29)	0.59
	TBI vs. CBV^{low}	1.03 (0.79-1.35)	0.81	1.16 (0.93-1.45)	0.19	1.23 (0.98-1.56)	0.07
	BuCy vs. CBV^{high}	0.76 (0.58-0.99)	0.04	0.79 (0.62-0.99)	0.04	0.77 (0.61-0.97)	0.03
	TBI vs. CBV^{high}	0.87 (0.64-1.19)	0.38	0.94 (0.73-1.22)	0.67	0.90 (0.69-1.17)	0.42
	TBI vs. BuCy	1.15 (0.85-1.54)	0.36	1.20 (0.94-1.54)	0.14	1.17 (0.91-1.50)	0.23
MCL							
	BEAM	1.00	**<0.001*1**	1.00	0.24*	1.00	0.81*
	CBV^{low}	**0.54 (0.34-0.84)**	**0.006**1	0.80 (0.58-1.12)	0.19	1.08 (0.74-1.56)	0.70
	CBV^{high}	1.16 (0.74-1.84)	0.51	0.94 (0.62-1.43)	0.78	0.98 (0.60-1.59)	0.94
	BuCy	1.14 (0.78-1.66)	0.50	1.02 (0.73-1.42)	0.90	1.23 (0.84-1.79)	0.29
	TBI	**0.52 (0.33-0.81)**	**0.004**1	0.71 (0.51-1.00)	0.05	0.99 (0.68-1.44)	0.95
	CBV^{high} vs. CBV^{low}	**2.17 (1.26-3.76)**	**0.005**1	1.17 (0.75-1.84)	0.48	0.91 (0.55-1.51)	0.72
	BuCy vs CBV^{low}	2.13 (1.31-3.44)	0.002[1]	1.27 (0.88-1.84)	0.20	1.14 (0.76-1.70)	0.52
	TBI vs. CBV^{low}	0.97 (0.57-1.65)	0.91	0.89 (0.62-1.27)	0.51	0.92 (0.62-1.35)	0.57
	BuCy vs. CBV^{high}	0.98 (0.60-1.60)	0.93	1.08 (0.69-1.70)	0.73	1.25 (0.75-2.08)	0.39
	TBI vs. CBV^{high}	**0.45 (0.26-0.77)**	**0.004**1	0.75 (0.48-1.19)	0.22	1.01 (0.61-1.67)	0.97
	TBI vs. BuCy	**0.46 (0.28-0.74)**	**0.001**1	0.70 (0.48-1.01)	0.06	0.81 (0.54-1.21)	0.29

* Overall p-values

1 Comparisons significantly associated with an outcome ($p < 0.01$).