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Treatment-related toxicity of the BEAM/BeEAM conditioning regimen in patients undergoing autologous hematopoietic stem cell transplantation

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Conditioning regimens prior to hematopoietic stem cell transplantation (HSCT) are highly intensive and associated with significant toxicity, which can influence survival and quality of life. This study aimed to analyze the incidence of gastrointestinal, hematological toxicity, changes in quality of life, and cognitive functions in lymphoma patients undergoing autologous HSCT with BEAM/BeEAM conditioning. A total of 27 lymphoma patients indicated for autologous HSCT were enrolled in this prospective observational study from January 2020 to August 2023. Data collection was performed at admission and at the end of hospitalization, prior to discharge. Monitored parameters included laboratory tests (hematology and biochemistry), patient-reported quality of life assessed using the QLQ-C30 questionnaire, and perceived cognitive function evaluated using the FACT-Cog questionnaire. Mucositis of any grade occurred in 25 patients (92.6%), with diarrhea being the most common gastrointestinal symptom (any grade 85.2%, grade 3–4 37.0%). Diarrhea severity was generally independent of age, baseline blood counts, engraftment, weight loss, or hospitalization, except for an association between severe diarrhea and lower pre-transplant TSH (p=0.03). All patients experienced grade 1–2 weight loss, and 81.5% developed febrile neutropenia. Quality of life declined during transplantation, notably in role functioning, social functioning, and cognitive performance, alongside worsening fatigue, nausea/vomiting, pain, appetite loss, and diarrhea (all p-values <0.05). FACT-Cog scores showed no significant cognitive decline. The 2-year overall survival was 92.1% (95% CI 81.6–100%), while patients with SII >520.81 had lower survival (82.5%, 95% CI 60.4–100%, p=0.04), with higher SII significantly associated with worse outcomes. Autologous transplantation and the BEAM/BeEAM conditioning regimen are associated with considerable mucosal and hematologic toxicity. Patients are at risk of infections, nutritional deficits due to reduced intake, and deterioration in quality of life.

Key words: stem cell transplantation, toxicity, diarrhea, quality of life, BEAM

Autologous hematopoietic stem cell transplantation (HSCT) has confirmed its role as the standard therapeutic approach for patients with relapsed/refractory Hodgkin (HL) and non-Hodgkin lymphoma (NHL), upfront consolidation in Mantle cell lymphoma (MCL), as well as in T-cell lymphomas [1–3]. Most patients experience toxicity from the conditioning regimen during the pancytopenic phase, which manifests as gastrointestinal adverse events, infectious complications, and impaired organ function. These side effects may interfere with the transplantation process, worsen overall survival, quality of life, and, in some cases, pose a life-threatening risk to the patient [4]. This is highlighted, for example, by a study on 191 lymphoma patients undergoing autologous transplantation, where severe mucositis and pre-transplant hypoalbuminemia were identified as risk factors for overall mortality [5]. Similarly, moderate to severe mucositis in another study in patients undergoing autologous or allogeneic HSCT was associated with increased risk of bloodstream infections and treatment-related mortality [6]. According to a retrospective study, which analyzed a cohort of 8,891 patients with multiple myeloma and lymphoma admitted to U.S. hospitals for autologous HSCT,

significant complications were observed in more than 50% of admissions. Infectious complications (~60%) and stomatitis (~40%) were the most frequent; in-hospital mortality was rare (<5%). Finally, the complications contributed to a substantial increase in the economic burden associated with hospitalization [4, 7]. The selection of a conditioning regimen for autologous HSCT is important and should meet the requirements of sufficient efficacy while maintaining the lowest possible and well-tolerated toxicity. BEAM regimen, comprising carmustine (BCNU), etoposide, cytarabine, and melphalan, has been one of the most commonly applied protocols in North America and Europe [8]. Nevertheless, the use of BEAM has been increasingly limited due to toxicities associated with carmustine, such as pneumonitis and the risk of secondary cancers, as well as issues related to cost and availability. To address these concerns, many centers changed the regimen for BeEAM, which replaces carmustine with bendamustine while keeping cytarabine, etoposide, and melphalan. A number of studies have reported BeEAM to be safe and effective for autologous HSCT in patients with malignant lymphoma [9–11]; however, caution regarding renal function should be increased [12]. A meta-analysis that compared outcomes of retrospective studies using BEAM and BeEAM in 1,304 lymphoma patients showed that the BeEAM regimen was associated with a slightly better PFS but higher mucositis, renal toxicity, and cardiotoxicity. There was no difference in neutrophil and platelet engraftment, as well as in the rate of non-relapse mortality between the BEAM and BeEAM group [13].

In this study, we aim to analyze the incidence of gastrointestinal and hematological toxicity of the BEAM/BeEAM conditioning regimen, as well as the occurrence of febrile neutropenia. We focus on the most common gastrointestinal symptom – diarrhea, and on potential laboratory markers that could predict its severe course. We also assess changes in quality of life and cognitive function using standardized questionnaires. Limited data are available on the overall toxicity profile and its potential laboratory predictors of the BEAM/BeEAM conditioning regimen, including its impact on patients' quality of life and cognitive function during transplantation.

Patients and methods

Patients. This was a prospective, non-randomized, observational study. Patients with lymphoma were eligible for the study if they provided signed written informed consent, were aged 18 years or older, and were planned to undergo high-dose chemotherapy BEAM/BeEAM followed by hematopoietic cell transplantation at the Transplantation Unit of the Department of Oncohematology, National Cancer Institute. Patients who did not meet these inclusion criteria were excluded from the study. Patient recruitment for the study was conducted between January and August 2020. Eligible individuals were invited to participate and provided with a full explanation of the study objectives and procedures at the time of admission to the Transplantation Unit. The preparative regimen was chosen according to the availability of the drugs, with the BEAM regimen consisting of carmustine, etoposide, cytarabine, and melphalan, and the BeEAM regimen replaced carmustine with bendamustine. Antimicrobial prophylaxis was provided according to local departmental practices from the day of stem cells' administration: fluconazole, acyclovir, and ofloxacin. The study PROBIO-006-SK was approved by the Ethics Committee of the National Cancer Institute on December 14, 2020.

Examined parameters. Clinical and laboratory variables were monitored at two time points: upon admission to the transplantation unit, designated as D-8 (±2 days), and at the time of discharge, D+12 (±2 days). The following parameters were assessed: clinical evaluation including medical history and physical examination, hematological and biochemical profiles, and inflammatory markers. Quality of life was assessed using the European Organisation for Research and Treatment of Cancer (EORTC) questionnaires – QLQ-C30 (Quality of Life Questionnaire), version 3, and cognitive function was evaluated using the FACT-Cog (Functional Assessment of Cancer Therapy – Cognitive Function), version 3. The Systemic Immune-Inflammation Index (SII) was calculated using platelet (P), neutrophil (Ne), and lymphocyte (L) counts, according to a previously published formula: SII = P× Ne/l [14]. Based on the median SII value in our cohort (520.81), we dichotomized SII into low (≤520.81) and high (>520.81) categories. The monitored variables are summarized in Supplementary Table S1.

Collecting samples. Patients were asked to provide blood samples before and after the transplantation procedure. Specifically, patients were asked to donate 2×6 ml of peripheral blood (PB) collected in EDTA vacutainer tubes (purple cap) for plasma isolation, and 6 ml of PB collected in serum tubes (red cap) for serum isolation, obtained on the day of admission to the Transplantation Unit and before discharge.

Outcomes and evaluation. At the end of hospitalization, hematological and gastrointestinal toxicity, with a specific focus on diarrhea (grades 0–2 and 3–4), and the incidence of febrile neutropenia were evaluated according to CTCAE v5.0 and correlated with the measured variables [15].

Questionnaire assessment. Patients were asked to complete standardized questionnaires from the European Organisation for Research and Treatment of Cancer (EORTC) at two time points – upon admission to the transplantation unit at the beginning of hospitalization and again before discharge to home care. Validated instruments were used: EORTC QLQ-C30 (Quality of Life Questionnaire), version 3, FACT-Cog, version 3. Questionnaires were completed in the patient's individual room under calm, standardized conditions without time pressure. The EORTC QLQ-C30 is one of the most widely used tools for assessing health-related quality of life in oncology patients. It consists of 30 self-reported questions evaluating five functional domains (physical, role,

emotional, cognitive, and social functioning), nine symptom domains (fatigue, pain, nausea and vomiting, dyspnea, loss of appetite, sleep disturbance, constipation, diarrhea, and perceived financial difficulties), and two global health and quality-of-life scales. Higher scores in functional and global health domains indicate better functioning and quality of life, whereas higher scores in symptom scales indicate more severe symptomatology [16]. The FACT-Cog questionnaire is a validated self-assessment tool for evaluating cognitive functioning in four domains: perceived cognitive impairment (CogPCI), perceived cognitive abilities (CogPCA), quality of life affected by cognitive impairment (CogQoL), and cognitive impairment perceived by others (CogOth). The total cognitive function score is calculated as the sum of these four domains, with lower scores reflecting lower levels of cognitive functioning [17]. Questionnaires completed at admission were compared according to sex and age. Age categories were defined as younger middle-aged patients (≤44 years) and older middle-aged patients (>45 years). Subsequently, changes in quality of life and cognitive functioning during transplantation were assessed by comparing scores from the baseline questionnaire with those obtained at the end of hospitalization.

Statistical analysis. Patient cohort characteristics were summarized as median and range for continuous variables and as absolute and relative frequencies for categorical variables. Overall survival (OS) was defined as the time from the date of transplantation to the date of death or last follow-up. OS probabilities were estimated using the Kaplan-Meier method, and differences between groups were assessed with the log-rank test. Questionnaires QLQ-C30 and FACT-Cog performed at the time of admission to the ward were correlated with age and sex by Kruskal-Wallis analyses. The changes in quality of life and cognitive functions over the course of transplantation, as established by comparing baseline and post-transplant questionnaire scores, were established by a paired t-test. All statistical analyses were performed using NCSS 11 software [18]. Statistical significance was evaluated based on two-sided p-values, with results considered significant at $p \leq 0.05$.

Table 1. Overview of hematologic and gastrointestinal toxicity in the patient cohort.

Toxicity	Any Grade	%	Grade 3–4	%
Anemia	26	96.30	16	59.26
Constipation	12	44.44	0	0.00
Nausea	10	37.04	1	3.70
Vomiting	6	22.22	1	3.70
Stomatitis	13	48.15	4	14.81
Mucositis	25	92.59	13	48.15
Diarrhea	23	85.19	10	37.04
Weakness	20	74.07	0	0.00
Weight loss	18	66.67	0	0.00

Results

Patients' characteristics. A total of 27 patients undergoing autologous HSCT were included (median age 52 years, range 27–68; 55.6% female). The cohort comprised T-cell lymphomas (18.5%; PTCL and T-LBL), HL (18.5%), and B-cell lymphomas (62.9%; FL, DLBCL, MCL). The main indications for transplantation were disease relapse (37%) and primary progression (33.3%). Only four patients were heavily pretreated (≥3 prior therapy lines); the rest had received 1–2 lines of therapy. BEAM was administered to 15 patients (55.6%), and BeEAM was used in 12 patients (44.4%). Pre-transplant objective responses (complete or partial) were documented in 25 patients by CT or PET/CT. As the first-line antibiotic therapy, 10 patients (37%) received piperacillin/tazobactam, 7 patients (25.9%) received cefepime, 5 patients (18.5%) received ceftazidime with metronidazole, and 4 patients (14.8%) did not receive any antibiotics.

Incidence of toxicity. All patients experienced hematologic toxicity, with grade 4 thrombocytopenia in 100% and grade 3–4 anemia in 59.3% of patients, as shown in Table 1. Among gastrointestinal toxicities, enterocolitis was the most frequent and prominent, occurring in 74.1% of patients. More than half of the patients (59.3%) required parenteral nutrition, with a median duration of 4 days. All patients experienced grade 1–2 weight loss. Febrile episodes during neutropenia occurred in 81.5% of patients, and escalation of antibiotic therapy was required in 59.3% of patients. No significant difference in toxicity was observed between the BeEAM and BEAM regimens (data not shown).

Diarrhea. In our cohort, 4 patients did not develop diarrhea during transplantation. Laboratory analysis of blood counts and biochemical parameters did not reveal any significant markers; however, patients without diarrhea showed trends toward lower baseline SII, lower triglyceride levels, and higher immunoglobulin levels, as summarized in Table S3. None of the patients without diarrhea required parenteral nutrition. Patients who developed diarrhea of any grade (grade 1–4) experienced significantly deeper thrombocytopenia, with a median platelet count of 10×10^9/l. When investigating potential laboratory predictors of severe diarrhea (grade 3–4), we found that these patients had significantly lower TSH levels. No other significant associations with laboratory parameters were observed. Regarding toxicity, severe diarrhea was associated with a higher requirement for erythrocyte transfusions and parenteral nutrition, whereas no significant associations were found with age, graft engraftment, weight loss, or the depth of thrombocytopenia as detailed in Tables S3 and S4.

Initial FACT-Cog assessment. Baseline FACT-Cog questionnaires, which assess patients' perception of their cognitive function, cognitive impairments, and impact on quality of life, were analyzed according to sex and age. Women reported a better quality of life affected by cognitive function (CogQoL) and higher overall cognitive function

scores compared with men, although differences were not statistically significant. Patients were also stratified by age: ≤44 years vs. >45 years. Older patients (>45 years) reported significantly greater perceived cognitive decline (Table S5).

Longitudinal changes in cognitive function. Paired t-tests were used to analyze changes in FACT-Cog scores during the transplantation period. No statistically significant changes were observed in any individual domains or in the total cognitive function score over the course of transplantation (Table S6).

QLQ-C30 questionnaire results. Analysis of the baseline QLQ-C30 questionnaire in relation to sex revealed that women reported significantly better overall health status and cognitive functioning compared to men. No significant differences were observed in emotional, social, or physical functioning, nor in the presence of treatment-related symptoms. In contrast, younger patients (<45 years) reported worse social and emotional functioning, while older patients (>45 years) more frequently reported dyspnea and financial difficulties compared to younger individuals (Tables S7, S8).

Longitudinal changes in quality of life. Notably, assessment of changes in QLQ-C30 scores during transplantation demonstrated a marked deterioration in overall health status and treatment-related symptoms. Patients reported significantly worse role functioning, social functioning, and cognitive functioning. At the end of transplantation, there was a significant worsening of fatigue, nausea and vomiting, pain, appetite loss, and diarrhea (Figure 1, Table S9).

Other variables significantly associated with toxicity. Several measured variables were correlated with toxicities other than diarrhea, including laboratory parameters and available patient data, revealing additional noteworthy associations. All available variables were analyzed in each domain, and here we report only those with statistical significance. Among laboratory parameters, a significant association was observed between SII and the need for parenteral nutrition, with patients presenting higher baseline SII requiring parenteral nutrition more frequently (p=0.00056). Analysis by age revealed that younger patients (≤44 years) required significantly more days of parenteral nutrition (p=0.01), exhibited more pronounced lymphopenia (p=0.01), and had higher SII (p=0.002). In contrast, older patients showed significantly lower total protein levels (p=0.02) and albumin (p=0.003).

OS in association with selected variables. At a median follow-up of 28.2 months (range 5–49.7), three patients (11.11%) had died. The 2-year OS for the cohort was 92.10% (95% CI 81.58–100%) (Figure 2A). Patients with a higher SII (SII>520.81) had a 2-year OS of 82% (95% CI 60.39–100%) compared to 100% (95% CI not estimated), p=0.04 (Figure 2B). We also analyzed potential associations of OS with preparative chemotherapy regimen (BeEAM vs. BEAM), BMI, occurrence of diarrhea, mucositis, weight loss during transplantation, total and visceral fat proportion, age >45 years, and lymphoma subtype (B-NHL vs. T-NHL and HL); however, none of these factors demonstrated statistically significant associations with OS (data not shown).

Discussion

In this study, we evaluated the toxicity profile of the BeEAM/BEAM conditioning regimen in 27 patients with lymphoma undergoing autologous stem cell transplantation. Our results demonstrated that the incidence of mucositis and diarrhea was comparable to that reported in previous studies,

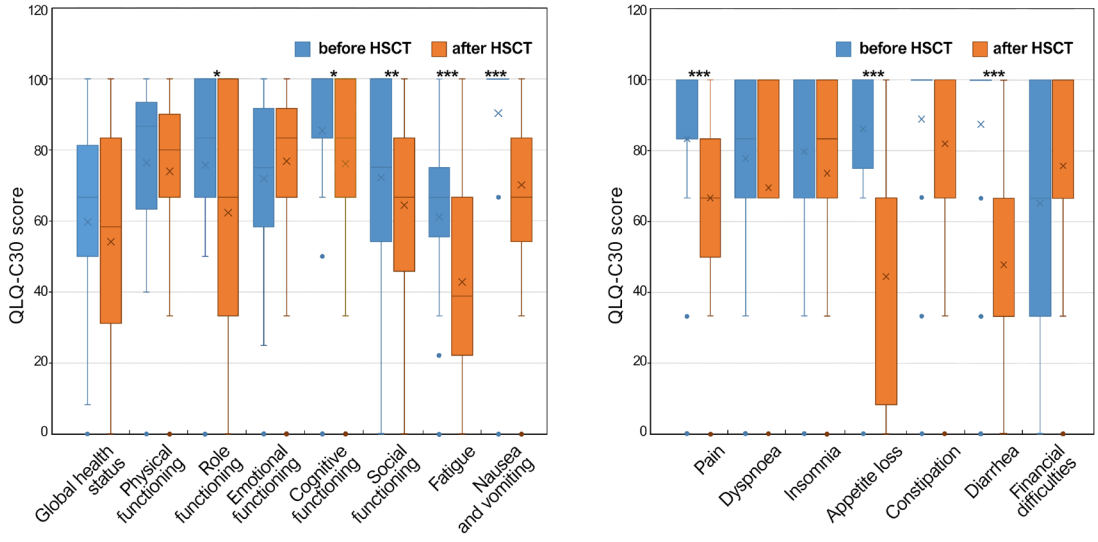

Figure 1. A graphical representation of individual domains before and after transplantation. Boxes represent the interquartile range per measurement. Horizontal lines dividing the boxes mark the median, and crosses indicate the mean. Outliers are represented by dots, lying outside the whiskers. *p<0.05; **p<0.01; ***p<0.001

although our rates were at the upper end of the published range. No significant difference in toxicity was observed between the BeEAM and BEAM regimens (data not shown), despite some reports describing a higher frequency of mucositis in patients receiving BeEAM.

The prevalence of BeEAM-related mucositis varies widely across studies, with reported rates ranging from 35% to 92% [19, 20]. In a study of 87 patients, Garciaz et al. observed mucositis in 89% of patients treated with BeEAM compared with 76% in the BEAM group. Similarly, in an analysis of 102 patients undergoing autologous transplantation between 2008 and 2015, severe mucositis in 50% of patients treated with BeEAM versus 38% in the BEAM group [21] has been found. When analyzing the relationship between diarrhea and laboratory parameters, we observed that lower TSH levels were associated with more severe diarrhea. The impact of TSH values on gastrointestinal (GIT) toxicity has not been clarified in the available literature. From a pathophysiological perspective, elevated TSH levels are known to increase mucopolysaccharide deposition within mucosal tissues, resulting in mucosal thickening and altered function. Thyroid hormones can modulate metabolic activity and may also influence the pharmacokinetics of chemotherapeutic agents through mechanisms involving cytochrome P450, which could hypothetically affect the severity of mucosal toxicity [22, 23]. Further studies with larger patient cohorts are needed to determine whether this observation reflects a true biological relationship or is simply a limitation of the small sample size in our study.

Patients who experienced severe diarrhea required more frequent and prolonged parenteral nutrition and significantly more erythrocyte transfusions, which is likely a consequence of increased overall treatment toxicity. According to the available literature, approximately 90% of patients with lymphoma or myeloma develop infections during the pancytopenic phase following HSCT [24]. In another study involving 82 lymphoma patients undergoing HSCT with BEAM/BeEAM conditioning, febrile neutropenia was documented in 58% of patients, while Krawiec et al. reported an incidence of 77.4% [25]. In our cohort, 22 patients (81.48%) developed febrile neutropenia despite prophylactic antibiotic therapy. This finding underscores that febrile neutropenia remains a frequent and significant complication of transplantation, highlighting the importance of timely initiation of broad-spectrum antibiotic treatment.

Among younger patients under 45 years of age, lymphopenia and significantly higher SII values were observed more frequently. According to the literature, lymphopenia in patients with lymphoma is considered a negative prognostic factor [26–28] and is incorporated into the calculation of inflammatory indices such as the neutrophil-to-lymphocyte ratio (NLR) and SII, as well as into the International Prognostic Score (IPS) in HL. In our cohort, SII was confirmed to have a significant impact on OS; however, neither age nor lymphopenia alone showed a statistically significant effect on OS.

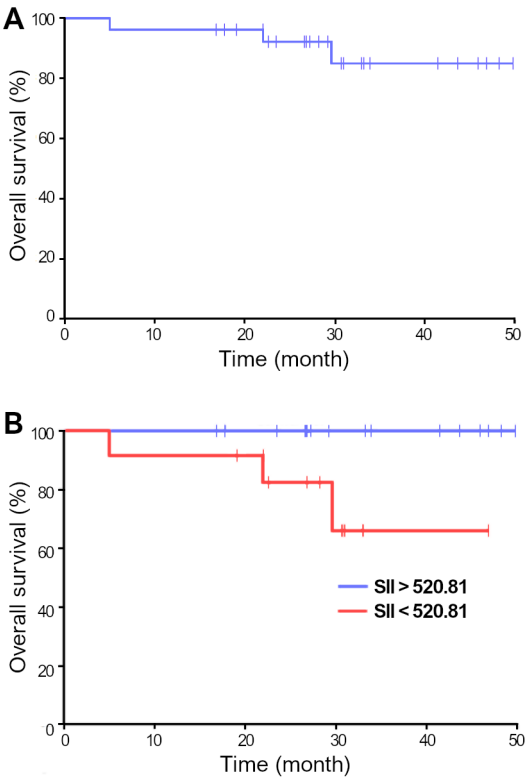

Figure 2. Overall survival in association with selected variables. A) OS for the cohort of patients. B) OS of patients after autologous HSCT according to the pre-transplant SII (p=0.04). The x-axis represents follow-up duration in months, and the y-axis represents the percentage of surviving patients.

In the FACT-Cog questionnaire assessing cognitive functioning, patients rated their perceived cognitive impairments, abilities, their impact on quality of life, and how others perceive their cognitive performance. No significant differences were observed between men and women. Patients older than 45 years reported greater perceived cognitive impairment, while no other age-related associations were found. According to the study by Jones et al. [29], which compared objective cognitive performance six months after HSCT with patients' self-perceptions, subjective assessment of cognitive abilities differed significantly from objective test results. The strongest correlation with objective testing was observed for the FACT-Cog subscale reflecting how patients believe others perceive their cognition (FACT-CogOth). Most studies have focused on the post-transplant evolution of cognitive function and its subjective perception. In our cohort, the findings from baseline likely reflect the influence of prior therapy and pre-transplant factors on cognitive perception. Other studies have identified several additional factors affecting pre-transplant cognitive function, including socioeconomic status, intelligence quotient, fear of cancer recurrence, depression,

and prior cranial or total body irradiation [30]. Analysis of the QLQ-C30 questionnaire revealed a notable decline in patients' quality of life during transplantation, particularly in role, social, and cognitive functioning, as well as a marked increase in symptoms related to treatment toxicity, including fatigue, nausea and vomiting, pain, appetite loss, and diarrhea. While most published QLQ-C30 studies focus on longer-term follow-up after transplantation, our assessment captures the acute impact of high-dose chemotherapy and autologous stem cell transplantation. Evaluation of baseline QLQ-C30 scores according to sex and age also highlighted differences prior to transplantation, reflecting the impact of prior treatments and pre-transplant patient status. Women generally reported better cognitive functioning and overall health status compared to men, whereas younger patients reported more pronounced emotional and social impairment, and older patients faced greater financial difficulties. These findings suggest that patient demographics and pre-transplant conditions can influence perceived quality of life and should be considered when planning supportive care interventions.

In our cohort, the overall 2-year survival rate was 92.1%. Patients with a higher SII (SII>520.81) had a lower 2-year survival rate of 82.5%, with elevated SII being significantly associated with poorer OS. The SII may serve as a potential prognostic marker, likely reflecting a pro-inflammatory state characteristic of lymphomas with a reactive inflammatory microenvironment, particularly in cases of disease progression or suboptimal treatment response. Previous studies have also demonstrated the prognostic relevance of SII in extranodal NK/T-cell lymphomas, classical HL, and diffuse large B-cell lymphoma (DLBCL) [31–33].

The limitations of this study include the small sample size, a non-randomized design without intervention, and a relatively short follow-up period for assessing changes in quality of life and cognitive function through questionnaires. Despite these limitations, the study provides novel insights into the toxicity of autologous transplantation, which could serve as a foundation for future observational and interventional studies.

Conclusion. The success of HSCT depends not only on the type and dose of the conditioning regimen but also on adequate supportive care, which critically affects patients' quality of life and survival. Early identification of reliable toxicity markers could guide tailored supportive interventions, such as prophylactic antibiotics, immunoglobulin replacement, nutritional and psychological support.

Supplementary information is available in the online version of the paper.

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Treatment-related toxicity of the BEAM/BeEAM conditioning regimen in patients undergoing autologous hematopoietic stem cell transplantation

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Supplementary Information

Table S1. Monitored Laboratory Parameters.

Hematology	red blood count, hematocrit, hemoglobin, platelet count, white blood cell count, differential blood count
Coagulation tests	prothrombin time, *activated partial thromboplastin time ratio,* international normalized ratio, fibrinogen
Urinanalysis	chemical and microscopic examination
Biochemistry	level of glucose, protein, albumin, uric acid, alanine aminotransferase, bilirubin total, urea, creatinine, potassium, sodium, chloride, alkaline phosphatase, aspartate aminotransferase, gama-glutamyl transferase, lactate dehydrogenase, calcium, phosphorus, magnesium, C-reactive protein, procalcitonin, immunoglobulins, thyrotropin, thyroxin, IL-6, inflamatory cytokines, vitamins, ferritin, lipid metabolism

Table S2. Characteristics of monitored variables in treatment-related toxicity.

Parameter	Median	Range	SD
Lowest platelet count ($\times 10^9$/L)	10	1–17	3.45
Platelet engraftment (day)	11	8–20	2.42
Number of platelet transfusions	4	1–15	3.45
Day of lowest platelet count	6	5–12	2.03
Number of red blood cell transfusions	1	0–7	1.72
Number of G-CSF doses	7	4–15	2.10
Neutrophil engraftment >1 × 10^9/L (day)	10	9–16	1.22
Days on parenteral nutrition	4	0–9	3.36
Length of hospitalization from stem cell infusion to discharge (days)	15	13–23	2.59

Abbreviations: G-CSF – granulocyte colony-stimulating factor; L – liter, SD - standard deviation

Table S3. Association of diarrhea occurrence – Grade 0 versus Grades 1–4 – with baseline laboratory parameters, age, and other toxicity characteristics.

Parameter	Characteristic	N	Median	SD	p-value
Age (years)	Diarrhea Gr. 0	4	51.00	5.12	0.89
	Diarrhea Gr. 1–4	23	53.00	12.92	
Length of hospitalization (days)	Diarrhea Gr. 0	4	17.00	2.52	0.65
	Diarrhea Gr. 1–4	23	15.00	2.65	
Leukocytes ($\times 10^9$/L)	Diarrhea Gr. 0	4	4.16	1.65	0.45
	Diarrhea Gr. 1–4	23	4.76	2.68	
Neutrophils ($\times 10^9$/L)	Diarrhea Gr. 0	4	2.03	0.60	0.31
	Diarrhea Gr. 1–4	23	2.93	2.25	
Platelets ($\times 10^9$/L)	Diarrhea Gr. 0	4	180.00	113.62	0.54
	Diarrhea Gr. 1–4	23	214.00	63.20	
Lymphocytes ($\times 10^9$/L)	Diarrhea Gr. 0	4	1.43	0.92	0.59
	Diarrhea Gr. 1–4	23	1.18	0.77	
NLR	Diarrhea Gr. 0	4	1.40	1.19	0.17
	Diarrhea Gr. 1–4	23	2.64	4.27	
SII	Diarrhea Gr. 0	4	282.72	83.36	0.07
	Diarrhea Gr. 1–4	23	589.20	801.29	

Table S3. ***Continued . . .***

Parameter	Characteristic	N	Median	SD	p-value
Transferrin (g/L)	Diarrhea Gr. 0	4	2.18	0.40	0.54
	Diarrhea Gr. 1–4	23	2.29	0.41	
Total proteins (g/L)	Diarrhea Gr. 0	4	63.90	5.37	0.66
	Diarrhea Gr. 1–4	23	63.50	6.60	
Cholesterol (mmol/L)	Diarrhea Gr. 0	4	5.27	1.47	0.49
	Diarrhea Gr. 1–4	23	4.58	1.07	
Triglycerides (mmol/L)	Diarrhea Gr. 0	4	1.18	0.40	0.08
	Diarrhea Gr. 1–4	22	1.96	0.96	
HDL (mmol/L)	Diarrhea Gr. 0	4	1.14	0.15	0.84
	Diarrhea Gr. 1–4	23	1.09	0.37	
LDL (mmol/L)	Diarrhea Gr. 0	4	3.62	1.21	0.16
	Diarrhea Gr. 1–4	21	2.84	0.81	
IgG (g/L)	Diarrhea Gr. 0	4	9.17	1.12	0.08
	Diarrhea Gr. 1–4	23	6.77	3.33	
Vitamin D (ng/mL)	Diarrhea Gr. 0	3	47.75	20.65	0.58
	Diarrhea Gr. 1–4	20	37.40	19.16	
Folic acid (nmol/L)	Diarrhea Gr. 0	3	13.00	6.09	0.23
	Diarrhea Gr. 1–4	19	10.40	7.57	
Vitamin B12 (pmol/mL)	Diarrhea Gr. 0	3	981.00	582.60	0.44
	Diarrhea Gr. 1–4	20	1422.00	422.21	
TSH (mIU/mL)	Diarrhea Gr. 0	4	1.44	4.17	0.59
	Diarrhea Gr. 1–4	23	1.71	1.33	
FT4 (pmol/L)	Diarrhea Gr. 0	4	11.32	2.67	0.34
	Diarrhea Gr. 1–4	23	13.15	1.82	
Albumin (g/L)	Diarrhea Gr. 0	4	40.50	4.11	0.92
	Diarrhea Gr. 1–4	23	40.00	3.35	
CRP (mg/L)	Diarrhea Gr. 0	4	1.79	3.05	0.49
	Diarrhea Gr. 1–4	23	0.53	23.30	
Cholinesterase (g/L)	Diarrhea Gr. 0	4	153.20	56.97	0.63
	Diarrhea Gr. 1–4	23	165.80	36.50	
Lowest PLT count ($\times 10^9$/L)	Diarrhea Gr. 0	4	13.00	1.83	**0.04**
	Diarrhea Gr. 1–4	23	10.00	3.45	
Day of lowest PLT count	Diarrhea Gr. 0	4	7.00	3.10	0.78
	Diarrhea Gr. 1–4	23	6.00	1.86	
PLT engraftment (day)	Diarrhea Gr. 0	4	10.50	2.16	0.73
	Diarrhea Gr. 1–4	23	11.00	2.50	
Number of PLT transfusions	Diarrhea Gr. 0	4	3.50	2.06	0.73
	Diarrhea Gr. 1–4	23	4.00	3.65	
NEU engraftment (day)	Diarrhea Gr. 0	4	10.50	0.58	0.70
	Diarrhea Gr. 1–4	23	10.00	1.31	
Number of G-CSF doses	Diarrhea Gr. 0	4	7.00	1.73	0.97
	Diarrhea Gr. 1–4	23	7.00	2.19	
Number of RBC transfusions	Diarrhea Gr. 0	4	1.00	0.50	0.48
	Diarrhea Gr. 1–4	23	1.00	1.82	
Days on parenteral nutrition	Diarrhea Gr. 0	4	0.00	0.00	**0.02**
	Diarrhea Gr. 1–4	23	4.00	3.26	
Weight loss (%)	Diarrhea Gr. 0	4	5.30	1.97	0.37
	Diarrhea Gr. 1–4	23	6.79	2.69	

*N – number of patients, SD – standard deviation, PLT – platelets, RBC – red blood cell concentrate, Gr. – grade, NEU – neutrophils, G-CSF – granulocyte colony-stimulating factor, NLR – inflammatory index, neutrophil-to-lymphocyte ratio, SII – systemic immune-inflammation index, L – liter, HDL – high-density lipoprotein, LDL – low-density lipoprotein, TSH – thyroid-stimulating hormone, fT4 – free thyroxine, CRP – C-reactive protein

Table S4. Association of diarrhea occurrence – Grade 0–2 versus Grade 3–4 with baseline laboratory parameters, age, and other treatment-related toxicity characteristics.

Parameter	Characteristic	N	Median	SD	p-value
Age (years)	Diarrhea Gr. 0–2	17	53.00	12.42	0.90
	Diarrhea Gr. 3–4	10	54.00	11.93	
Length of hospitalization (days)	Diarrhea Gr. 0–2	17	15.00	2.78	0.46
	Diarrhea Gr. 3–4	10	15.00	2.36	
Leukocytes ($\times 10^9$/L)	Diarrhea Gr. 0–2	17	5.11	2.81	0.58
	Diarrhea Gr. 3–4	10	4.28	2.15	
Neutrophils ($\times 10^9$/L)	Diarrhea Gr. 0–2	17	2.93	2.33	0.96
	Diarrhea Gr. 3–4	10	2.57	1.84	
Platelets ($\times 10^9$/L)	Diarrhea Gr. 0–2	17	198.00	69.03	0.39
	Diarrhea Gr. 3–4	10	214.50	72.83	
Lymphocytes ($\times 10^9$/L)	Diarrhea Gr. 0–2	17	1.43	0.73	0.24
	Diarrhea Gr. 3–4	10	0.74	0.86	
NLR	Diarrhea Gr. 0–2	17	2.42	4.59	0.35
	Diarrhea Gr. 3–4	10	3.26	3.03	
SII	Diarrhea Gr. 0–2	17	478.60	664.73	0.21
	Diarrhea Gr. 3–4	10	731.33	895.76	
Transferrin (g/L)	Diarrhea Gr. 0–2	17	2.23	0.38	0.33
	Diarrhea Gr. 3–4	10	2.33	0.41	
Total proteins (g/L)	Diarrhea Gr. 0–2	17	63.90	4.64	1.00
	Diarrhea Gr. 3–4	10	63.30	8.80	
Cholesterol (mmol/L)	Diarrhea Gr. 0–2	17	5.20	1.31	0.16
	Diarrhea Gr. 3–4	10	4.38	0.57	
Triglycerides (mmol/L)	Diarrhea Gr. 0–2	16	2.03	1.02	0.23
	Diarrhea Gr. 3–4	10	1.40	0.80	
HDL (mmol/L)	Diarrhea Gr. 0–2	17	1.08	0.37	0.71
	Diarrhea Gr. 3–4	10	1.18	0.33	
LDL (mmol/L)	Diarrhea Gr. 0–2	16	3.09	1.03	0.21
	Diarrhea Gr. 3–4	9	2.72	0.55	
IgG (g/L)	Diarrhea Gr. 0–2	17	7.91	2.28	0.37
	Diarrhea Gr. 3–4	10	6.68	4.36	
Vitamin D (ng/mL)	Diarrhea Gr. 0–2	14	36.73	16.80	0.34
	Diarrhea Gr. 3–4	9	39.20	22.16	
Folic acid (nmol/L)	Diarrhea Gr. 0–2	13	12.50	8.46	0.24
	Diarrhea Gr. 3–4	9	10.40	5.22	
Vitamin B12 (pmol/mL)	Diarrhea Gr. 0–2	14	1422.00	420.99	0.59
	Diarrhea Gr. 3–4	9	1083.00	471.03	
TSH (mIU/mL)	Diarrhea Gr. 0–2	17	1.99	2.24	0.03
	Diarrhea Gr. 3–4	10	1.18	0.38	
FT4 (pmol/L)	Diarrhea Gr. 0–2	17	12.38	1.69	0.45
	Diarrhea Gr. 3–4	10	13.20	2.30	
Albumin (g/L)	Diarrhea Gr. 0–2	17	40.00	3.42	0.42
	Diarrhea Gr. 3–4	10	41.50	3.43	
CRP (mg/L)	Diarrhea Gr. 0–2	17	0.53	26.73	0.57
	Diarrhea Gr. 3–4	10	0.74	1.58	
Cholinesterase (g/L)	Diarrhea Gr. 0–2	17	157.50	42.86	0.51
	Diarrhea Gr. 3–4	10	165.15	32.71	
Lowest PLT count ($\times 10^9$/L)	Diarrhea Gr. 0–2	17	11.00	3.85	0.69
	Diarrhea Gr. 3–4	10	9.50	2.83	
Day of lowest PLT count	Diarrhea Gr. 0–2	17	6.00	1.76	0.66
	Diarrhea Gr. 3–4	10	7.00	2.46	
PLT engraftment (day)	Diarrhea Gr. 0–2	17	11.00	1.90	0.61
	Diarrhea Gr. 3–4	10	10.50	3.24	

Table S4. ***Continued . . .***

Parameter	Characteristic	N	Median	SD	p-value
Number of PLT transfusions	Diarrhea Gr. 0–2	17	4.00	3.41	0.67
	Diarrhea Gr. 3–4	10	4.00	3.68	
NEU engraftment (day)	Diarrhea Gr. 0–2	17	10.00	0.62	0.69
	Diarrhea Gr. 3–4	10	10.00	1.87	
Number of G-CSF doses	Diarrhea Gr. 0–2	17	7.00	1.37	0.68
	Diarrhea Gr. 3–4	10	6.00	3.06	
Number of RBC transfusions	Diarrhea Gr. 0–2	17	1.00	1.71	0.02
	Diarrhea Gr. 3–4	10	3.00	1.49	
Days on parenteral nutrition	Diarrhea Gr. 0–2	17	0.00	3.18	0.02
	Diarrhea Gr. 3–4	10	6.00	2.80	
Weight loss (%)	Diarrhea Gr. 0–2	17	5.26	2.32	0.11
	Diarrhea Gr. 3–4	10	7.42	2.99	

*N – number of patients, SD – standard deviation, PLT – platelets, RBC – red blood cell concentrate, Gr. – grade, NEU – neutrophils, G-CSF – granulocyte colony-stimulating factor, NLR – inflammatory index, neutrophil-to-lymphocyte ratio, SII – systemic immune-inflammation index, L – liter, HDL – high-density lipoprotein, LDL – low-density lipoprotein, TSH – thyroid-stimulating hormone, fT4 – free thyroxine, CRP – C-reactive protein

Table S5. Initial FACT-Cog Scores Stratified by Age and Sex.

FACT-Cog domain	Characteristic	N	Median	SD	p-value
CogPCI	Male	11	47	3.45	0.26
	Female	14	50	3.42	
CogQOL	Male	11	8	4.45	0.08
	Female	14	15	3.90	
CogOth	Male	11	13	2.39	0.26
	Female	14	14	3.25	
CogPCA	Male	11	17	6.00	0.23
	Female	14	25.5	5.69	
Total Cog score	Male	11	87	13.01	0.08
	Female	14	102.5	14.18	
CogPCI	≤44 years	7	46	4.16	**0.02**
	>45 years	18	50	2.54	
CogQOL	≤44 years	7	8	5.07	0.20
	>45 years	18	14	4.07	
CogOth	≤44 years	7	12	3.55	0.10
	>45 years	18	13.5	2.32	
CogPCA	≤44 years	7	18	6.63	0.12
	>45 years	18	25.5	5.46	
Total Cog score	≤44 years	7	87	14.98	0.06
	>45 years	18	102	12.42	

*Perceived Cognitive Impairment – CogPCI, Perceived Cognitive Abilities – CogPCA, Quality of Life Impacted by Cognitive Impairment – CogQoL, Cognitive Impairment Perceived by Others – CogOth, N – number of patients, SD – Standard Deviation

Table S6. Changes in FACT-Cog Questionnaire Scores During Transplantation.

FACT-Cog domain	N	Mean difference	T-value	SE	p-value
CogPCI	22	1.25	0.99	1.27	0.33
CogPCA	19	0.31	0.31	1.00	0.76
CogQoL	19	0.96	1.03	0.93	0.32
CogOth	20	–0.75	–1.54	0.49	0.14
Total cognitive function score	19	1.32	0.61	2.17	0.55

*Perceived Cognitive Impairment – CogPCI, Perceived Cognitive Abilities – CogPCA, Quality of Life Impacted by Cognitive Impairment – CogQoL, Cognitive Impairment Perceived by Others – CogOth, N – number of patients, SD – Standard Deviation

Table S7. QLQ-C30 Questionnaire Results at Admission Stratified by Sex.

QLQ-C30 domain	Sex	N	Median	SD	p-value
Global health status	Male	10	50.00	25.46	**0.04**
	Female	13	66.67	17.53	
Physical functioning	Male	10	86.67	10.45	0.97
	Female	13	86.67	20.25	
Role functioning	Male	10	66.67	30.23	0.17
	Female	13	100.00	20.24	
Emotional functioning	Male	10	75.00	23.24	1.00
	Female	13	75.00	22.31	
Cognitive functioning	Male	10	83.33	16.57	**0.03**
	Female	13	100.00	10.51	
Social functioning	Male	10	66.67	20.86	0.27
	Female	13	83.33	28.37	
Fatigue	Male	10	66.67	15.89	0.70
	Female	13	66.67	22.15	
Nausea and vomiting	Male	10	100.00	10.54	0.97
	Female	13	100.00	27.73	
Pain	Male	10	83.33	20.79	0.46
	Female	13	100.00	12.80	
Dyspnea	Male	10	66.67	22.45	0.35
	Female	13	100.00	22.01	
Insomnia	Male	10	100.00	17.21	0.67
	Female	13	100.00	22.01	
Appetite loss	Male	10	100.00	16.10	0.49
	Female	13	100.00	24.46	
Constipation	Male	10	100.00	22.50	0.71
	Female	13	100.00	12.51	
Diarrhea	Male	10	100.00	22.50	0.78
	Female	13	100.00	19.98	
Financial difficulties	Male	10	66.67	40.06	0.37
	Female	13	66.67	30.89	

* N – number of patients, SD – Standard Deviation

Table S8. QLQ-C30 Questionnaire Results at Admission Stratified by Age.

QLQ-C30 domain	Age	N	Median	SD	p-value
Global health status	≤44 years	6	50.00	27.39	0.20
	>45 years	17	66.67	21.25	
Physical functioning	≤44 years	6	83.33	21.36	0.91
	>45 years	17	86.67	15.18	
Role functioning	≤44 years	6	83.33	25.09	0.74
	>45 years	17	83.33	26.70	
Emotional functioning	≤44 years	6	62.50	18.76	**0.01**
	>45 years	17	91.67	19.37	
Cognitive functioning	≤44 years	6	91.67	16.39	0.56
	>45 years	17	100.00	14.50	
Social functioning	≤44 years	6	58.33	32.77	**0.05**
	>45 years	17	83.33	18.13	
Fatigue	≤44 years	6	55.56	22.95	0.20
	>45 years	17	66.67	18.37	
Nausea and vomiting	≤44 years	6	100.00	0.00	0.39
	>45 years	17	100.00	25.08	
Pain	≤44 years	6	91.67	26.70	0.68
	>45 years	17	83.34	11.69	
Dyspnea	≤44 years	6	66.67	21.08	**0.05**
	>45 years	17	100.00	20.61	
Insomnia	≤44 years	6	83.34	27.21	0.52
	>45 years	17	100.00	16.09	
Appetite loss	≤44 years	6	100.00	17.21	0.50
	>45 years	17	100.00	25.72	
Constipation	≤44 years	6	100.00	13.60	0.92
	>45 years	17	100.00	18.74	
Diarrhea	≤44 years	6	100.00	13.60	0.87
	>45 years	17	100.00	22.86	
Financial difficulties	≤44 years	6	66.67	34.43	**0.03**
	>45 years	17	100.00	31.55	

* N – number of patients, SD – standard deviation

Table S9. Changes in QLQ-C30 Questionnaire scores during transplantation.

QLQ-C30 domain	N	Mean difference	T-value	SE	p-value
Global health status	19	9.21	1.72	5.37	0.10
Physical functioning	18	8.52	1.75	4.87	0.10
Role functioning	19	19.30	2.36	8.19	0.03
Emotional functioning	20	–3.33	–0.64	5.25	0.53
Cognitive functioning	20	11.67	2.40	4.85	0.03
Social functioning	19	13.16	2.91	4.52	0.009
Fatigue	20	27.50	5.12	5.37	<0.001
Nausea and vomiting	20	27.50	5.82	4.73	<0.001
Pain	20	20.00	4.06	4.93	<0.001
Dyspnea	19	14.04	1.80	7.78	0.09
Insomnia	20	10.00	1.24	8.06	0.23
Appetite loss	20	46.67	6.66	7.01	<0.001
Constipation	20	8.33	1.56	5.34	0.14
Diarrhea	20	46.67	5.09	9.18	<0.001
Financial difficulties	19	–8.77	–1.23	7.14	0.23

* N – number of patients, SE – Standard Error